

WEAKENED BY STRENGTHS: DRUGS IN SOLUTION, MEDICATION ERROR AND DRUG SAFETY

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SUMMARY

WEAKENED BY STRENGTHS: DRUGS IN SOLUTION, MEDICATION ERROR AND DRUG SAFETY

The concentrations of some drug solutions are often expressed as ratios or percentages. This system simplified prescription and dispensing when Imperial measures such as grains and minims were used. Ampoules of powerful vasoactive drugs such as catecholamines and potentially toxic local anaesthetics are still labelled as ratios and percentages, seemingly through habit or tradition than for any useful clinical reason. This thesis argues that adherence to this outdated system is confusing, causes drug administration errors, and puts patients at risk.

Internet-based questionnaires were used to quantify medical students' and doctors' understanding of ratios and percentages. A substantial minority of almost 3 000 doctors could not convert between ratios, percentages and mass concentration correctly, made dosing errors of up to three orders of magnitude in written clinical scenarios, and struggled with conversions between metric units.

These findings are strong arguments for expressing drug concentrations as mass concentration and providing better drug administration teaching. High fidelity patient simulation was used to examine the influence of clearer ampoule labelling and intensive drug administration teaching. This allowed critical incidents to be reproduced realistically, clinical performances to be assessed, and outcome measures to be accurately recorded. Randomised controlled trials were conducted that demonstrated positive influences of both interventions for doctors and students. The difficulties that nurses encounter when preparing infusions of these drugs on critical care units were also studied and are reported.

The findings presented should be sufficient to persuade regulatory authorities to remove ratios and percentages from ampoule labels – a straightforward, cheap, commonsense intervention. The lack of effective clinical error reporting systems and the extreme practical difficulties of conducting clinical trials in this field mean that a firm link between this intervention and patient outcome is unlikely ever to be made, but this should not be an excuse for maintaining the *status quo*.

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Many people have helped me over the long time it has taken me to complete the research presented in this thesis. I registered for a DM as an ‘insurance policy’ when my basic science PhD seemed to be disappearing down the tubes and I had hit a rich vein of drug administration error research and funding. Of course, when the basic science project finally began to pay dividends, I had to juggle both projects with all the difficulties that go with trying to complete two higher degrees at once. None of this would have been possible without **Sarah**, who has made a sterling job of bringing up **Thomas, Edward** and **Joseph** whilst I gawp at the computer on the landing. Things were particularly tough whilst writing up (again), so thanks Sarah for making all this possible.

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I’ll stop now or I might have another **Gwyneth Paltrow** moment...

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ABBREVIATIONS

ACRM	Anesthesia Crisis Resource Management
ADE	Adverse drug event
AIMS	Australian Incident Monitoring Study
ASHP	American Society of Health-System Pharmacists
BA	Batchelor of Arts
BNF	British National Formulary
CMA	California Medical Association
CPOE	Computerised physician order entry
CRM	Crew (Cockpit) Resource Management
ERWeb	Educational Resources Web of the University of Cambridge School of Clinical Medicine
GLMM	Generalised linear mixed model
GMC	General Medical Council
HMPS	Harvard Medical Practice Study
HPS	Human Patient Simulator
ICU	Intensive care unit
IP	Internet Protocol address
IQR	Interquartile range
MB	Final examination in Bachelor of Medicine at the University of Cambridge
MEDMARX	US Database to reduce hospital medication errors
METI	Medical Educational Technologies, Inc.
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NHSE	National Health Service Executive
NPSA	National Patient Safety Agency
OSCE	Objective structured clinical examination
OSPE	Objective structured practical examination
SEE	Sentinel Events Evaluation
UKCEA	UK Conference of Educational Advisors
USP PRN	US Pharmacopeia Practitioners' Reporting Network
WHO	World Health Organization

DECLARATION

This dissertation is my own work and contains nothing which is the outcome of work done in collaboration with others, except as specified in the text and Acknowledgements.

No part of this thesis has already been submitted, accepted, or is concurrently being accepted, for any degree or diploma or certificate or other qualification in this University or elsewhere.

Daniel Wren Wheeler

20th June 2007

“I had rather undertake the practice of physick with pure air, pure water and good food alone than with all the drugs in the pharmacopoeia.”

Thomas Sydenham 1624-89

CHAPTER 1

INTRODUCTION 1: ERRORS IN ANAESTHESIA AND CRITICAL CARE MEDICINE

Clinical error is a huge global problem. The press and public are unforgiving of those perceived to have harmed patients as a result of seemingly basic mistakes, inattention, or carelessness and equate such mistakes with medical negligence. More than half the public believe that suspending doctors who have committed clinical errors is an effective prevention strategy (Blendon et al., 2002).

The foundations of research into clinical error were laid in the 1970s and 1980s when large epidemiological studies based on retrospective case note reviews, self-reporting systems and analyses of malpractice claims yielded evidence that medication errors are common and result in substantial disability, mortality and expense. Little of this research was relevant to (or even mentioned) anaesthesia and critical care. Research techniques have evolved to include prospective studies using observers, assessments of interventions and high fidelity patient simulators; anaesthetists are at the forefront of much of this endeavour. Meanwhile, cognitive psychologists are expanding our understanding of human error, theories of consciousness, memory, attention and performance, which are fundamental to the understanding of medication error research.

The definition of error and an introduction to cognitive psychology

‘Knowledge and error flow from the same mental sources, only success can tell one from the other’

Ernest Mach 1905 (English trans 1976)

An error is a failure to perform an action as intended. There is no universally agreed classification of human error; indeed, many who have published in the

field have developed their own taxonomy. Many investigators have adopted James Reason's classification (Reason, 1990), which draws widely from the aviation and nuclear industries as well as medicine as well as that of Jens Rasmussen (Rasmussen, 1986). He divides errors into slips, lapses and mistakes.

Slips

A slip results from a failure in the execution of an action, whether or not the plan behind them was adequate to reach its objective. Slips are said to be skill-based, occurring during the execution of smooth, automated and highly integrated tasks that do not require conscious control or problem solving. For example, writing the year incorrectly in the date shortly after New Year is a slip.

Lapses

The distinction between a slip and a lapse can be very subtle. Lapses involve memory failure, and may only be apparent to the person who experiences them, an example being forgetting to administer antibiotic prophylaxis before tourniquet inflation.

Mistakes

Slips and lapses occur when actions do not go to plan, mistakes happen when a plan proves inadequate. The operator is aware of the problem and begins to use rules or knowledge to solve it. When knowledge or rules are lacking, a mistake occurs. A rule-based mistake is due to the failure to apply or the misapplication of normally good rules, or the application of bad rules. Rules may be the individual's, or protocols drawn up by external bodies. A rule-based mistake was committed by an anaesthetist who intubated a child orally with a nasotracheal tube and did not recognise that it had become kinked. The child became profoundly hypoxic and died; the anaesthetist was convicted of manslaughter (Anon, 1974; Ferner, 2000; Ferner and McDowell, 2006).

Knowledge-based mistakes can be considered errors of judgement, occurring during ‘on the hoof’ problem-solving when all pre-packaged solutions are exhausted: a highly error prone endeavour, especially if an individual lacks knowledge or judgement (Reason, 1997; Merry and McCall Smith, 2001a). An example is of another anaesthetist convicted of manslaughter after failing to recognise a disconnected tracheal tube for a prolonged period, until the patient suffered a cardiac arrest and died (Ferner, 2000). Other types of error include the violation (when rules of correct behaviour are consciously ignored), whilst some still defy classification.

The foundations of research into clinical error and adverse events

In the 1970s, the US was witnessing a huge increase in the number of malpractice claims for medical negligence. Malpractice claims reviews only detect errors that result in a financial settlement, so there was little empirical knowledge of the incidence and causes of medical error. The California Medical Association’s (CMA) Medical Insurance Feasibility Study of 1977 was the first attempt to measure the incidence of medical error (California Medical Association, 1977). The retrospective examination of 20 000 medical records found that 4.6% contained events likely to result in successful litigation.

Retrospective case note review is frequently criticised as a research technique. In the 1980s the Harvard Medical Practice Study (HMPS) established a more precise method of retrospective case note examination, using teams of experienced case note examiners, more accurate sample weighting, and independent doctors who sought to identify causative factors (Brennan et al., 1989; Hiatt et al., 1989; Brennan et al., 1990; Brennan et al., 1991). Having screened 30 000 medical records randomly selected from the 2.7m patients who attended acute hospitals in New York State in 1984, they found that 3.7% of inpatients experienced an adverse event, with the elderly at most risk. Adverse events were attributed to a specialty, but anaesthesia was not amongst them! Most were attributed to surgical specialties; nearly half (48%) were associated with an operation. Over half of the adverse events resulted in minor impairment that resolved within a month. A

further 13% led to disability that resolved within 6 months, but 2.6% caused permanent disability and 13.6% were fatal. Negligence was thought to have played a part in over a quarter of errors, the elderly once again being particularly at risk.

The CMA and HMPS studies caused huge interest and increased awareness of the extent of the problem. A new field of research sprang up, culminating in the widely quoted US Institute of Medicine report of 1999, which estimated that there are between 44 000 and 98 000 fatal medical errors annually in the US (Kohn et al., 1999). The costs are also staggering: US\$17 – 29bn annually in the US, £6bn in the UK and Au\$5bn in Australia (Wilson et al., 1995; Kohn et al., 1999; Vincent et al., 2001).

Where do anaesthesia and critical care fit in?

In the HMPS, anaesthetic errors were probably attributed to surgical specialties. A retrospective chart review of 15 000 surgical admissions to Colorado and Utah hospitals during 1992 found the annual incidence of surgical adverse events to be 3.0%, but anaesthetic injuries only accounted for a very small proportion (table 1) (Gawande et al., 1999).

Whilst the large epidemiological trials seemed to have ignored anaesthesia, anaesthetists had been studying error all along. Ever since the first anaesthetic death in 1848 (Anon, 1848; Snow, 1849), there have been many investigations into anaesthetic risk, initially concentrating on the contribution of anaesthetic technique to mortality (Beecher and Todd, 1954; Edwards et al., 1956; Dripps et al., 1961; Clifton and Hotten, 1963; Phillips and Capizzi, 1974). Cooper was the first to apply the concept of critical incident reporting, developed by military aviators (Flanagan, 1954), to improving safety in anaesthesia (Cooper et al., 1978). This and other studies, which predate the HMPS by at least 13 years, showed that medication errors were amongst the most frequent anaesthetic mishaps (Wylie, 1975; Taylor et al., 1976; Cooper et al., 1978; Craig and Wilson, 1981; Cooper et al., 1984; Gaba et al., 1987).

Type of event	Incidence per 10 000 operations (95% confidence intervals)
Technique-related complications	90 (71-114)
Postoperative bleeding	47 (34-65)
Other infection	28 (18-42)
Wound infection	27 (17-42)
Drug-related injury	27 (17-41)
Deep venous thrombosis	14 (8-26)
Postpartum / neonatal-related	11 (6-22)
Wound problem (non-infectious)	10 (5-21)
Acute myocardial infarction	10 (5-21)
Nonsurgical procedure injury	10 (5-20)
Diagnostic error or delay	9 (4-19)
Injury not classified	8 (4-19)
Pulmonary embolus	8 (4-18)
Inappropriate therapy	6 (3-16)
Anaesthesia injury	6 (2-15)
Congestive heart failure	6 (2-15)
Stroke	6 (2-15)
Pneumonia	3 (1-11)
Fall	1 (0-10)
Other	19 (12-32)

Table 1: Incidence of surgical adverse events among Colorado and Utah inpatients by type of injury, 1992 (Gawande et al., 1999).

A prospective critical incident reporting system formed the basis of the Australian Incident Monitoring Study (AIMS), which involved anaesthetists from more than 90 hospitals (Webb et al., 1993a). Analysis of the first 2 000 incidents provided data on all aspects of anaesthetic error (Fox et al., 1993; Klepper et al., 1993; Ludbrook et al., 1993a; Ludbrook et al., 1993b; Morgan et al., 1993; Osborne et al., 1993; Runciman et al., 1993a; Runciman et al., 1993b; Russell et al., 1993; Van der Walt et al., 1993; Webb et al., 1993b), and although medication error accounted for 7.2% of incidents, none were fatal (Currie et al., 1993).

What is a medication error?

The definition of a medication error given in the US National Library of Medicine Medical Subject Headings is an ‘error in the prescription, dispensing, or administration of a medication with the result that the patient fails to receive the correct drug or the indicated proper drug dosage’. It does not necessarily result in injury. There is wide and sometimes interchangeable use of other terms such as ‘prescription error’, ‘drug error’, ‘dose error’, ‘adverse drug event (ADE)’, ‘potential ADE’ and ‘preventable ADE’, used to define the location of the error in the pathway between pharmacy and patient more precisely or indicate that a patient has been harmed (table 2). It is often difficult to compare the results of studies into medication error research when so many different primary outcome measures are used.

What is an Adverse Drug Event (ADE)?

An ADE is *any injury related to the use of a drug* (AHSP, 1993), so includes adverse drug reactions such as anaphylactic and other allergic reactions. Therefore, a medication error only becomes an ADE when a patient is harmed, and not all ADEs are caused by a medication error. To complicate matters further, in 1998, the American Society of Health-System Pharmacists refined the definition of an ADE to include *[injury caused by] the lack of an intended medication* (AHSP, 1998). It is important to be clear which definition research groups use as it would be reasonable that those using the latter might find a higher incidence of ADEs, since errors of omission are generally considered to outnumber errors of commission by two to one (Wilson et al., 1995). Care must also be taken over the terms preventable ADE and potential ADE, which are clearly different but both frequently abbreviated to pADE (Bates et al., 1995a; Leape et al., 1995; Kaushal et al., 2001; Koren, 2002; McDonnell and Jacobs, 2002; Holdsworth et al., 2003).

Term	Definition	References
Medication error	An error in the process of prescribing, dispensing, or administering a drug, whether there are adverse consequences or not	(Allan and Barker, 1990; Dean et al., 2000; van den Bemt et al., 2000)
Adverse drug event (ADE)	An injury related to the use of a drug	(AHSP, 1993)
Prescription error	A prescribing decision or written prescription resulting in an unintentional significant: - reduction in the probability of treatment being timely or effective <i>or</i> - increase in the risk of harm	(Dean et al., 2000)
Drug administration error	Misinterpretation of correctly written prescription, leading to: - administration of the wrong drug <i>and/or</i> - administration of the wrong dose <i>and/or</i> - administration of a drug at the wrong rate <i>and/or</i> - administration of the wrong formulation or concentration <i>and/or</i> - administration by the wrong route <i>and/or</i> - administration at the wrong time <i>and/or</i> - administration to the wrong patient	(Allan and Barker, 1990; Dean et al., 2000; van den Bemt et al., 2000)
Dose error	Administration of the wrong dose of a drug	(Allan and Barker, 1990; Dean et al., 2000)
Adverse drug reaction	Any response to a drug which is noxious and unintended that occurs in doses normally used in man	(WHO, 1969)

Table 2: The definitions of a variety of different terms used in the research and discussion of drug safety, adapted for relevance to anaesthesia and critical care (Wheeler et al., 2004b).

Methods of studying medication error

Establishing a reliable, reproducible and precise method of detecting medication errors in hospitals has proved to be a long-standing problem (Barker and McConnell, 1962). Retrospective case note review and analysis of malpractice claims only detect incidents recorded in the notes or that resulted in litigation. Incident reporting systems are popular and cheap but unnoticed errors go unreported, assessment of what constitutes an error is subjective, and they tend to

detect ADEs rather than medication errors (Cullen et al., 1995; Leape, 2002). It is now accepted that overt or disguised observation is the best way of collecting accurate data about medication error, although it is expensive (Barker, 1969; Flynn et al., 2002). Prospective drug chart review by pharmacists has yielded important data about the frequency and causes of prescription error, and although it may miss medication errors, it is popular and much cheaper than observation (Dean et al., 2002a; 2002b). Some investigators use a combination of techniques to improve the validity of their data (Bates et al., 1995a).

Detecting anaesthetists' medication errors in the operating theatre presents a particular problem. Review of drug charts and direct observation are techniques best suited to the wards. Often, anaesthetic drugs are recorded on separate anaesthetic charts rather than patients' drug charts, and anaesthetists prepare and give drugs unsupervised, although practice varies between countries. From a practical point of view, direct observation of an anaesthetist at work would detect far fewer drug administration episodes than the drug round on a busy ward. Despite its limitations, all the data concerning medication error in theatres has been collected by incident reporting. Direct observation and drug chart review have been used in critical care.

How common are medication errors?

There have been many studies looking at the frequency of medication error. The study generally accepted as having identified the baseline medication error frequency used direct observation on adult wards and reported a 19% frequency of drug administration error, of which 17% were dose errors (Barker et al., 2002). These figures have little relevance to anaesthesia where the majority of drugs are given intravenously. Medication error rates as high as 98% have been reported using disguised observation of intravenous drug administration in a children's hospital, but only 2% involved the wrong dose (O'Hare et al., 1995). These are by no means the only studies into the frequency of medication error, but are given as examples of the range of frequencies reported. The variability arises from the use of very different study populations, and different, broad definitions of medication

error that often include incorrect timing of administration. Hence the frequency, cost and associated morbidity and mortality of medication errors are still unclear, nor do we know whether the problem is improving or getting worse (Ferner and Anton, 1998; Phillips et al., 1998a; Phillips et al., 1998b).

How common are ADEs?

The CMA study and HMPS demonstrated that medical errors, many of which were medication errors, were causing substantial injury. Many groups began systematic, controlled studies into the relationship between medication error and ADEs so as to identify prevention strategies. They used combinations of incident reporting, chart review and direct observation. Although many of the investigators were anaesthetists, data were gathered on the wards. The results showed broad agreement and suggested an incidence of approximately six ADEs and five potential ADEs per 100 hospital admissions (Classen et al., 1991; Bates et al., 1995b; Barker et al., 2002), with only 1% of medication errors causing an ADE (Bates et al., 1995a).

At the time, the only published data specific to anaesthesia were based on incident reporting, suggesting that medication error occurred in 0.012 – 0.15% of anaesthetics (Craig and Wilson, 1981; Chopra et al., 1990) but there was no indication of ADE rates. Anaesthesia was considered to be increasingly safe; between the 1970s and 1990s intraoperative mortality had fallen from 1 in 10 000 to 1 in 200 000 (Pierce, 1996; Kohn et al., 1999; Cooper, 2001), although the data upon which these figures are based have been questioned (Lagasse, 2002). The systems changes initiated by anaesthetists that have reduced perioperative mortality are often quoted as models of patient safety (Leape, 1994).

Meanwhile, circumstantial evidence was emerging that the incidence of medication error and ADE in anaesthesia had been underestimated. First, the ADE Prevention Study had found that the ADE rate was much higher on intensive care units (ICUs) than the wards, with analgesics causing the most problems (Bates et al., 1995b). Second, a disguised observational study of intravenous drug

administration had found alarmingly high rates of error (O'Hare et al., 1995). As anaesthetists prescribe, prepare *and* administer intravenous drugs (especially analgesics), and work in theatre or ICU it seemed likely that medication error and ADEs might be more frequent in anaesthesia than previously thought.

How common are medication errors in anaesthesia?

Webster and colleagues used a prospective anonymous incident reporting system to establish the frequency of anaesthetic medication error and 'near misses' in two New Zealand hospitals (Webster et al., 2001a). To improve compliance and provide denominator data, anaesthetists completed a study form *whether or not* a drug administration error had occurred. Response rates were high and data were collected for 8 000 anaesthetics. The drug administration error rate was 0.75%, with a 'near miss' rate of 0.37%. The most frequent errors were dose errors (20%) and drug substitutions (20%). Most (63%) errors involved intravenous boluses, 20% involved infusions and 15% inhalational agents. This study of medication error in anaesthesia is the only one based on an accurate denominator. Previous studies had used the number of anaesthetics administered during the reporting period as the denominator (Craig and Wilson, 1981; Chopra et al., 1990), which lacks the benefit of explicitly negative responses and yielded much lower medication error frequencies of 0.012% – 0.15%. A confidential, self-reporting survey of drug administration errors by South African anaesthetists yielded only an 18.5% response rate but the vast majority admitted to having inadvertently administered a wrong drug, many on multiple occasions (Gordon et al., 2006).

The highest estimate of drug administration error in anaesthesia, 0.75% (Webster et al., 2001a), seems to compare favourably with that of the wards (19%) (Barker et al., 2002). However, incident reporting systems are far less sensitive than observational studies. A recent observational study detected 456 errors out of 2 557 doses given, but only one of these was detected by a concurrent incident reporting system (Flynn et al., 2002). Although Webster and colleagues took steps to encourage reporting it is unclear whether this added any extra sensitivity.

There are no direct comparisons of medication error rates in theatre and on the wards and there is little prospect of any in the future.

How common are ADEs in anaesthesia?

Webster and colleagues also listed the consequences of the medication errors they detected. No reported errors resulted in death or permanent disability. Several involved muscle relaxants, with one case of awareness and two of unplanned periods of postoperative ventilation and prolonged time in theatre. In addition, 47 transient physiological effects were reported, five of which required intervention. The authors suggest that this is compatible with the view that 1% of medication errors are adverse drug events, the case of awareness representing the only example of serious harm. The study was not designed to detect or establish the consequences of ADEs, and they were so rare that no meaningful statistical conclusions can be drawn about ADE in anaesthesia from this study. Gordon and colleagues' (2006) survey of South African anaesthetists lacked denominator data but reported five deaths and 3 non-fatal cardiac arrests.

How common are medication errors in critical care?

It seems reasonable to expect a high level of medication error on ICU considering the stressful, busy environment and the number of powerful drugs given. Early studies based on incident reporting substantiated this belief (Abramson et al., 1980; Girotti et al., 1987; Hart et al., 1994; Donchin et al., 1995; Beckmann et al., 1996). The first observational studies in critical care were small but reported the same findings. A study conducted on a Canadian paediatric critical care unit detected 147 errors made in 18 12-hour shifts. The vast majority (84.4%) involved drugs with high potential for serious consequences. The total error rate was 17.4% in the high dependency unit and 38.0% in the ICU, falling to 7.1% and 11.7% respectively when timing errors were excluded (Tisdale, 1986). A similar study on a paediatric ICU in Switzerland found an error frequency of 26.9%; the most frequent were errors of timing (32.4%), administration technique (32.4%) and preparation (23.0%) (Schneider et al., 1998).

The observational technique of detecting medication error was initially applied to oral drugs (Barker and McConnell, 1962). Tissot and colleagues recognised that on ICU there is potential for multiple errors to be made per administration episode, so recorded errors in every stage of drug preparation and administration on their ICU (Tissot et al., 1999). They overtly observed 132 errors in 2 009 administration episodes, a frequency of 6.6%. Most (31%) were dose errors, 22% were infusion rate errors, 18% preparation errors, 14% resulted from physicochemical incompatibility, 8% were errors of administration technique and only 7% were due to timing errors.

However, a disguised observational study conducted in two Dutch hospitals detected an error frequency of 44%, falling to 33% when timing errors were excluded (van den Bemt et al., 2002). A study from the US focusing on particularly error-prone drugs found an error rate of only 3.3%, although pharmacists played a much more active role on the ICUs studied (Calabrese et al., 2001). How can such a wide range of medication error rates be reconciled, and why are timing errors so important in some studies (O'Hare et al., 1995; Schneider et al., 1998) yet not others (Tissot et al., 1999; Calabrese et al., 2001)? Different data collection techniques and international practices or differences between adult and paediatric ICUs are probably responsible. For example, the low medication error rate of 6.6% reported by Tissot and colleagues could be accounted for by their recognition that more than one error can be made during a drug administration episode, which substantially increases the size of the denominator (Tissot et al., 1999).

Is it correct to assume that medication errors are more likely on ICU? Comparing these findings with those from the wards is perhaps more justifiable as the same data collection techniques were used. Unfortunately, such comparisons are unhelpful. Using Barker and colleagues' medication error frequency of 19% on the ward as a benchmark (Barker et al., 2002), medication error may be less likely (Tissot et al., 1999; Calabrese et al., 2001), about the same (Schneider et al., 1998) or more likely (van den Bemt et al., 2002) on ICU.

How common are ADEs in critical care?

Critically ill patients, with little physiological reserve, might be particularly at risk of injury from the powerful drugs given on ICU, so the proportion of medication errors that cause an ADE might be greater than 1% (Bates et al., 1995a).

Our early understanding of ADEs on ICU comes from studies using ‘stimulated self-reporting’ combined with chart review, a technique used in the ADE Prevention Study (Bates et al., 1995b). Ward nurses and pharmacists report incidents to a research nurse who visits the wards frequently and reviews all drug charts regularly. A panel of experts then determines the significance and severity of each detected ADE (Bates et al., 1995a). This technique is more sensitive than a traditional incident reporting system; detecting 54 ADEs during a study when only three incident reports were submitted (Cullen et al., 1995). A 6-month study conducted in two teaching hospitals found an ADE frequency of 6.1% and a potential ADE frequency of 4.8% (Bates et al., 1995b). The highest ADE rates were on the medical ICU with broadly similar results for surgical ICU, surgical and medical wards. Even after adjustment for the higher number of drugs prescribed on the medical ICU within the day before the ADE, patients there were at the greatest risk of an ADE.

The same investigators later published another paper based on the same data but using different primary outcome measures, the combined rate of preventable ADEs and potential ADEs (Cullen et al., 1997). As before, this was highest in the medical ICU, where patients received significantly more drugs. In this paper, rather than adjusting the ADE rate by the number of drugs ordered within the previous day *by the unit*, they adjusted by the number of drugs ordered within the previous day for *each patient*. Now, there was no difference between ICU and the wards. The authors did not mention this different approach to data analysis, but made two important points: whatever outcomes are measured or adjustments made, many ADEs occur on ICU, and that polypharmacy on the ICU should be addressed.

A study conducted on a paediatric unit using similar data collection methods yielded largely similar results (Holdsworth et al., 2003). Using the broader definition of an ADE that included errors of omission, ADE frequency was 6% and the potential ADE rate was 8%. Polypharmacy was again found to be the biggest risk factor. Nearly a quarter of ADEs were judged to be serious or life threatening but few actually caused any disability. Recent prospective studies have been more ambitious, in that they have aimed to detect the incidence *and* preventability of medication errors and potential or actual ADEs (Kopp et al., 2006; Buckley et al., 2007), or adverse events of all kinds (Rothschild et al., 2005b). They have detected similar incidences of ADEs and broadly similar causes.

Prescribing errors and anaesthetists

Incorrectly written prescriptions often cause medication errors. There are errors in 1 – 2% of written inpatient prescriptions (Folli et al., 1987; Blum et al., 1988; Lesar et al., 1990; Leape et al., 1991; Lesar et al., 1997a). Prescribing errors are the most common type of avoidable medication error and are most likely to cause an ADE (Bates et al., 1995b; Leape et al., 1995). Anaesthetists record rather than prescribe the drugs they administer in theatre, but do prescribe pre- and post-operatively, and in critical care. Ludbrook and colleagues used data from the first 2 000 incident reports recorded in the AIMS database to examine incidents occurring before induction of anaesthesia (Ludbrook et al., 1993a). Only 35 (2%) involved pre-operative events, only 2 of these appear to have been prescribing errors. There are no published data concerning post-operative prescription errors. In paediatric critical care, incident reporting systems have yielded prescription error rates of 3.1% (Raju et al., 1989) to 5.9% (Bordun and Butt, 1992), or 13.4 (Vincer et al., 1989) to 56.2 (Wilson et al., 1998a) per 1 000 patient days. Drug chart review of prescriptions written in a UK teaching hospital found an error rate of 1.5%, but the ICU was amongst the places where errors were most likely (Dean et al., 2002b). A prescription error rate of 15% was detected by a multi-centre study based on chart review of more than 21 000 prescriptions written on 24 critical care units in the UK over a four week period in 2003 (Ridley et al., 2004).

There were very substantial differences in error rates between different units (range 8.5 – 493 errors per 1 000 new prescriptions), explained by interobserver variation amongst the local volunteer doctors, nurses and pharmacists who collected the data, but it is not clear how this could account for an error rate of ten times that seen on the wards. The only observational study of prescription error on an adult ICU found an error rate of 4% (Pourrat et al., 2003).

Transcribing drug (Wagner and Hogan, 1996) or numerical (Black et al., 2004) data is prone to error: rewriting drug charts or transcribing prescriptions is associated with an error rate of 1%, a third of which are serious (Dean et al., 2002b). In critical care, anaesthetists often need to rewrite or transcribe many drugs on to new drug charts, or from ICU charts to ward charts. Whilst computerised note keeping and drug ordering systems reduce such errors (Bates et al., 1998), most anaesthetists still work with paper-based records. The frequency or consequences of anaesthetists' transcription errors is not known, but on paediatric ICUs transcription errors are the most common prescribing errors (Wilson et al., 1998a).

Quantifying the frequency of prescription errors, medication errors, and ADEs is dogged by problems with definitions, data collection methods and study populations, but all must be a problem in the areas in which anaesthetists work. Quantifying them is also difficult and time-consuming, but essential for the assessment of interventions. Meanwhile common sense dictates that anaesthetists should also be looking for solutions to these problems.

The causes of error: the person approach versus the system approach

Reason's 'Swiss cheese model', when the holes in a stack of imaginary slices happen to align so that one can see right through the pile, aptly describes the chain of error causation when a series of seemingly minor events combine by chance

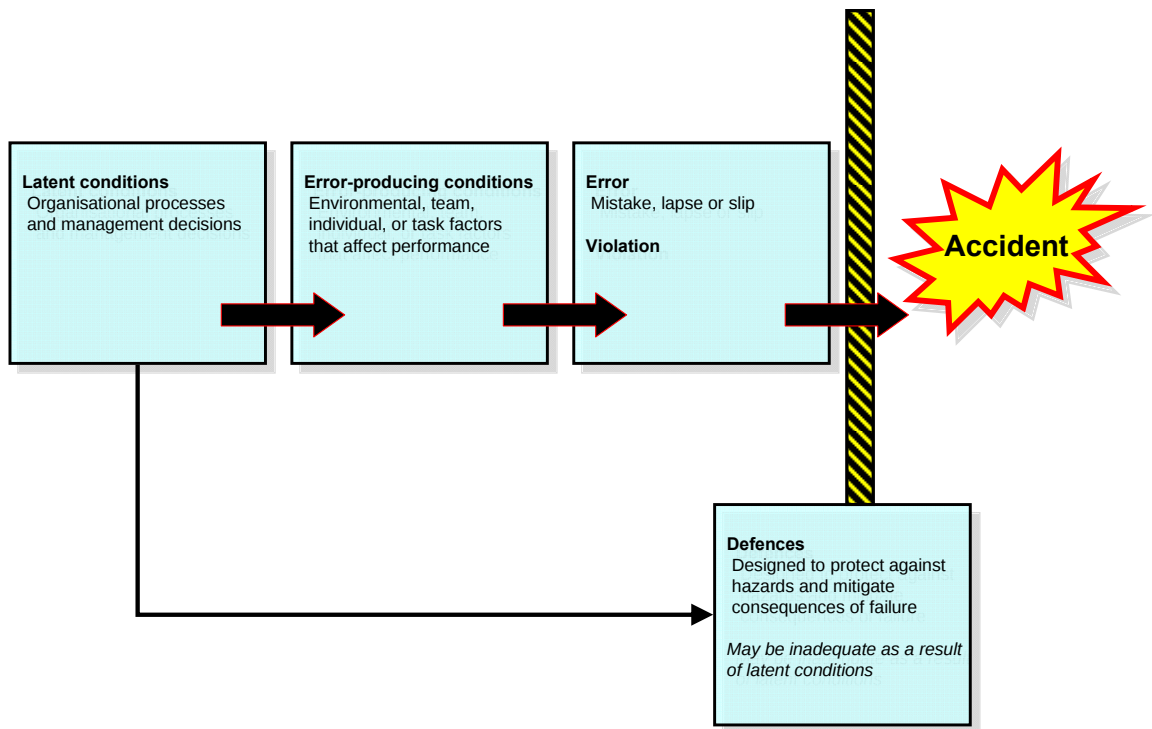


Figure 1: How a series of small problems may combine to cause a systems failure, also known as Reason's 'Swiss cheese' model (Reason, 2000).

and result in an accident (Reason, 2000). The prescriber, person giving the drug, lack of communication, environment, formulation and presentation of drugs, or patient may contribute towards a medication error despite seemingly adequate defences (figure 1).

After an error, it is easiest to blame an individual for their carelessness, inattention, recklessness or lack of education, which Reason describes as the 'person approach' (Reason, 2000). Cognitive psychologists believe that slips, lapses and mistakes are the price we pay for advanced higher cerebral function, and so are inevitable. The physicians and nurses at the end of the chain are only part of a systemic failure; what Reason describes as the 'system approach'.

Considering medication error, 'the system' is the means of ordering and prescribing drugs, their storage and presentation, layout of drug charts, management and bureaucratic issues, and equipment used, as well as the staff.

The system fails when several of these factors interact by chance to cause an error. For example, a fatality occurred when the flow rate of a patient's epidural pump was increased to 125 mL.hr⁻¹ by a ward nurse who wished to give an intravenous fluid bolus, despite the pump being correctly labelled and the patient receiving parenteral fluids via a gravity-fed drip set (Sayers, 2000). The person approach would be to blame the nurse. The system approach would highlight the fact that epidural pumps should have a maximum infusion rate of 20 mL.hr⁻¹, and that patients with epidural infusions should remain in high dependency areas where staff are more experienced.

A system failure that had profound implications for anaesthesia in the UK was the case of Woolley and Roe: two patients were left paraplegic after undergoing spinal anaesthesia at Chesterfield Royal Hospital in 1947 (Cope, 1954). At the time, their injuries were thought to be due to microscopic cracks in the local anaesthetic ampoules, through which phenol had seeped during the sterilisation process. In fact, it would appear that a batch of reusable spinal needles had not been removed from a bath of acidic descaler and boiled in distilled water before use because a member of staff was off sick (Maltby et al., 2000), a classic system failure. High profile cases of fatalities caused by accidental injection of intrathecal vincristine have resulted in blame, charges and convictions for the individuals involved rather than recognition that they result from system failures (Ferner, 2000; Ferner and McDowell, 2006).

What are the causes of medication error in anaesthesia and intensive care?

There is substantially less evidence about the causes of medication error than there is about its frequency, reflecting the difficulty of conducting quantitative research in this field. Currently, information about the likely causes must be pieced together from evidence about the causes of clinical error in general and ADEs, with far more information from critical care than anaesthesia.

Error traps

So what is it about the healthcare system that causes medication errors? There is much to be learnt from examining errors that occur and are reported again and again, described by Reason as ‘error traps’ (Reason, 1990). Examples include over-anticoagulation resulting in haemorrhage, the prescription of antibiotics despite the patient reporting an allergy, failure to prescribe prophylaxis against venous thromboembolism, and difficulties with opioids, theophyllines, antimicrobials, anticonvulsants, anticancer drugs and muscle relaxants (Bordun and Butt, 1992; Currie et al., 1993; Lesar et al., 1997a; Ross et al., 2000; Kanjanarat et al., 2003).

Analysis of a database of reported drug errors compiled by the US Pharmacopeial Convention revealed that the drugs most commonly involved in errors were heparin, adrenaline (epinephrine), potassium chloride and lidocaine (lignocaine), the latter being implicated in the most fatalities (Edgar et al., 1994). The accidental injection of intrathecal vincristine rather than methotrexate during chemotherapy for acute lymphoblastic leukaemia has devastating consequences and seems to occur with depressing regularity (Fernandez et al., 1998). These findings reflect that some drugs are intrinsically more harmful than others and that medication errors in their use are more likely to be detected and reported.

The epidural route of administration represents another error trap; most anaesthetic drugs and many others seem to have been inadvertently administered down an epidural catheter (Loderer and Suppan, 1979; Cay, 1984; Patel et al., 1984; Lejuste, 1985; Dror and Henriksen, 1987; Wells et al., 1987; Atanassoff and Alon, 1988; Nakazawa et al., 1988; Van Hemelrijck et al., 1989; Kopacz and Slover, 1990; Gentili and Samii, 1991; Fox et al., 1993; Tripathi et al., 1997; Whiteley and Laurito, 1997; Kasaba et al., 2000; Kostopanagiotou et al., 2000; Weigert and Lawton, 2000; Webster et al., 2001a; Hew et al., 2003; Olmez and Yalinkaya, 2004), and many destined for the epidural space seem to have been given intravenously (Ryan, 1973; Singh, 2004). Similarly drug infusions are an error trap on the ICU: problems drawing up infusions, administering drugs at the correct rate and delivering incompatible drugs via the same intravenous cannula

are the most common medication errors (Allen-Webb et al., 1994; Allen et al., 1995; Tissot et al., 1999; Ferner et al., 2001; Parshuram et al., 2003; Herout and Erstad, 2004).

Causes of prescribing error

A prospective analysis of prescribing error in a UK teaching hospital detected 88 potentially serious prescribing errors and interviewed 44 of the prescribers in order to establish the cause (Dean et al., 2002a). More than half (57%) were skill-based slips or lapses, 39% were rule-based mistakes and 4% were violations. None of the prescribers could explain why these arose; however, doctors often mentioned that they were busy, tired, had been interrupted, had poor knowledge of a particular drug, or were confused by looking after other teams' patients.

The role of the environment

Evidence from the nuclear and aviation industries shows that errors are more likely in busy, stressful environments (Chou et al., 1996; Park et al., 2004), but the situation in healthcare is not so clear-cut. Medication error rates appear to be higher during day shifts, when the majority of drug orders are made, rather than at night (Raju et al., 1989; Lesar et al., 1990). The balance of evidence implies that medication error is more common on the ICU (Tisdale, 1986; Bates et al., 1993; Bates et al., 1995b; Schneider et al., 1998; Tissot et al., 1999), and ICUs are certainly busy and stressful places to work (Oates and Oates, 1995; Coomber et al., 2002). However, the same investigators who measured broadly similar medication error rates on the ICU and the wards were unable to detect evidence of excess workload, fatigue or stress amongst the ICU staff (Cullen et al., 1997). The first observational study of medication errors in a European ICU attributed errors to lack of knowledge and communication, incomplete, illegible or verbal prescriptions, preparation errors, transcription errors, and problems with infusion pumps. The only environmental factors mentioned – excessive workload and lack of an effective incident reporting system – were amongst the least important causes (Tissot et al., 1999).

Transferring patients is associated with substantial morbidity and mortality (Kanter and Tompkins, 1989; Kanter et al., 1992; Barry and Ralston, 1994; Duke and Green, 2001). The AIMS-ICU study received 11 000 incident reports over 6 years but surprisingly only 176 concerned intra-hospital transfer (Beckmann et al., 2004). About 40% reported equipment problems and the rest concerned management issues, especially lack of communication between teams. One third of incidents resulted in a significant adverse outcome. Twenty (11%) incidents involved drugs and seven (4%) involved failure of infusion devices. Although there is no denominator data, this study shows that medication errors are an important cause of patient injury during transfers. Transcription errors and illegible discharge summaries and omissions can also lead to medication errors at the patient's destination, a problem well documented in patients transferred between acute and long-term care facilities (Boockvar et al., 2004) and on discharge from ICU (Pronovost et al., 2003).

The role of staff

An observational study, specifically designed to establish the cause of intravenous drug errors in two UK hospitals, found considerable cultural and management failings amongst staff (Taxis and Barber, 2003). More than half of drug administration episodes were associated with an error, and most of these were deliberate violations of the guidelines that boluses should be injected over 3 – 5 minutes. The nurses felt the guidelines were inappropriate as they added substantially to the length of the drug round. Problems also arose in the preparation and administration of unusual drugs or very small volumes, the causes being lack of experience or education and complex equipment. Nurses presented with new bar-code technology to reduce medication error have been shown to quickly employ workaround strategies when the technology is not tailored to their everyday practice or deployed inappropriately. For example, nurses working in long term care facilities were much less likely to scan a patient's identification wristbands before administering their drugs for the simple reason that they knew the patients well (Ghajar et al., 1995). These studies raise the interesting question of when is it appropriate to ignore guidelines and to whom they apply: in anaesthesia most intravenous boluses are given in less than 3 minutes.

Inexperience might be expected to contribute towards medication errors, but the published evidence concerns prescription error only. First year residents are five times more likely to make prescribing errors than those with more experience (Lesar et al., 1990), and more recent studies found that prescribing errors in cardiology double at the start of new rotations (Wilson et al., 1998a; LaPointe and Jollis, 2003). Inexperienced clinicians and unsupervised trainees are more likely to make clinical errors (Wu et al., 1991; Donchin et al., 1995). However, one study has shown that senior nurses are *more* likely to make dose calculation errors (Koren et al., 1983), and whilst other small studies have shown inadequate calculation skills amongst medical students and residents, there were no significant correlations with seniority (Rowe et al., 1998; Boreham et al., 2000; Scobie et al., 2003; Wheeler et al., 2004b). Conducting mathematical tests under examination conditions is open to criticism anyway, as on busy wards distractions and interruptions probably play an important role in the error causation. Any potential link between clinician experience and medication error remains to be studied.

Latent conditions that lead to medication errors

There are many hidden problems in the hospital that contribute to systems failure. Although the ADE Prevention Study Group found that prescription errors were most likely to cause an ADE, they also established other latent systems failures including failure to check drugs before administration, lack of communication, inadequate monitoring of treatment or side effects, and lack of standardisation of labels and protocols (Leape et al., 1995).

It is widely quoted that 80% of medication errors in hospitals are caused by human error, the remainder being due to equipment error (Reason, 1997; Dean et al., 2002a). In the West, anaesthetists are becoming increasingly reliant on sophisticated equipment, which has been implicated in 7 – 40% of incidents (Webb et al., 1993b; Frey et al., 2000; James, 2003). Recent reports from Pakistan and Zimbabwe, where equipment is less reliable, suggest that 50% of incidents are caused by equipment failure (Khan and Hoda, 2001; Madzimbamuto and Chiware, 2001). Equipment does not need to fail to cause an error. There are

many examples of errors occurring when staff are confronted with new, unfamiliar or non-standard equipment (Carlisle et al., 1996; Brown et al., 1997a; Brown et al., 1997b; Lin et al., 1998; Wilson et al., 1998b), so-called errors of transference (Reason, 1990). Much of the problem lies with ease of use of equipment, familiarity, experience, education and ergonomics rather than reliability. The consequences of equipment error in anaesthesia may be grave; there are several reports of fatal errors with opioid infusions (Carlisle et al., 1996; Vicente et al., 2003). The patient who succumbed in the scenario given as an example of systemic failure on page 32 (Sayers, 2000) would not have died if it had been impossible to turn up the rate of epidural infusion so high.

Patient factors in medication errors

The ADE Prevention Study Group examined the possibility of identifying inpatients at risk of an ADE on the basis of their demographic profile and clinical characteristics (Bates et al., 1999b). They recorded the details of a cohort of over 4 000 patients in a nested case-control study, but only found a few independent predictors of ADE with little predictive power. This was surprising, as previous studies had shown that age (Hanlon et al., 1997), polypharmacy (McMillan et al., 1986; Colley and Lucas, 1993) and impaired renal function (Cullen et al., 1997) predispose patients to ADEs. The authors argued that rather than identifying patients at high risk of ADE, efforts should be diverted towards improving safety for all patients.

What is being done about medication error?

In light of the increasing number of high profile criminal prosecutions of healthcare workers who have made medication errors, there is an increasing perception that ‘the system’ prefers the person approach. The UK Chief Medical Officer’s report ‘An organisation with a memory’ (Donaldson, 2002) called for changes to systems of work, singling out the problem of the accidental administration of intrathecal vincristine as an error that should be completely eliminated. Many processes and actions need to be considered afresh as if they

had just been invented. If petrol stations were a new idea, would untrained motorists be allowed to freely pump and potentially spill large quantities of flammable material in public areas? Similarly, if epidural catheters had just been invented, would they be designed with universal connectors allowing connection to intravenous giving sets (Laws, 2001; Cyna et al., 2002; Lanigan, 2002)? Thousands of tasks must be subjected to the same analysis, which will be expensive, time consuming and controversial. For example, equipment transference errors could be eliminated if an institution used one model of syringe driver. However, replacing equipment is expensive and different departments have different requirements. Features considered essential in theatre or ICU might not be needed on the wards and could even lead to more confusion. ‘Smart’ infusion technology is a recent innovation to reduce programming errors and allocate minimum and maximum doses for continuous and bolus infusions in an institution (Wilson and Sullivan, 2004), but may sacrifice flexibility. Perhaps manufacturers should consider developing an infusion device that can automatically recognise both drug and patient?

Technology and defence against error

Technology can substantially improve patient safety, but as it is only as effective as its designers and programmers it is essential that clinicians, especially anaesthetists, are involved in development. In New Zealand, Merry’s group is developing novel, technological solutions to the problem of medication error in anaesthesia. They have developed a computerised bar-code system to cross check all drug administrations and automatically generate an anaesthetic record (Merry et al., 2001b). Using bar-codes to record the drugs given during an anaesthetic is not a new idea (Block et al., 1985), but Merry’s group have exploited the increased processing power of modern computers to integrate many initiatives into a multi-layered system of defence against error. All drugs are given a label, and scanned by the bar-code reader before administration. The computer displays and announces the name of the drug and identifies a default dose, which may be altered if necessary. Evaluations in pilot studies (Merry et al., 2000), a simulator (Merry et al., 2002) and a randomised clinical evaluation (Webster et al., 2004)

have shown that the system appears to improve safety, is acceptable to clinicians, and reduces drug preparation time. Although it adds to the cost of an anaesthetic, the authors argue that this should be offset by potential reductions in costly iatrogenic harm.

Prescribing using computers, computerised physician order entry (CPOE), is often said to substantially improve patient safety. Bates and colleagues used complicated outcome measures when assessing it as an intervention, but found that non-intercepted, serious medication errors decreased by more than half, non-missed dose medication errors by 81% and non-intercepted potential ADEs declined by 84% (Bates et al., 1998; Bates et al., 1999a). When linked to electronic laboratory and patient records, these systems can assist physicians by reminding prescribers to order monitoring tests for new treatments, so called computerised decision physician support (Bates, 2000), for example alerting the prescriber to hypokalaemia in a patient on digoxin (Overhage et al., 1997; Raschke et al., 1998; Anton et al., 2004). A program designed to improve antibiotic prescribing significantly reduced prescriptions for drugs to which the patients had reported allergies, the magnitude of dose errors and the mean number of days of excessive drug dosage. There were also significant savings to the drug budget and reductions in the length of hospital stay (Evans et al., 1998).

CPOE may prevent problems with illegibility, verbal orders and dose errors (Koren and Haslam, 1994; Winslow et al., 1997; Meyer, 2000; Bizovi et al., 2002; Gupta et al., 2003; Tissot et al., 2003) but it cannot address knowledge-based prescribing errors, many errors of omission, the problem of prescribing the wrong drug due to look-alike and sound-alike drug names (Lambert, 1997; Hoffman and Proulx, 2003), drug administration errors, or the problem of prescribing drugs to the wrong patient (Koppel et al., 2005). Some studies have shown that whilst medication errors fall after CPOE is introduced, ADE rates remain static (King et al., 2003; Potts et al., 2004). One study even showed that mortality increased on a paediatric ICU after its introduction (Han et al., 2005). There are dissenting voices that believe that CPOE may prejudice patient safety if the system is not carefully tailored to an institution and staff are not given proper training (Berger and Kichak, 2004), and that the expense is unjustified (Doolan and Bates, 2002).

Computers have revolutionised the collection, collation, storage, transfer and analysis of incident data (Webb et al., 1993a). The means now exist for some anaesthetists to submit critical incident reports to their institution using their personal digital assistants (Bent et al., 2002). It is hoped that ease of access to databases and better feedback will improve future incident reporting. Web-based incident reporting now allows national and international collaboration, for example between Australian and American ICUs (Wu et al., 2002). In the US, MEDMARX has been operational since the late 1990s (Cousins, 1998) and has reported widely, most recently focusing on peri-operative drug administration error (Hicks et al., 2006).

Causing the next error by trying to prevent the last one

The use of technology to solve one problem can replace it with another, unforeseen one. The increasing sophistication of electronic equipment and information technology means that the expertise required to design the hardware or writing the software is frequently beyond that of the final user. Many features add complexity and can themselves fail. Reason describes this concept as 'Dangerous Defence' and gives an example to illustrate this point (Reason, 1997). In the 1950s several aircraft crashed shortly after taking off from slushy runways as they failed to gain height quickly enough. A new flight deck instrument was introduced to ensure an adequate climb angle. The pilot had to match a cursor indicating the aircraft's angle of climb with a cross. Shortly afterwards an aircraft stalled after adopting an unusually steep angle of climb at takeoff and crashed. Accident investigators found that the new monitor had malfunctioned and displayed that the angle of climb was too shallow. Despite the fact that all their other instruments were functioning correctly, the pilots obeyed the faulty monitor with disastrous consequences. New technology can completely capture the attention, termed 'fascination', and attempts to distance operators from direct control and can create unforeseen types of human error.

Keeping it simple – removing complexity

Strategies that reduce complexity are most likely to improve safety. As well as developing technological approaches, Merry's group has produced evidence-based guidelines that aim to reduce medication error in anaesthesia (Jensen et al., 2004). When reviewing the literature for evidence, they mainly found case reports and short case series, i.e. the lowest level in the hierarchy of evidence-based medicine. They argue that the lack of randomised or controlled trials in this field does not preclude an evidence-based approach to the problem, as long as 'the best external evidence with which to answer clinical questions [is sought]' (Sackett et al., 1996). They ranked the evidence using a points system, allowing them to validate their recommendations. They recommended that a drug's label should always be read carefully, the legibility and contents of ampoule and syringe labels should be optimised to agreed standards, syringes should nearly always be labelled, pre-filled syringes should be used whenever possible, and labels should be checked with another person or device before drugs are given (Jensen et al., 2004). These recommendations concur with those of others (Currie et al., 1993; Orser and Oxorn, 1994; Orser, 2000b), but are the first to be evidence-based and crosschecked against actual incident data.

There are numerous examples of simple but effective improvements to drug charts and paperwork that reduce medication error. In one hospital, pharmacists exhorted prescribers to write legibly and not use felt-tipped pens (which make carbonless copies difficult to read), after which illegible prescriptions fell from 10% to 1% (Meyer, 2000). Simple changes to ICU drug charts have also significantly reduced errors with antibiotic prescriptions (Wasserfallen et al., 2004).

Most studies into medication error conclude that education must be improved, but there are few interventional studies looking at the impact of better drug education. Nelson and colleagues devised a written, eight-question test of residents' understanding of prescribing and dose calculation, and discussed the correct answers after the test. Six weeks later, the doctors performed significantly better in a repeat test, and better than a control group (Nelson et al., 2000). Medical

students also struggle with dose calculations (Boreham et al., 2000), and also benefit from practical training sessions in drug administration (Scobie et al., 2003). High fidelity patient simulators offer excellent opportunities to evaluate educational interventions in the future (Schwid and O'Donnell, 1992; Garden et al., 2002).

Improving staffing has also been suggested as a way of reducing errors. The high medication error rates recorded in the first observational study of medication error on a paediatric ICU was used to justify the establishment of a 24 hour paediatric critical care satellite pharmacy with unit dose drug distribution to reduce the incidence of errors (Tisdale, 1986). Another observational study found that medication errors were more frequent on an ICU that did not have full time physician cover (van den Bemt et al., 2002). Since, there have been many examples of studies that have shown the benefit of involving pharmacists in medical, surgical or critical care teams, using outcome measures as diverse as medication error rates (Folli et al., 1987), ADE rates (Leape et al., 1999), drug budgets (Bjornson et al., 1993; Montazeri and Cook, 1994; Baldinger et al., 1997; Boyko et al., 1997; Devlin et al., 1997; Krupicka et al., 2002), length of hospital stay (Bjornson et al., 1993; Boyko et al., 1997), and mortality (Bond et al., 1999). However, one study showed that greater involvement of pharmacists on the ICU did not confer any additional benefit over and above introducing CPOE (Bates et al., 1998).

Conclusion

The contribution of the practice of anaesthesia and critical care medicine to the global problem of medication error is far from clear and very difficult to study. Efforts to do so have tended to rely on incident reporting, the only practical approach when funding is limited, and the safety of routine anaesthesia. The heterogeneity of critically ill patients as a group means that huge study populations would be required if other research techniques were to be used. In the meantime, efforts have begun to reduce medication error without waiting for the problem to be quantified. In the era of evidence-based medicine, anaesthetists are

looking for evidence-based solutions to problems that we may have to accept we cannot quantify for good practical reasons. In the global context of medication error, investment should be made in reliable audit, detection and reporting systems. The growing recognition that medication errors usually result from a failure of a system rather than an individual should be fostered to allow more lessons to be learnt, an approach that has been successful in other, safety-critical industries. New technology has a great deal to offer and investment is warranted in novel fail-safe drug administration systems, yet the importance of simple and sensible changes and better education should be remembered.

CHAPTER 2

INTRODUCTION 2: DRUG LABEL DESIGN AND PATIENT SAFETY

Drug labelling as a latent cause of medication error

The systems failures that underlie errors causing ADEs and potential ADEs were first analysed by the ADE Prevention Group in 1995, who performed a systems analysis of events from a prospective cohort study in two US tertiary care hospitals over 6 months (Leape et al., 1995). During the study period, 334 errors were detected as the causes of 264 preventable ADEs and potential ADEs. The most common systems failure was in the dissemination of drug knowledge, particularly to doctors, accounting for 29% of the 334 errors. Inadequate availability of patient information, such as the results of laboratory tests, was associated with 18% of errors. Seven systems failures accounted for 78% of the errors; all could have been improved by better information systems. Drug labels were not identified as an important factor in this study, but more recent research strongly implicates packaging and label design as causative factors of medication error.

In an editorial on medication error published in 2004, Berman suggested that up to one third of all medication errors might be attributable to packaging and/or labelling confusion (Berman, 2004), an opinion backed up by data from error reporting systems. Confusing, inaccurate or incomplete labels and packaging were found to contribute to 21% of the 1 143 actual or potential drug errors reported the US Pharmacopeia Practitioners' Reporting Network (USP PRN) in one calendar year in 1999 (Orser, 2000a). A later survey of the medication errors experienced by Canadian anaesthetists found that "syringe swaps" (70.4%) and the misidentification of the label (46.8%) were the most common contributing factors. The majority of anaesthetists reported that they read the ampoule label "most of the time" but used the colour of the label or box as a secondary cue (Orser et al., 2001). In this survey, 84% agreed that improved standards for drug

labels would reduce the incidence of error. There are many other examples of confusion over packaging or labelling causing dispensing (Peterson et al., 1999) or drug administration errors (Malhotra et al., 2001; Mohan et al., 2001; Guchelaar et al., 2004).

It is generally agreed that legibility and contents of ampoule and syringe labels should be optimised to established standards (Currie et al., 1993; Orser and Oxorn, 1994; Orser, 2000b; Jensen et al., 2004). However, some argue that ampoules should be similar to ensure that the labels are read, pointing out that the range of injectable drug preparations far outnumbers the possible combinations of usable colours and shapes (Wildsmith, 2002). To date the research that has examined the effects of package design characteristics on drug handling has been sparse and piecemeal, often focusing on single drugs and subjective methods of effectiveness. In other areas, such as food, pesticide and warning labelling, research is better developed and clear links have been established between the design features of labels and packaging and human behaviour (Wogalter et al., 1999; Edworthy et al., 2004). Colour, shape, font size and the use of signal words such as 'warning' or 'danger' seem to have the most consistent effects (Hellier et al., 2006). Label colour has proved to be a controversial topic in the UK, as anaesthetic syringe labels were changed to concur with the standardised code used in the US, Australia and New Zealand in 2004, and evidence suggests that the process of moving between systems poses risks in itself (Haslam et al., 2006).

Wording of labels

There have been a few studies from a variety of fields that have considered how label wording influences various outcome measures. On alcohol warning labels, the statement 'If you drink when you are pregnant, your child may be born with Foetal Alcohol Syndrome and require institutionalisation' was, perhaps unsurprisingly, found to convey risk better than 'Mixing alcohol and medicines can be life-threatening' (Laughery et al., 1993), but explicit warnings appear to improve both believability and compliance (Frantz and Rhoades, 1993; Heaps and Henley, 1999). In medicine, most of the research on wording has been performed

in the context of patient information leaflets, especially in the area of patients' understanding of absolute *versus* relative risks of side effects (Berry et al., 2002a; Berry et al., 2002b; Berry et al., 2003; Berry et al., 2004; Knapp et al., 2004; Berry et al., 2006).

The influence of medication dosage forms

However the information concerning the identity of a drug is presented, labels are open to misinterpretation by pharmacists, nurses and doctors. One drug may be presented in several different forms, for example a 'delayed' or 'sustained' release preparation, an enteric coated preparation or solutions for administration *via* different parenteral routes, all aiming to facilitate final dose preparation processes or preparation for children and ultimately improve patient convenience. However, such a wide variety of dosage forms increases the risk of prescription error. Prescribing errors involving medication dosage forms has repeatedly been found to account for more than 10% of all errors in a long-running error detection programme conducted in New York (Lesar et al., 1990; Lesar et al., 1997a; Lesar et al., 1997b; Lesar, 1998; Purdy et al., 2000). These investigators and others have identified substantial deficiency in the understanding of dosage formulation issues (Cohen and Davis, 1992; Grunewald and Mack, 2001).

Misinterpretation of labels can also lead to tenfold dosing errors, when an order-of-magnitude error results from a dose miscalculation. When converting micrograms to milligrams, hundred- or even thousand-fold errors are also possible. Although it is unlikely that a healthcare professional would open 100 or more ampoules of a drug solution to administer to an adult; just because a scenario is unlikely does not mean that it will never occur. Children are still at risk because the required volume of stock solution is generally small, so even a tenfold higher volume may appear deceptively normal (figure 2). Nearly one third of intravenous drug prescriptions on neonatal units are for doses less than one tenth of a single drug ampoule (Chappell and Newman, 2004).

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Baby died after 'decimal' error

A mistake over a decimal point caused the death of a Derby baby who was given 10 times the recommended amount of heart medication, a coroner has ruled.

Two nurses gave the wrong dosage to 15-day-old baby George Bartram when trying to reduce his rapid heartbeat.

The massive influx of the drugs caused him to have a cardiac arrest.

Coroner Martin Symington ruled the two nurses were not guilty of neglect, but said a verdict of accidental death would not tell the full story.

Breathing problems

"The mistake made by the nurses was a mathematical miscalculation which in other working environments might not have been quite so catastrophic," the coroner said in recording a narrative verdict.

"They made a mistake and they accept that, but it was a mistake any of us could have made."

The baby, who was born with a congenital heart defect, was taken to Leicester's Glenfield Hospital less than two weeks after his birth in March 2002 after experiencing breathing problems.

He died a few days later after being given the drug Digoxin, which slows the rate of heartbeat.

One of the doses was calculated at 220 micrograms when the correct amount should have been 22 micrograms.

Yvonne Jordan and Angela Fitzsimmons told the hearing they checked and double-checked the drug levels before administering the injection to baby George.

Staff levels

Blaming pressure and time on the ward, Ms Fitzsimmons said: "Because we had calculated it both separately and together and checked it to make sure it was accurate to the book, we believed that we were giving the right dose."

"If we had any doubt whatsoever we would not have given the dose."

Following the hearing, George's parents issued a statement which said the couple hoped that lessons had been learned following the tragedy.

The University Hospitals of Leicester NHS Trust said new measures, including new labelling for drug vials, had been put in place for medical staff.

Consultants now have to agree to prescriptions and the drug amount double-checked by pharmacists.

Staff levels have also been reviewed on the ward where George died.

Baby George died at Glenfield Hospital in Leicester

BBC Leicester

Information and features on the BBC website for Leicester

BBC Derby

Sport, travel, leisure and more from the BBC website for Derby

FROM OTHER NEWS SITES:

Derby Evening Telegraph 'Maths error led to death of baby' - 9 hrs ago

Leicester Mercury Mistake that gave baby a fatal drug overdose - 32 hrs ago

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Figure 2: Reproduced web page from BBC Leicestershire News reporting the death of a 15 day old baby as a result of a tenfold dose error with digoxin (Anon, 2005).

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There are many case reports of tenfold dose errors in the literature (Matzkin and Nili, 1984; Koren et al., 1986; Rieder et al., 1988; Patermann et al., 2004), but the problem has been studied more systematically. The extent of tenfold medication errors was examined in three Canadian tertiary children's hospitals using three detection methods. Analysis of the data from the local incident reporting systems found the incidence to be 1 in 22 500 doses prescribed. However, an audit of 1 500 prescription charts in the emergency departments revealed two tenfold errors in 1 678 drug orders. Finally, a prospective study of medication error occurring during mock resuscitation scenarios identified four tenfold errors in eight mock resuscitations that included 125 orders for drugs (Kozar et al., 2006). Retrospective review of incident reporting data from a UK children's hospital found 15 tenfold errors in five years (Ross et al., 2000). The implications that the rate of tenfold error may be especially high in resuscitation situations and is underestimated by spontaneous reporting are particularly worrying.

An evaluation of 200 consecutively detected prescriptions with tenfold dose errors in a different teaching hospital found that overdoses were prescribed in 61% of the cases and inadequate doses in 39% of the cases. Nearly half of the errors (45%) were rated as potentially serious or severe, but only one-fifth occurred in children. The main factors associated with errors were multiple zeroes in the dose (45%), use of equations or calculations to determine the correct dose (27% of total cases but 92.3% of paediatric cases), a dose amount less than 1 (25%), and when conversion between different units was required (23%). The tenfold errors were produced by a misplaced decimal point in 87 cases (43.5%), adding an extra zero in 63 cases (31.5%), and omitting a zero in 50 cases (25%) (Lesar, 2002).

It is not clear from these studies whether the label, the nurse or doctor administering the drug is at fault, or a combination of all three. What is certain is that doctors and nurses have great difficulty calculating drug doses, presumably because of a lack of understanding or slips and lapses in arithmetic. In a written examination of 21 paediatric residents in Miami Children's Hospital, only 70% of calculations were made correctly, even though electronic calculators were permitted (Glover and Sussman, 2002). Notably, seven residents committed tenfold dosing errors, and one resident committed a 1 000-fold dosing error, in

accord with a similar study carried out 4 years earlier (Rowe et al., 1998). Although more experienced paediatricians were no better at the calculations, general practice trainees asked to undertake a similar study performed even worse than paediatricians, implying that exposure to the specialty plays a role (Potts and Phelan, 1996). All indications are that nurses are no better than doctors in this regard (Koren et al., 1983; Adams and Duffield, 1991; Calliari, 1995; Schneider et al., 1998).

Expression of the concentration of drug solutions

Analysis of a database of reported drug errors compiled by the United States Pharmacopeial Convention and the Institute for Safe Medication Practices revealed that the drugs most commonly involved in errors were heparin, lidocaine, adrenaline, and potassium chloride; lidocaine was implicated in the largest number of fatalities (Edgar et al., 1994). It may be no coincidence that these drugs are all presented in solution.

When a drug in solution is administered, the correct volume must be calculated. The steps in this calculation require an understanding of the many different ways that the concentration of a drug in solution may be expressed. Some of these are potentially confusing. For instance, the concentration of bleomycin, a chemotherapeutic agent, has been expressed in milligrams (by potency), milligrams (by weight), International Units or United States Pharmacopeia Units. The potential for dose error resulting from this variety of expressions of drug concentration has already been highlighted (Stefanou and Siderov, 2001).

The concentration of drugs in solution may also be expressed as mass per unit volume (e.g. milligrams or millimols per millilitre), ratios (e.g. 1 in 1 000), or percentages. As the metric system is based on thousands whilst percentages are based on hundreds, even these simpler means of expressing drug concentration can cause confusion. Calculating the safe volume of drug mixtures is even more difficult, for example the mixture of 1% lidocaine and 1 in 200 000 adrenaline used in infiltration anaesthesia (Lawrence, 1996).

In 1995 Rolfe and Harper showed that there is substantial confusion about the different means by which the concentrations of drugs in solution are expressed (Rolfe and Harper, 1995). They conducted a survey of 150 doctors in a UK university teaching hospital, and demonstrated that barely half could correctly identify the mass of drug in a solution when its concentration was expressed as a ratio. There were also problems with percentages: less than half could convert the concentration of lidocaine from a percentage to mass concentration, and only one-third knew how many millimols of sodium bicarbonate are in 100 mL of an 8.4% solution. Less than a third could work out the mass of adrenaline in 10 mL of a mixture of 0.25% bupivacaine with 1:200 000 adrenaline. Anaesthetists performed substantially better than physicians and surgeons. The authors recommended that the expression of drug concentration should be standardized to mass concentration for all solutions (e.g. milligrams per millilitre). It seems a compelling argument as it involves little or no cost and should only reduce the likelihood of dosing errors.

Rolfe and Harper's message was not new: two studies in the 1980s had highlighted problems with drug solutions presented as percentages. In 1983, Kelly and Henderson quizzed trainees from acute specialties about use of local anaesthetics in their clinical practice (Kelly and Henderson, 1983). Lidocaine was the drug of choice, with 70% using it in the previous month. However, more than 70% did not know how to calculate the maximal safe volume, or the maximal recommended dose.

In 1989 Scrimshire, a senior house officer in anaesthetics, performed a survey of her colleagues' understanding of local anaesthetic concentrations (Scrimshire, 1989). Less than half knew that a 1% solution contains 10 milligrams in 1 millilitre, and in a brief written scenario would have given an unacceptably large dose of 2% lidocaine to a patient with a laceration requiring suturing.

Each of these publications concluded with recommendations that expressions of drug strength such as ratios and percentages were outmoded and confusing, and that the strength of drug solutions should be expressed as mass concentration only.

The correspondence generated by Rolfe and Harper's study debated whether it was desirable, sensible or possible to make these changes. Some argued that not all drugs were suited to having their concentration expressed as mass concentration, for example vaccines (Nunn, 1995). This correspondent, a senior executive in the medicines sourcing department of the National Health Service (NHS) Executive who had also previously called for a universal labelling standard of mass concentration (Nunn, 1992), then reported that wider discussion of the proposed changes had identified potential hazards, although these were not specified (Nunn, 1995). Another correspondent highlighted the importance of education and experience, suggesting that students should be drilled rigorously in calculating doses of important emergency drugs (Baldwin, 1995).

Despite these calls, and those made by me and my research associate in an editorial in 2004 (Wheeler and Wheeler, 2004c), many drug solutions are still presented with their concentrations expressed as ratios and percentages alongside mass concentration. It is alarming that these drugs tend to be powerful sympathomimetic inotropes and local anaesthetics respectively, and as such are some of the most potentially toxic drugs in the formulary and are frequently administered in emergencies. Concern that this ampoule labelling policy might still be causing drug administration errors and harming patients informed the generation of the hypotheses examined by the experimental work in this thesis.

Hypotheses

1. Expressing the concentration of drug solutions as ratios or percentages is confusing, leads to dose calculation errors and may result in patient harm.
2. Removing these outmoded means of expressing drug concentration from ampoules is likely to improve patient outcome.

CHAPTER 3

PILOT: MEDICAL STUDENTS' UNDERSTANDING OF RATIOS AND PERCENTAGES

Medical students' numeracy skills

Medical students' numeracy and arithmetical skills have often been shown to be deficient, a matter of concern for those teaching critical appraisal skills. One study of 62 first year medical students' ability to interpret risk-reduction information asked three straightforward questions:

- How many times would heads be expected in 1 000 coin tosses?
- What is 1% of 1 000?
- What is 1 in 1 000 expressed as a percentage?

The answers are 500, 10 and 0.1% respectively. The investigators found that 77% of students answered all three questions correctly, 18% answered two correctly, and 5% answered one or none correctly (Sheridan and Pignone, 2002).

These deficiencies are not peculiar to medical students. As well as nurses and doctors, as previously described, well educated members of other professions struggle to differentiate and perform simple mathematical operations when using percentages and proportions, converting percentages to proportions, converting proportions to percentages, and converting probabilities to proportions (Lipkus et al., 2001).

A general lack of understanding about numbers needed to treat and relative risk reduction may make medical evidence difficult to interpret, however it may also contribute to dose calculation error when ratios and percentages are involved. Therefore, a pilot study was planned to examine these issues in medical students at the University of Cambridge.

A web-based questionnaire

One difficulty of conducting such a project is gathering a large number of students together, when in the clinical course they are split by year group and dispersed widely across the region (and even the globe during the elective) undertaking attachments in different specialties and hospitals. To address this problem the questionnaire was administered on the Internet by means of the University of Cambridge School of Medicine Educational Resources Web (ERWeb). This resource is a secure, web-based, virtual learning and communication environment created in 1998 to distribute teaching material, provide learning resources and improve the efficiency of administering many cohorts of students attending attachments in numerous locations (Wheeler et al., 2003). It provides audiovisual material on practical procedures, the means to perform end of attachment assessments, a program to detect collusion in such assessments (Ercole et al., 2002), and a streamlined and efficient way of submitting student appraisals. Its contact system, with student photographs, is used extensively for communication between staff and students. Each student logs in with their unique username and password, allowing their activity within the ERWeb environment to be recorded in a database. This includes information such as the time of access to a resource, the computer used and any data entered by the student in response to questions.

Study design and methods

The medicine course at the University of Cambridge follows a traditional format. Undergraduate medical students study pre-clinical medicine for 3 years, learning basic sciences such as anatomy, physiology and pharmacology with very little clinical teaching – although this is beginning to change. After 3 years the students gain a bachelors degree and reapply to clinical school; about 75% remain in Cambridge studying at Addenbrooke's Hospital and the surrounding district general hospitals. The clinical course spans 2½ years culminating in the Final MB examination. Clinical pharmacology teaching spans all clinical years;

Q1.

The first picture shows a vial of epinephrine (adrenaline).
It contains 1ml of 1 in 1000 epinephrine.
How much epinephrine is there in the vial?

- A. 10 micrograms
- B. 100 micrograms
- C. 10 milligrams
- D. 1 milligram**
- E. 1000 milligrams



Q2.

The second picture shows a vial of lidocaine (lignocaine).
It contains 10ml of 1% w/v lidocaine.
How much lidocaine is there in the vial?

- A. 0.1 milligrams
- B. 1 milligram
- C. 10 milligrams
- D. 100 milligrams**
- E. 1000 milligrams



Q3.

What is the toxic dose of lidocaine (lignocaine)?

- A. 1 mg.kg⁻¹
- B. 2 mg.kg⁻¹
- C. 3 mg.kg⁻¹**
- D. 8 mg.kg⁻¹
- E. 16 mg.kg⁻¹

Figure 3: The questions asked to clinical medical students in the online multiple choice questionnaire. Correct answers in bold. Reprinted from *Drug Safety* (Wheeler et al., 2004b).

anaesthesia teaching is confined to the final year. The ERWeb was used to invite clinical students from all year groups to attempt the online questionnaire. As an incentive to take part, those responding were entered into a prize draw. Those choosing to participate were directed to a web page and were asked to answer three multiple-choice questions under timed conditions (figure 3). The questions were devised to test knowledge of drugs used in many specialties that should be familiar to all students. Students were thought to be more likely to complete the survey if it was brief (Adams and Gale, 1982). Although answers were submitted anonymously, students collaborating could be detected and excluded by software which analyses the timing of each student's answers and the Internet Protocol (IP) address of their computer to identify students sitting together in information

technology facilities (Ercole et al., 2002). The examination structure could not eliminate the use of calculators or formularies. Time taken to answer each question and seniority of the student (first, second or final / third clinical year) were also recorded. The survey was conducted for three weeks in November 2002, just before the third year students' Final MB examination. The correct answers were e-mailed to all participants a week later.

Statistical analysis

Data were entered into spreadsheets on a personal computer and transferred into the Statview (SAS Institute, 1998) statistical programme for further analysis. Each dataset was tested for normality by comparing it using the Kolmogorov Smirnov test to a dataset generated using the random number generator function within Statview. None of the datasets in this study proved to be normally distributed. To assist statistical analysis, the probability that each student would correctly answer each question was calculated, which is also expressed as the proportion of students answering correctly in the Results section. Paired means comparisons were performed using the t test to examine whether there were statistically significant differences in the probability of a correct answer to each question. These datasets were subject to further analysis with factorial ANOVA testing to examine the influence of student seniority by including nominal year group data. The F statistic and p value are quoted in the text and figure legends, and error bars shown in graphs represent 95% confidence intervals. One sample t test analysis was also employed to compare the proportion answering each question correctly with the expected 20% that would have been correct by guessing.

Time data were not transformed. They too were not normally distributed and were subject to non-parametric testing using the Kruskal-Wallis test. The H statistic and p value are quoted in the figures and text. These data are presented either in bar charts with error bars representing 95% confidence intervals, or in box and whisker plots that show the median, interquartile range (IQR) and 10th – 90th centiles. Where appropriate, further comparisons between groups were made using the Mann-Whitney U test. Tied z and p values are shown unless otherwise

stated. For all analyses, p values < 0.05 were considered to be statistically significant.

Results

Of the 350 medical students enrolled in the Clinical School, 168 took part in the survey, a response rate of 48%. No students were found to have collaborated or were excluded, but some students did not answer every question. The response rate of first and second year students was 46.3%, and 48.9% respectively, and although only 33.3% of final year students took part (figure 4) these differences were not significantly different ($p = 0.079$). Students' scores in the online questionnaire are summarised in Table 3.

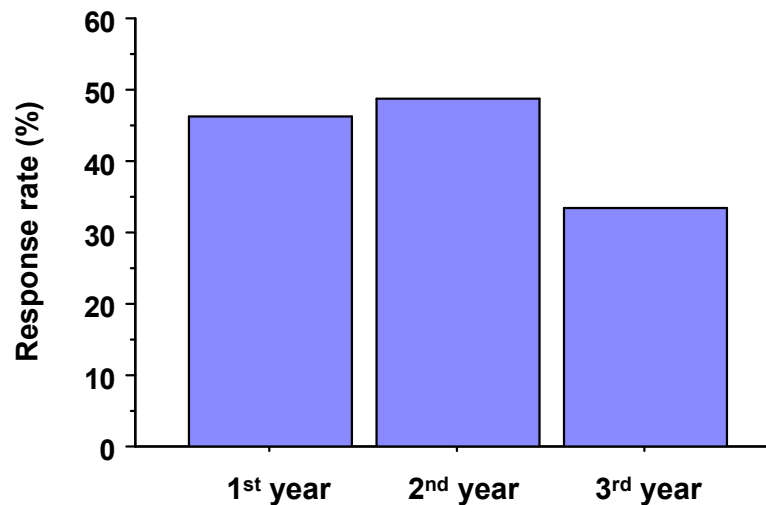


Figure 4: The proportion of students taking part in the online questionnaire plotted against their year group. No significant difference in response rate is evident ($H = 5.1$, $p = 0.079$).

Analysis of results by student seniority

The mean score for all students was 1.24 out of three. Out of 168 participants, 45 students (27%) got all three questions wrong, whilst only 17 (10%) answered all

three correctly. The mean score of each year group improved significantly with the seniority of the students: for first years the mean score was 1.00, for second years it was 1.27, and third years 1.56 (figure 5, $p = 0.016$). The mean time taken to answer – whether correctly or incorrectly – was 239 s, and did not differ significantly between year groups ($p = 0.949$, figure 6).

		No. years of clinical training			Total
		1	2	3	All years
Question 1	No. answering correctly	29	37	35	101
	No. attempting question	58	61	43	162
	% answering correctly	50.0%	60.7%	81.4%	62.3%
Question 2	No. answering correctly	14	23	22	59
	No. attempting question	57	58	42	157
	% answering correctly	24.6%	39.7%	52.4%	37.6%
Question 3	No. answering correctly	19	17	10	46
	No. attempting question	57	56	39	152
	% answering correctly	33.3%	30.4%	25.6%	30.3%

Table 3: The results obtained by medical students who completed the online multiple-choice questionnaire.

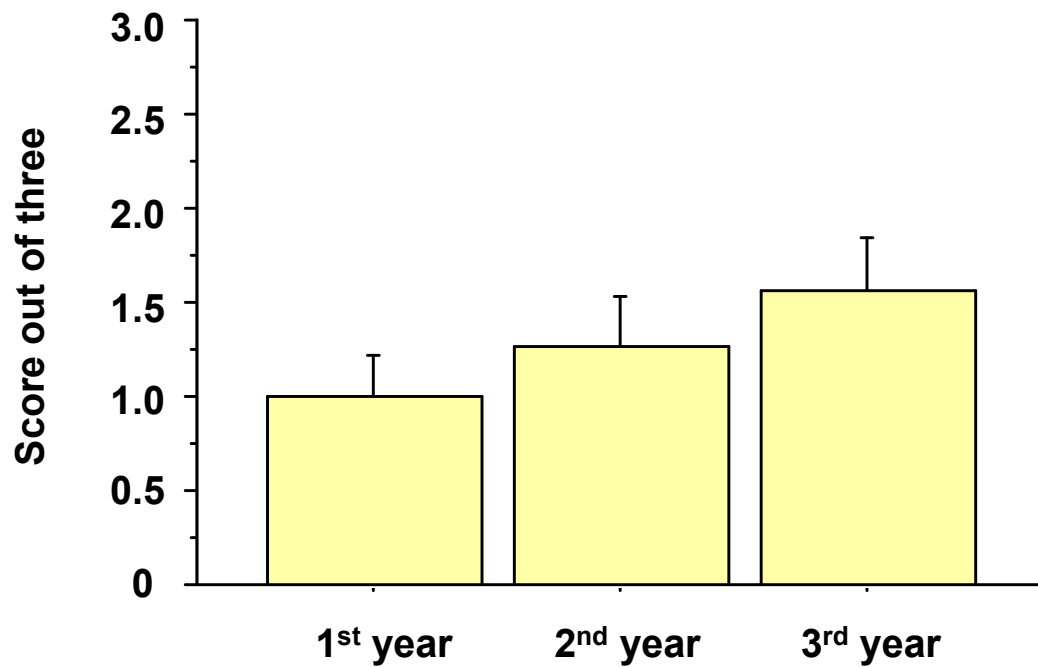


Figure 5: Mean student score out of three in the entire questionnaire for students plotted against their seniority, represented by year group. The improvement seen with student seniority is significant ($H = 8.3$, $p = 0.016$). Error bars represent 95% confidence intervals.

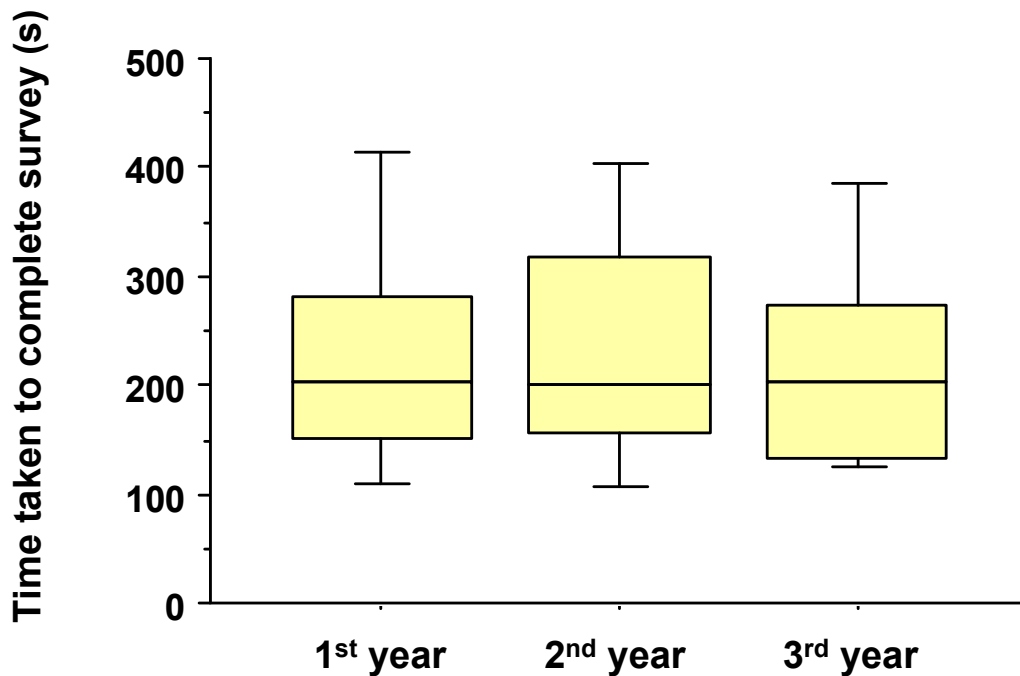
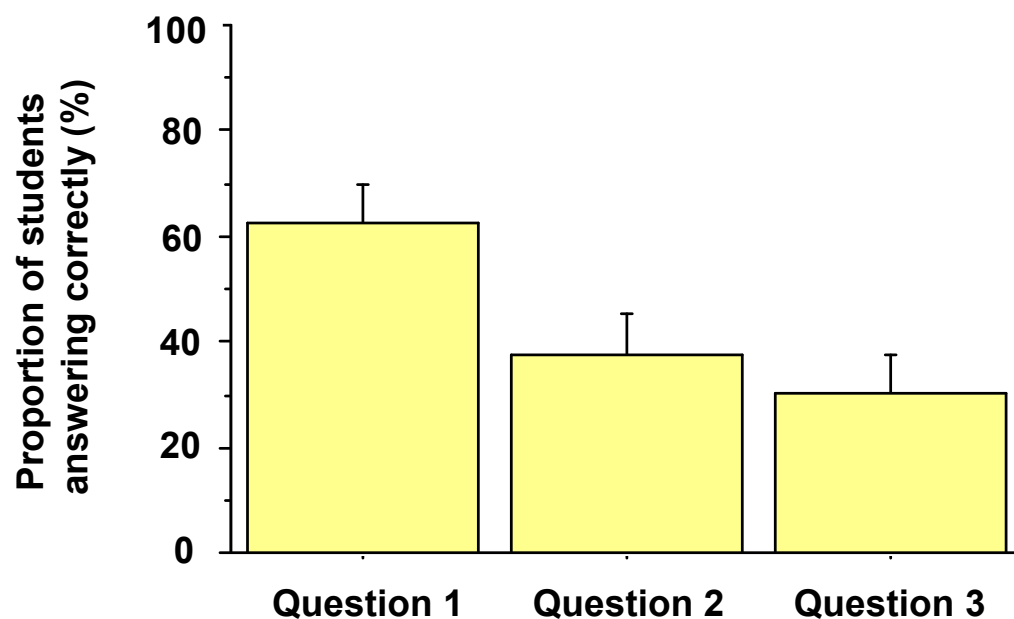


Figure 6: Box and whisker plot of mean time to complete questionnaire against year group ($H = 0.1$, $p = 0.949$).

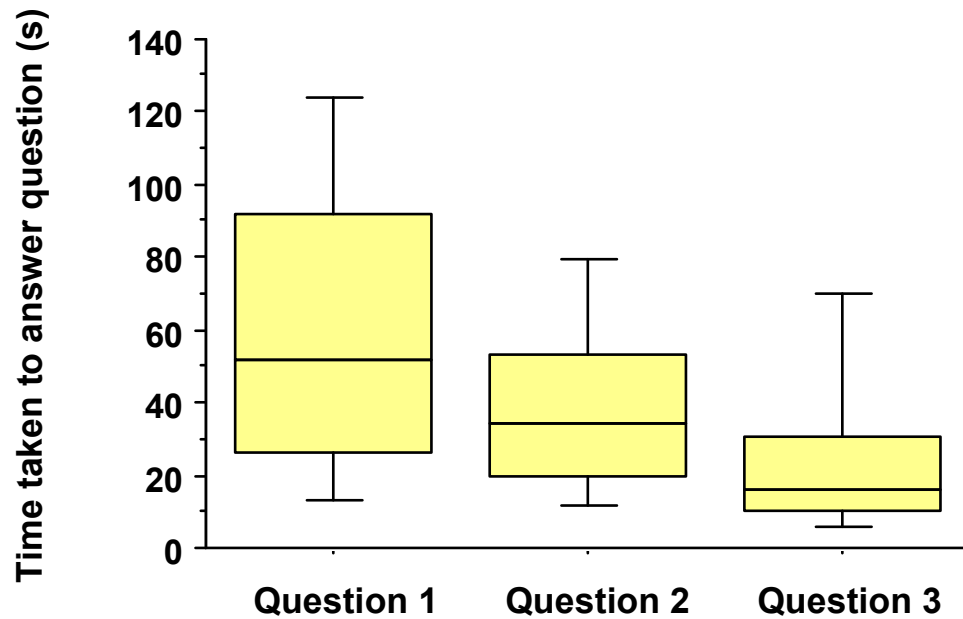
Analysis of results by question

The first question, concerning the conversion of the ratio 1:1 000 to 1 milligram per millilitre, was answered correctly by 62.3% of students (figure 7). A significantly smaller proportion answered the second and third questions correctly (37.6% and 30.3% respectively). The time taken to answer each question also showed significant differences (figure 8). Question 1 was most likely to be answered correctly, but also took the longest to answer. Question 3 was least likely to be answered correctly, but answers were given more promptly.



Answers	Mean difference	p value	95% lower confidence interval	95% higher confidence interval
Question 1 vs Q2	0.255	<0.0001	0.171	0.338
Question 1 vs Q3	0.322	<0.0001	0.214	0.431
Question 2 vs Q3	0.072	0.167	-0.030	0.175

Figure 7: Plot of the proportion of students answering each question correctly. Error bars are 95% confidence intervals. Statistical analysis by paired comparisons with hypothesised difference of zero.



<i>Time taken</i>	<i>Mean difference</i>	<i>p value</i>	<i>95% lower confidence interval</i>	<i>95% higher confidence interval</i>
Question 1 vs Q2	22.1	<0.0001	13.9	30.2
Question 1 vs Q3	31.2	<0.0001	19.8	42.6
Question 2 vs Q3	8.5	0.062	-0.4	17.4

Figure 8: Box and whisker plot of time taken to answer each question correctly.

Analysis of results by student seniority and question

Further analysis of the answers given by the students revealed that the relationship between student seniority and increased chance of giving a correct answer was borne out for questions 1 and 2 (figure 9). Thus, for both these questions – the ones that required an arithmetical calculation to be made – there were significant differences between each year group's performance (question 1 $p = 0.017$; question 2 $p = 0.023$). The knowledge-based question 3 concerning the maximal safe dose of lidocaine shows an inverse relationship, namely an apparent decline in proportion answering correctly with student seniority, however this proved not to be statistically significant ($p = 0.727$).

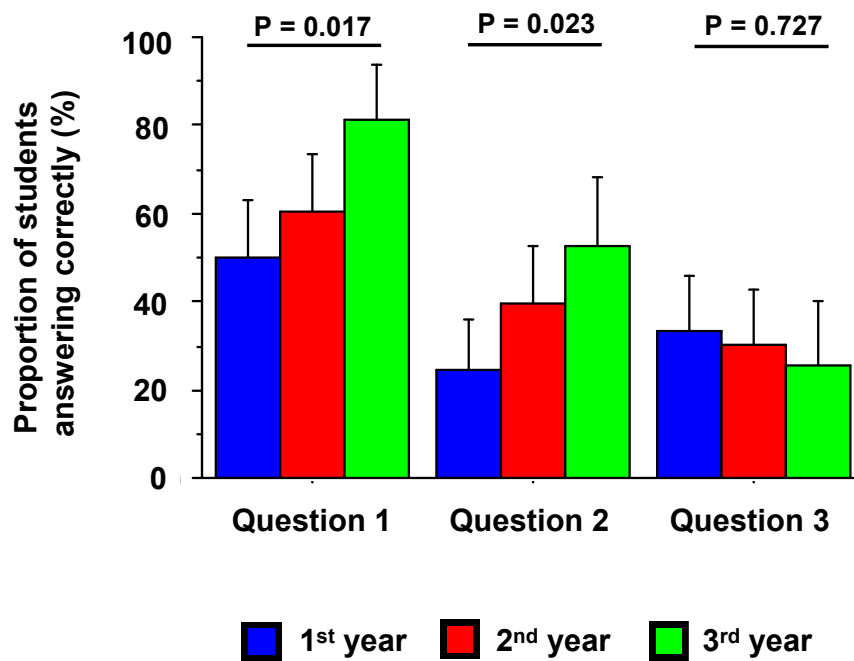


Figure 9: Plot of the relationship between proportion answering correctly and student seniority for each question. Error bars are 95% confidence intervals. Factorial ANOVA testing used on transformed data.

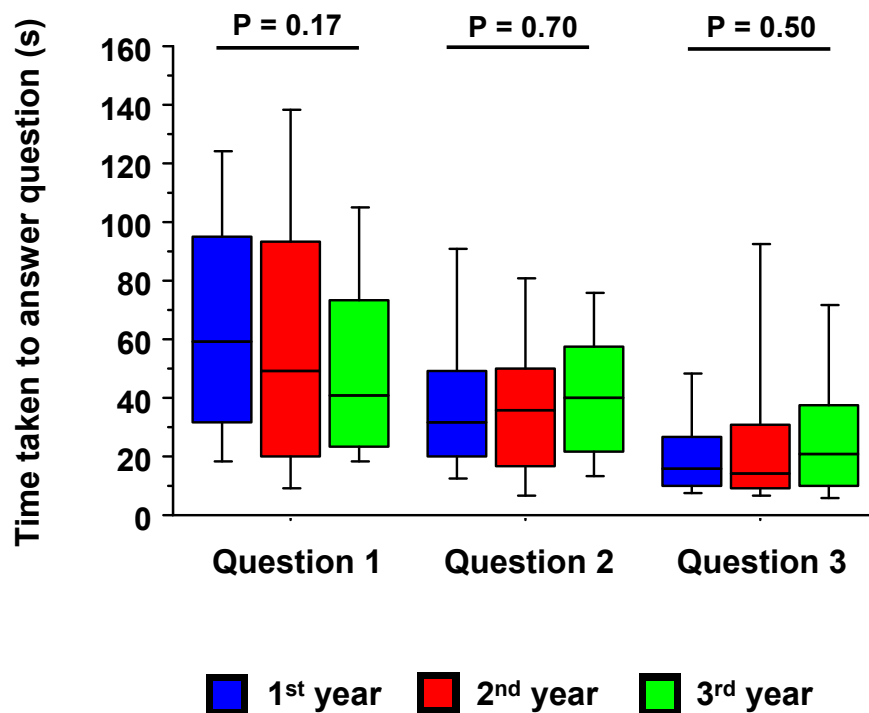


Figure 10: Box and whisker plot of the relationship between time taken to answer and student seniority for each question.

Although there were significant differences between the time taken to answer each question, there were no significant differences seen between the performances of different year groups (figure 10).

Were the students just guessing?

Considering the five stem format of the questionnaire, 20% of the students would have been expected to answer correctly by guessing alone. In a relatively small sample such as this, it is conceivable that the finding that only 30.3% could answer question 3 correctly might not differ significantly from 20%. To explore this possibility, the data were transformed into the probability of a correct answer, then compared with a hypothesised difference of 0.20 using the Mann-Whitney U test (see Appendix 4). From table 4 it is evident that the students were performing better in the first two questions than if they had been guessing, but it seems likely that they were guessing maximal safe dose of lidocaine.

Probability of correct answer in question	Mean	Degrees of freedom	p value	95% lower confidence interval	95% higher confidence interval
1	0.623	161	<0.0001	0.548	0.699
2	0.376	156	0.022	0.299	0.452
3	0.303	151	0.412	0.229	0.376

Table 4: Data showing the difference between the mean probability of a correct answer in each question compared with a hypothesised difference of 0.20 using the Mann-Whitney U test.

Discussion

The mean score (1.24 out of 3) and the fact that only 10% of clinical students answered all three questions correctly are disappointing but perhaps not surprising. The relatively simple skills of drug prescribing and preparation are not taught formally at many medical schools. At the time of this pilot study, no formal teaching was given in drug administration to clinical medical students at the University of Cambridge. The better mean scores of the final year students, mainly as a result of their better performance in the first two questions, imply that some students are acquiring these skills informally during the course. However knowledge of the maximal recommended dose of lidocaine was uniformly poor. This question had been chosen to test an observation – and confirmed my suspicions – that many students are unaware that there is a limit to the amount of local anaesthetic that can be administered safely, and because this knowledge forms the next step when calculating a safe dose for a patient.

The magnitude of the confusion is also worthy of comment. Whilst 62.3% of the students answered question 1 correctly, only approximately one third of the students gave the right answer to questions 2 and 3. The incorrect stems in the first two questions were wrong by between one and three orders of magnitude, so the consequences of making these errors or guessing in real life would have been very serious.

It is interesting that question 1 was most likely to be answered correctly but took longest to answer. With the other two questions, the more likely the students were to be wrong, the quicker they gave their answers – strongly implying that many of the students were guessing. The lack of a significant difference between the probability of a correct answer and the hypothesised level of 0.20 achieved by guessing suggests that few students in each year knew the correct answer to question 3.

The questionnaire study format is frequently criticised. First, the abilities and knowledge of those who did not respond are unknown. It can only be speculated

whether students choosing not to participate would have been more or less likely to make errors. Using the 'intention to treat' argument, even if the 182 students that did not reply had scored three out of three, a substantial minority of approximately 13% would have got every question wrong, which is arguably still unacceptable. Second, those participating in voluntary surveys may not take answering the questions as seriously as they would under examination conditions, or in a real clinical scenario. Additionally and as previously described, the act of opening multiple ampoules in a clinical situation should alert most doctors to the fact that they have made a dose error. This was addressed to a certain extent by showing pictures of the ampoules next to the questions in this study. These criticisms may explain why previous survey-based studies highlighting the dangers of ratios and percentages seem to have made so little impact on ampoule labelling policy. Finally, the third question may have been a little unfair. Kelly and Henderson recommend a dose of 3 mg.kg^{-1} of plain lidocaine and 7 mg.kg^{-1} when infiltrated with adrenaline (Kelly and Henderson, 1983). The most recent edition of the British National Formulary states that the maximal safe dose of lidocaine is 200 mg, without mentioning weight (BNF, 2007). The concept that there is a maximal safe dose of a local anaesthetic determined on the basis of the patient's weight is considered controversial by many, as other factors such as site of injection, age, organ dysfunction, acid-base disturbance and pregnancy are probably more important (Benowitz and Meister, 1978; Tucker, 1986; Rosenberg et al., 2004).

There were also positive aspects to the study design and findings. Administering the questionnaire online allowed a large number of students to be enrolled with minimal effort, when a paper-based study would have been very difficult to organise as the students are so rarely gathered in the same place at the same time. It also allowed the time taken to answer to be recorded, which would not have been possible on paper.

To conclude, the pilot study showed that a substantial proportion of clinical medical students at the University of Cambridge struggle with drug dose calculations. Clearly the lack of formal drug administration teaching needed to be addressed. It has been suggested that to reduce prescribing errors, hospitals

should train junior doctors in the principles of drug prescribing (Dean et al., 2002a). These findings demonstrate that even correctly and clearly written prescriptions are open to misinterpretation and dose error, and add weight to the argument that medical schools should teach dose calculation skills as part of the undergraduate and clinical pharmacology curricula rather than waiting until doctors are practicing (Langford et al., 2001). The effect of such an intervention will be described in more detail in Chapter 5.

This pilot also showed that the concept of an online questionnaire was apparently successful, and might be useful to examine the interesting and possibly more worrying question of whether doctors might also have similar difficulties with ratios and percentages when making drug dose calculations. The next chapter will discuss how the questionnaire was adapted and made available to a large population of doctors online.

CHAPTER 4

DOCTORS' UNDERSTANDING OF RATIOS AND PERCENTAGES

Doctors and their difficulties with ratios and percentages

Each of the previous four studies conducted between 1983 and 2004 that examined doctors' understanding of different means of expressing drug concentrations used a paper-based survey to collect data. Each was based in one institution, and as a result the numbers of participants were slightly limited. Kelly and Henderson recruited 57 doctors (Kelly and Henderson, 1983), Scrimshire recruited 100 (Scrimshire, 1989), Rolfe and Harper recruited 150 (Rolfe and Harper, 1995), and Oldridge and colleagues recruited 39 (as part of a larger study group that included 28 nurses, 22 pharmacists, 22 medical students, 20 registrars and 19 house surgeons) (Oldridge et al., 2004). In each study the participants performed surprisingly poorly.

The pilot study described in the previous chapter demonstrated the potential of the Internet as a means of collecting data easily and conveniently. The ease of access to the Internet also allows a questionnaire to be made available to a far wider audience, yet the main difficulty lies in specifically attracting doctors to the website and encouraging them to participate.

Using the Internet to attract participants

To this end a collaboration was forged with Doctors.net, a website based in Abingdon in the United Kingdom that is exclusively for doctors (www.doctors.net.uk). Doctors.net was established in 1998 and provides a number of online services, including continuing medical education and professional development resources, communication via email and discussion

fora, medical news and is also an Internet Service Provider. The service has more than 140 000 registered users all of whom are doctors registered with the General Medical Council (GMC) or medical students. The company receives income from market research and has a well-developed system for targeting specific groups of users, inviting them to participate and gathering data. Doctors.net agreed to allow their market research system to be used to run a refined and improved drug safety questionnaire.

Refining the questionnaire

A new questionnaire was developed to address the issues identified in the pilot study. Six questions were written and are shown in figure 11. The rationale behind the choice of questions was to test doctors' knowledge of ratios and percentages but also include a brief clinical scenario that required a calculation to be made. Once again the incorrect answers were wrong by factors of up to 1 000. Questions about another emergency drug with its concentration expressed as mass concentration were added as a control.

Methods

Subscribers to Doctors.net were invited to answer the six multiple choice questions about the three drug solutions in common clinical scenarios over three weeks in September 2003. The invitation included information that answers would be recorded, that anonymity would be maintained, and data of interest published, however written consent was not obtained. All respondents were entered into a prize draw funded by Abbott Laboratories (Queenborough, Kent) to encourage participation.

Each participant's age, specialty, grade, and medical school were obtained. Their length of medical practice was calculated by subtracting their year of qualification from 2003. The software did not allow the time taken to answer to be recorded.

All data were recorded anonymously, and in addition it was ensured that there were no incidences of participants potentially being identified by any other means, such as being the only respondent from a medical school. Participants were not able to go back and change their answers after they had been given. The study structure did not aim to eliminate the use of calculators or formularies. The extent to which the study population represented the UK medical workforce was assessed by comparison with data supplied by the UK Department of Health (Sang, 2003).

At the end of the study period participants were sent the correct answers and directed towards an online continuing medical education module about drug administration reproduced in Appendix 1.

Statistical analysis

Each dataset was tested for normality by comparing it to a dataset generated using the random number generator function within Statview using the Kolmogorov Smirnov test. The Kolmogorov Smirnov test was also used to compare the study population with Department of Health workforce data. Ordinal scores in individual multiple choice questions were transformed into the probability of a correct answer to aid statistical analysis. These datasets were subject to further analysis with factorial ANOVA testing, the F statistic and p value are quoted in the text and figure legends, and error bars shown in graphs represent 95% confidence intervals. *Post hoc* testing of statistically significant datasets was performed with Bonferroni / Dunn analysis. Logistic regression was employed to examine the relationship between normally distributed dependent variables; F, R^2 and p values are cited in the text.

Datasets that were not normally distributed were subject to non-parametric testing using the Kruskal-Wallis test. The H statistic and p value are quoted in the figures and text. These data are presented either in bar charts with error bars representing 95% confidence intervals, or in box and whisker plots that show the median, interquartile range (IQR) and 10th – 90th centiles. Where appropriate,

Q1: The first picture shows an ampoule of adrenaline (epinephrine). It contains 1 millilitre of 1 in 1 000 adrenaline. How much adrenaline is there in the ampoule? A. 10 micrograms B. 100 micrograms C. 10 milligrams D. 1 milligram E. 1 000 milligrams	
Q2: You are treating a ten year old whom you suspect is in anaphylactic shock. The protocol says the recommended intramuscular dose of adrenaline is 250 micrograms. What volume of solution in the picture will you give? A. 2.5 millilitres B. 0.25 millilitres C. 0.025 millilitres D. 2.5 microlitres E. 25 microlitres	
Q3: The second picture shows an ampoule of lidocaine (lignocaine). It contains 10 millilitres of 1% w/v lidocaine. How much lidocaine is there in the ampoule? A. 100 micrograms B. 10 grams C. 10 milligrams D. 100 milligrams E. 1 000 milligrams	
Q4: You find yourself treating a 60 kg patient with a laceration that you will need to suture under local anaesthetic. Given that the maximal safe dose of lidocaine is 3 mg/kg, what is the maximum volume of the solution in the picture that can be administered safely? A. 60 millilitres B. 6 millilitres C. 180 millilitres D. 18 millilitres E. 180 microlitres	
Q5: Here is a Mini-Jet™ of atropine as found on emergency drugs trolleys. There is 1 milligram in 10 millilitres. What is the concentration of the solution? A. 1 mg/mL B. 10 micrograms/mL C. 0.1 mg/mL D. 1 micrograms/mL E. 0.1 micrograms/mL	
Q6: At work, you come across a patient with an acute symptomatic bradycardia. A pulse is present and the blood pressure is 85 systolic. You estimate their weight is 60 kg. You choose to treat this with atropine at 20 micrograms/kg. How much of this solution will you need to give? A. 12 millilitres B. 1.2 millilitres C. 6 millilitres D. 8.5 millilitres E. 0.6 millilitres	

Figure 11: Questions and images in the online questionnaire (correct answers in bold italic)

further comparisons between groups were made using the Mann-Whitney U test. Tied H, Z and p values are shown unless otherwise stated. Contingency tables were constructed to establish whether observed relationships were independent. When data were nominal, correlation coefficient and Cramer's V value are quoted. For all analyses, p values < 0.05 were considered to be statistically significant.

Results

Response rate

There were 2 975 participants during the three week study period. The web page containing the link to the study was viewed by 12 096 subscribers over that time, hence the response rate was calculated to be 24.6%.

Comparison of study participants with NHS workforce data

NHS workforce census data were kindly provided by Naomi Sang of the Department of Health workforce statistics department (Sang, 2003). The data showed how the workforce was constituted on the basis of specialty and age in 2002. Tables 5 and 6, and figures 12 and 13 show how the proportions of each compared with the participants in the questionnaire.

All but 40 doctors participating in the survey identified themselves as belonging to one of 42 specialties. The Department of Health recognised all these specialties except medical management, a group to which four participants (0.14%) assigned themselves. Notably a larger proportion of anaesthetists participated in the study than expected from the census data, and fewer participated from obstetrics and gynaecology, ophthalmology and oral and maxillofacial surgery. These differences were not statistically significant (Kolmogorov Smirnov test: $\chi^2 = 3.86$, $p = 0.29$).

The proportions of study participants and members of the NHS workforce when grouped by age are shown in figure 13. The proportion of study participants exceeds that of the workforce in the younger age ranges, a trend that is reversed in the older groups. This seems to imply that older members of the workforce are less likely to be members of Doctors.net, however the observed differences were not statistically significant (Kolmogorov Smirnov test: $\chi^2 = 0.89$, $p > 0.999$).

Analysis of overall results

The mean score was 4.80 out of six (IQR 2.0, 95% confidence intervals 4.75 – 4.85). Figure 14 shows the proportion of participants answering each question correctly. The question concerning the mass of adrenaline was answered correctly by 85.2% of participants (2 535). Only 65.8% (1 958) chose the correct amount of lidocaine in the ampoule. However, 93.1% (2 768) identified the correct concentration of atropine in milligrams per millilitre ($p < 0.0001$ for all comparisons).

Participants found two of the clinical scenarios easier than the raw calculations. Whilst 85.2% had correctly identified the mass of adrenaline in the ampoule, a larger proportion, 89.4% (2 660), would have given the correct volume in the ensuing clinical scenario. Similarly whilst only 65.8% had correctly identified the mass of lidocaine in the ampoule, 81.0% (2 410) identified the correct volume. Although 93.1% had calculated the concentration of the atropine solution correctly, only 65.5% (1 949) would have administered the correct volume ($p < 0.0001$ for all comparisons).

Analysis of results by question

The vast majority (85.2%) of participants correctly identified that 1 mL of 1:1 000 adrenaline contains 1 mg. However, 7.2% thought that there was only 100 µg, presumably confusing a 1:1 000 solution with a 1:10 000 solution (figure 15). A further 3.9% thought that the solution was an order of magnitude even

Specialty	Proportion of NHS workforce (%)	Proportion of study participants (%)
Accident and emergency	3.39	4.27
Anaesthetics and ICU	8.13	15.69
Audiological medicine	0.03	0.06
Cardiology	1.80	1.54
Cardiothoracic surgery	0.61	0.48
Chemical pathology	0.22	0.17
Chest medicine	1.09	1.17
Dermatology	1.08	0.59
Endocrinology	1.02	1.07
Gastroenterology	1.33	0.89
General practice	30.77	34.35
General surgery	5.28	3.72
Genetics	0.17	0.07
Genitourinary medicine	0.85	0.38
Geriatric medicine	2.67	2.41
Haematology	1.13	0.65
Immunology	0.11	0.07
Infectious diseases	0.24	0.34
Internal medicine	4.49	5.22
Medical management	Not recorded	0.14
Microbiology	0.61	0.24
Nephrology	0.71	1.06
Neurology	0.76	0.55
Neurosurgery	0.46	0.21
Obstetrics and gynaecology	4.32	1.86
Occupational health	0.22	0.61
Oncology	0.78	0.99
Ophthalmology	2.09	0.87
Oral and maxillofacial surgery	1.13	0.10
Orthopaedics and trauma	3.97	1.65
Otorhinolaryngology	1.35	0.93
Paediatric surgery	0.29	0.21
Paediatrics	5.42	7.84
Palliative medicine	0.35	0.61
Pathology	1.35	0.45
Plastic surgery	0.60	0.31
Psychiatry	4.84	4.20
Public health	1.73	0.48
Radiology	2.50	1.55
Rehabilitation medicine	0.23	0.24
Rheumatology	0.91	0.55
Urology	1.14	1.00

Table 5: The proportions of each specialty amongst the study participants and NHS workforce expressed as percentages.

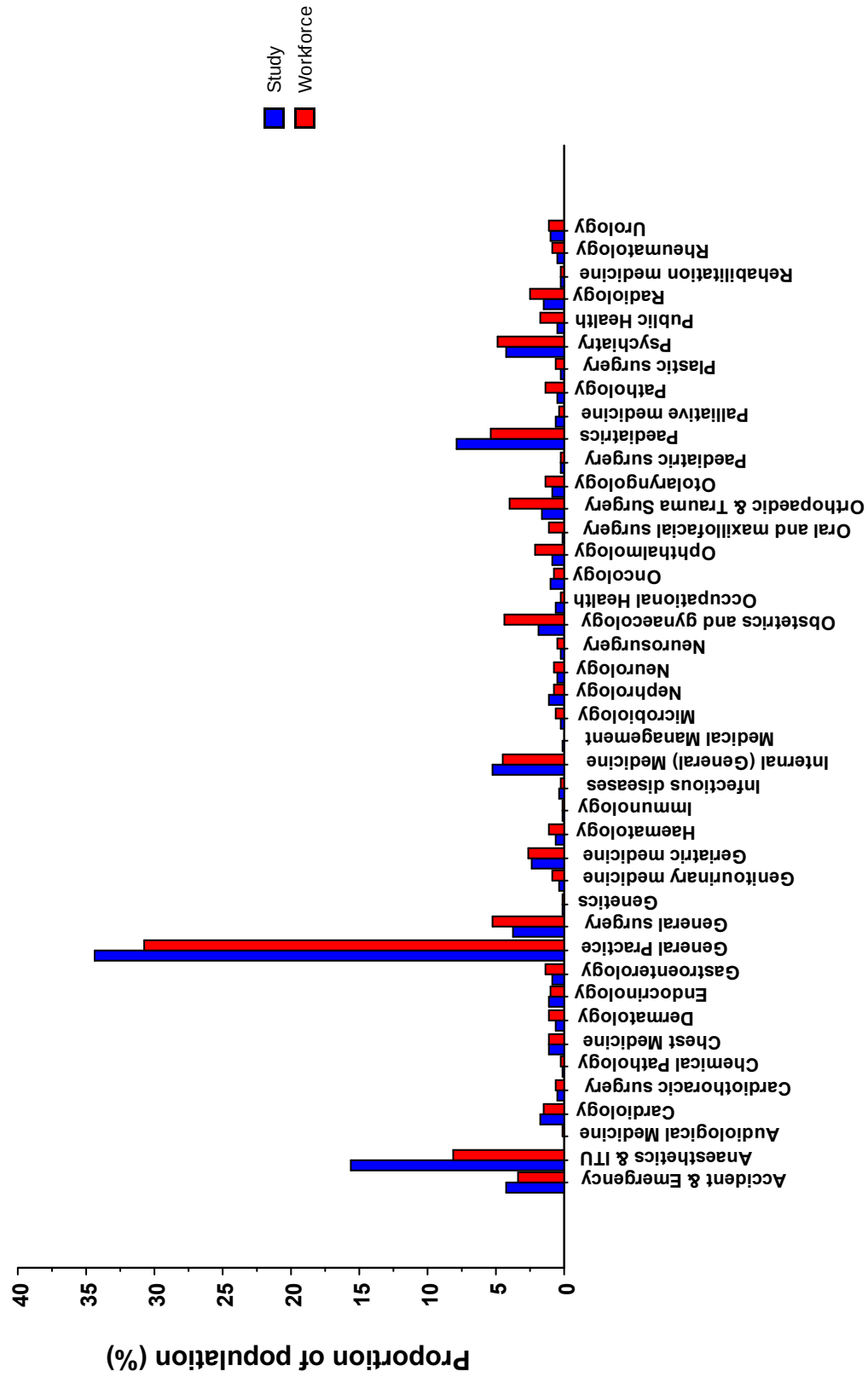


Figure 12: Comparison of the specialties of doctors undertaking the online multiple choice questionnaire (blue) with data about the proportion of specialties in the NHS workforce (red).

Age range	Proportion of NHS workforce (%)	Proportion of study participants (%)
20 to 30	15.6	22.8
30 to 35	14.5	21.8
35 to 40	15.8	15.7
40 to 45	15.2	12.1
45 to 50	12.6	11.1
50 to 55	10.5	7.7
55 to 60	7.9	4.6
60 to 65	3.3	1.3
65 to 70	0.8	0.5

Table 6: The age ranges of the study participants compared to the NHS workforce expressed as percentages.

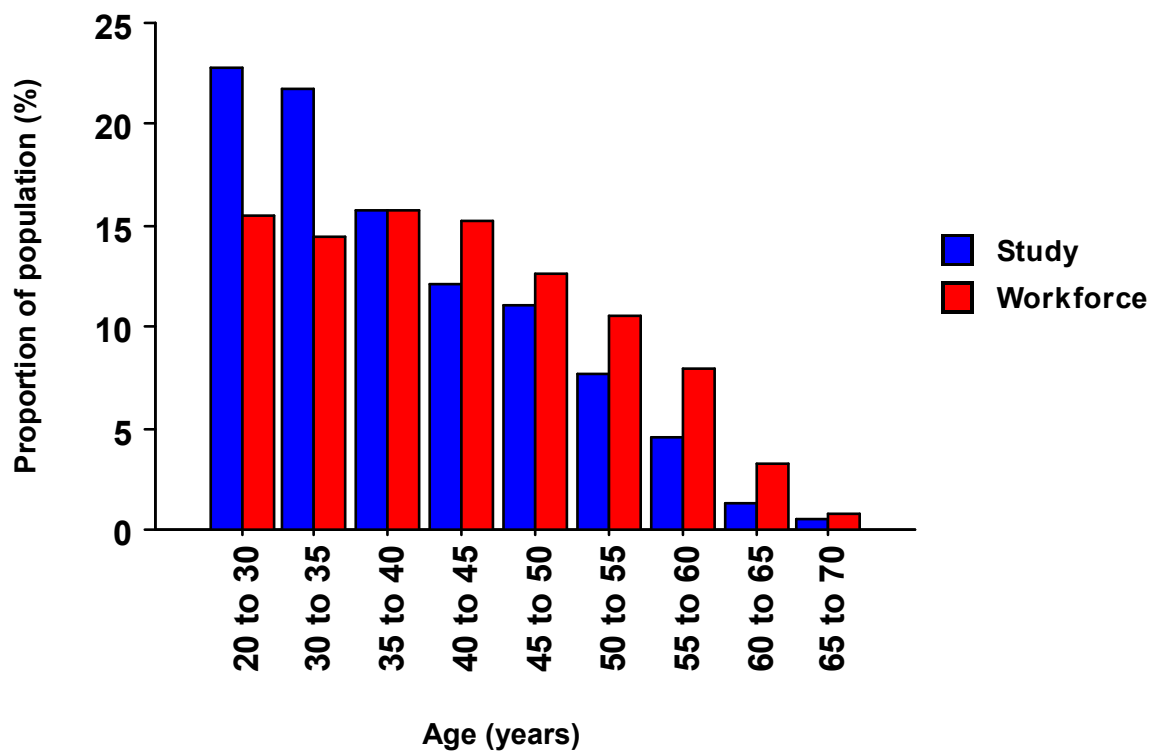


Figure 13: Comparison of the age of study participants (blue) with data provided about the age of the NHS workforce (red).

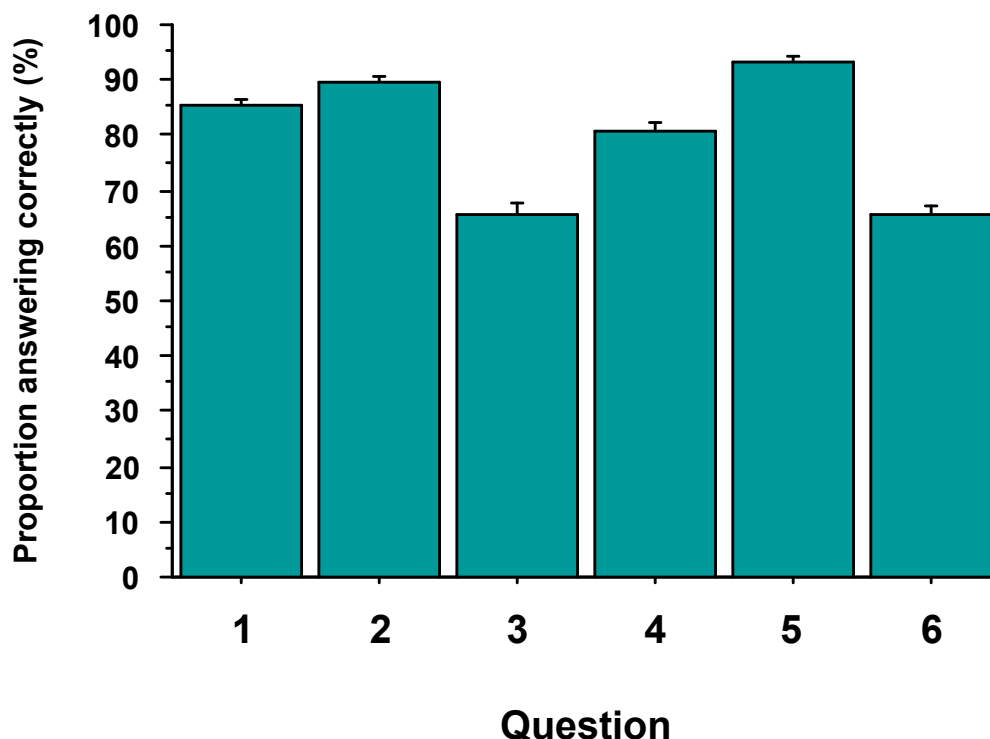


Figure 14: Plot of the proportion of respondents answering each of the multiple choice questions correctly. Error bars represent 95% confidence intervals.

more dilute. Thus 11.1% of participants thought that a 1: 1 000 solution is more dilute than it really is, and risk of overestimating the amount to administer in a clinical scenario. A smaller proportion thought that there was either 10 mg or 1 000 mg in the ampoule (1.5% and 1.7% respectively), and would therefore be likely to give too little in reality. More doctors would have administered the correct volume of adrenaline in the clinical scenario than knew the mass in the ampoule. Those that were wrong, however, were much more likely to give too much; 8.3% would have given 2.5 mL of the 1:1 000 solution to the child, a tenfold dosing error. Only a tiny fraction would have given too little.

Barely two thirds of doctors knew that a 1% solution contains 10 mg.mL^{-1} . Most underestimated the amount of drug in the ampoule of lidocaine: 22.2% thought that it contained 10 mg (another tenfold error) and 9.4% thought that it only

contained 100 µg. This suggests that almost one third could have given too much lidocaine in a real life clinical situation. Very few (1.7%) overestimated the amount in the ampoule. Whilst 81.0% would have given the correct volume when presented with the patient requiring suturing, 12.7% would have made a tenfold overdose and 2.0% a fivefold overdose, with the remainder (3.2%) giving too little.

Working out the concentration of atropine was far more straightforward: 93.1% were correct and only a very small proportion made mistakes. Essentially the calculation required was to divide 1 by 10, but 6.9% still made an error, with 2.4% making tenfold over- or under-calculations and 3.4% wrong by three or four orders of magnitude. In the bradycardia scenario 30.1% and 1.2% would have given ten and twenty times too little respectively. The remaining 2.2% would have also given too little atropine, but only by factors of 50 – 70%.

Analysis of results by specialty

Figure 16 represents the mean score for each specialty and shows clear and highly significant differences between the specialties ($F = 6.80$, $p < 0.0001$). The two immunologists and one audiologist that took part all scored six out of six, and the performance of six paediatric surgeons made them the next best scoring specialty. Anaesthetists were an overrepresented group and were the best performing major specialty (mean score 5.50, 95% confidence intervals 5.43 – 5.58). The mean score for paediatricians was 4.91 (95% confidence intervals 4.72 – 5.09), making them the eighteenth best performing specialty. General practitioners made up more than a third of the respondents and had a mean score of 4.57 (95% confidence intervals 4.48 – 4.65). Orthopaedic surgeons performed better than general physicians. When considering only specialties represented by more than 10 participants, *post hoc* testing revealed that anaesthetists performed better than the 13 worst scoring specialties; other analyses did not survive corrections for multiple comparisons.

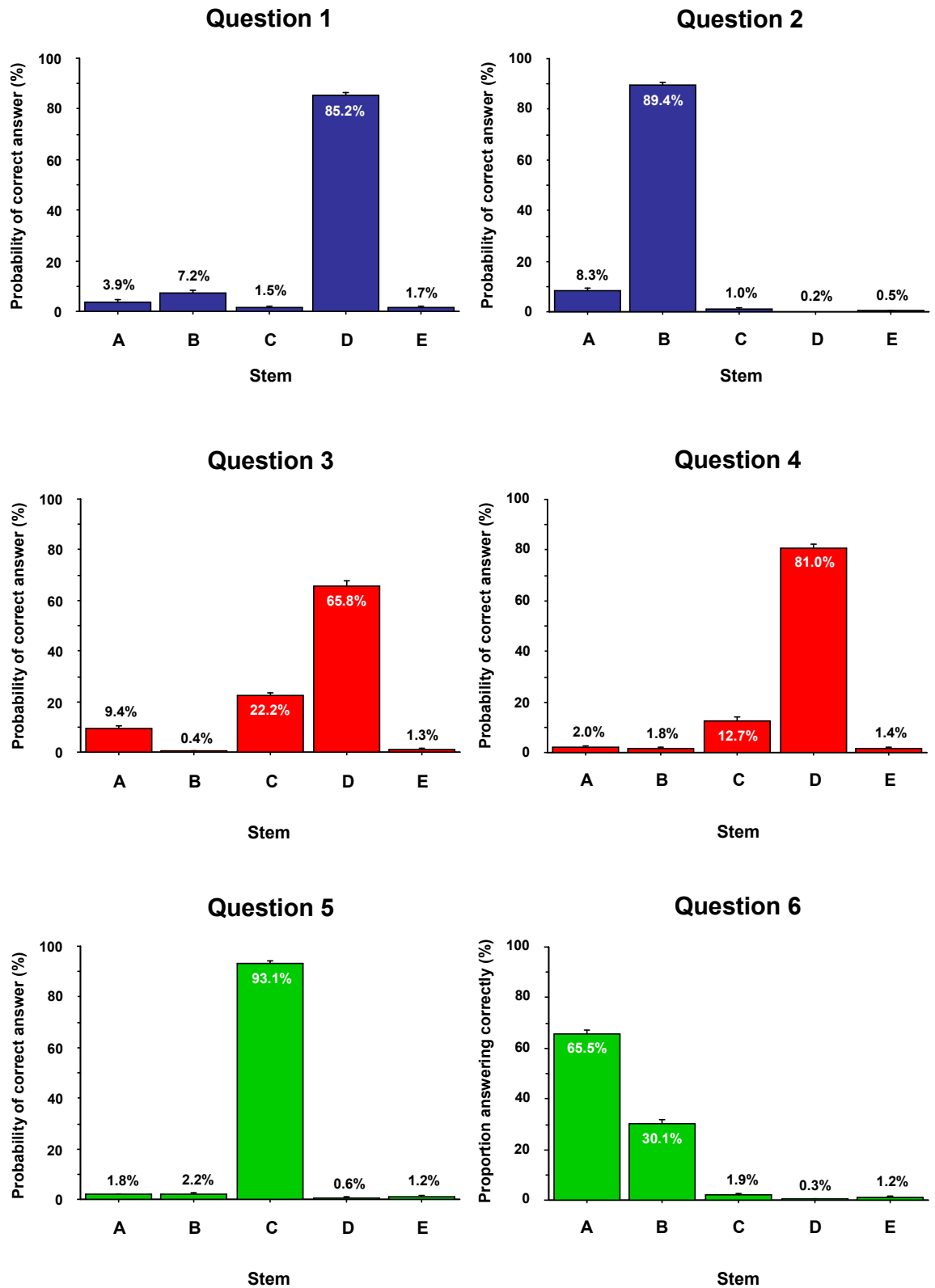


Figure 15: The probability of a correct answer in each of the stems of all the multiple choice questions.

The influence of experience

The mean length of experience was 14.8 years (range 1 – 44, IQR 15). When all participants were considered together, their amount of experience was not a factor influencing the likelihood of a correct answer in the questionnaire; with no evident relationship between the number of years clinical experience and score in the multiple choice questionnaire ($F = 0.32$, $R^2 = 1.04 \times 10^{-4}$, $p = 0.572$) in a logistic regression analysis plotted in figure 17a. However, when retired doctors and those working in the community were excluded from the analysis (figure 17b), a strong and significant relationship is seen ($F = 18.83$, $R^2 = 0.01$, $p = 0.001$).

The influence of grade

A doctor's grade also influences performance in the multiple choice questionnaire. Table 7 and figure 18 show the grades in order of decreasing mean rank, along with an explanation of each position for those that are unfamiliar with the training system in the UK. There were highly significant differences between the performances of doctors in some grades ($H = 131.9$, $p < 0.0001$). The table also shows the results of comparing each grade with the best performing grade using Mann-Whitney analysis. This relationship persisted, but was slightly less strong, when clinical assistants were excluded from the analysis on the basis of the small number responding ($H = 63.3$, $p < 0.0001$, data not shown).

The influence of medical school

The medical school attended is also a highly significant determinant of performance in the multiple choice questionnaire ($H = 70.9$, $p < 0.0001$) as shown in figure 19, a plot in which medical schools are shown in order of decreasing mean rank. Medical schools contributing less than 10 respondents are not shown, and the identities of each school have been hidden.

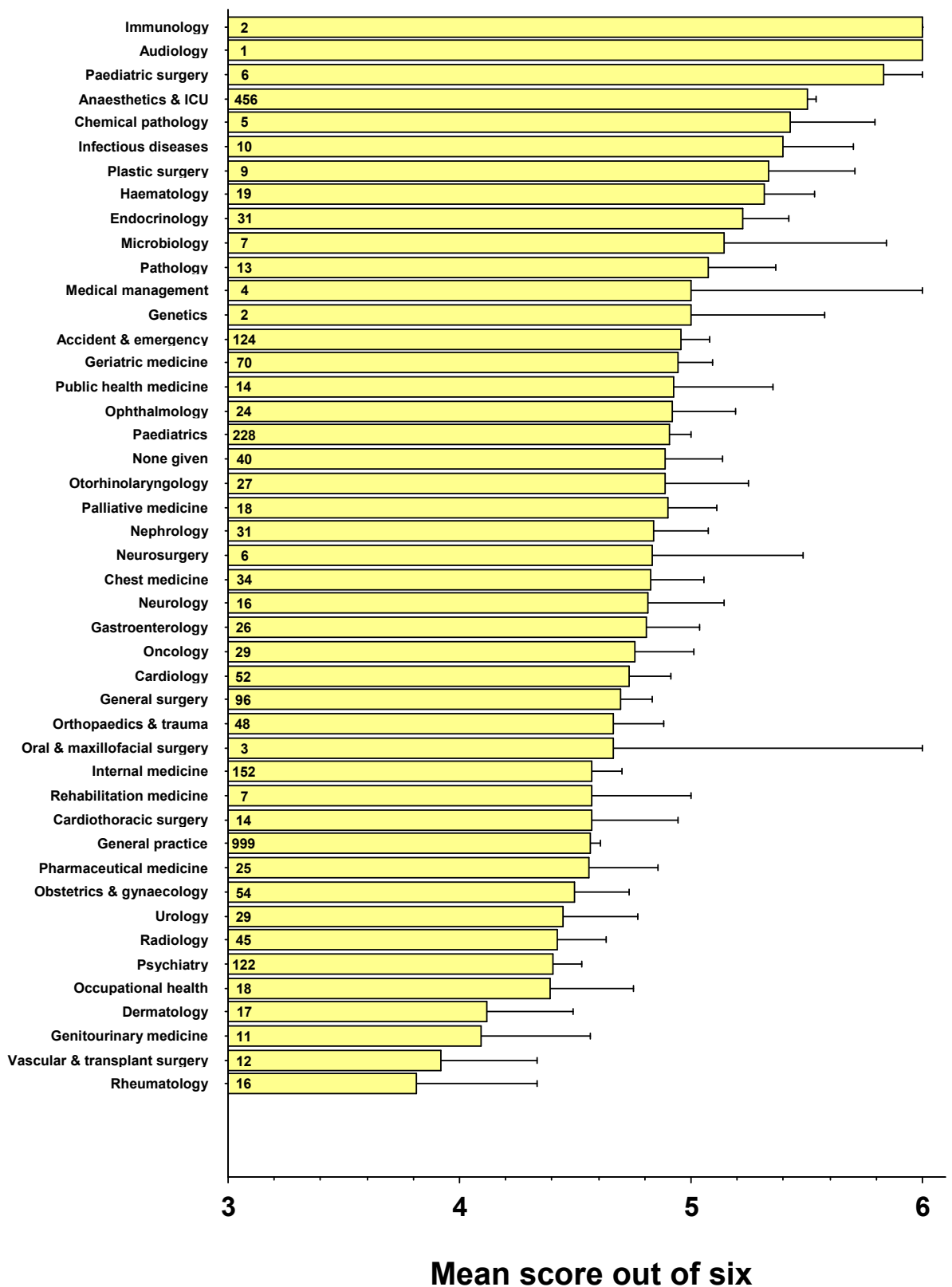


Figure 16: The mean score out of six in the questionnaire for each specialty, presented in descending order of mean score, with the numbers from each specialty presented at the left hand end of the bar. Error bars are 95% confidence intervals.

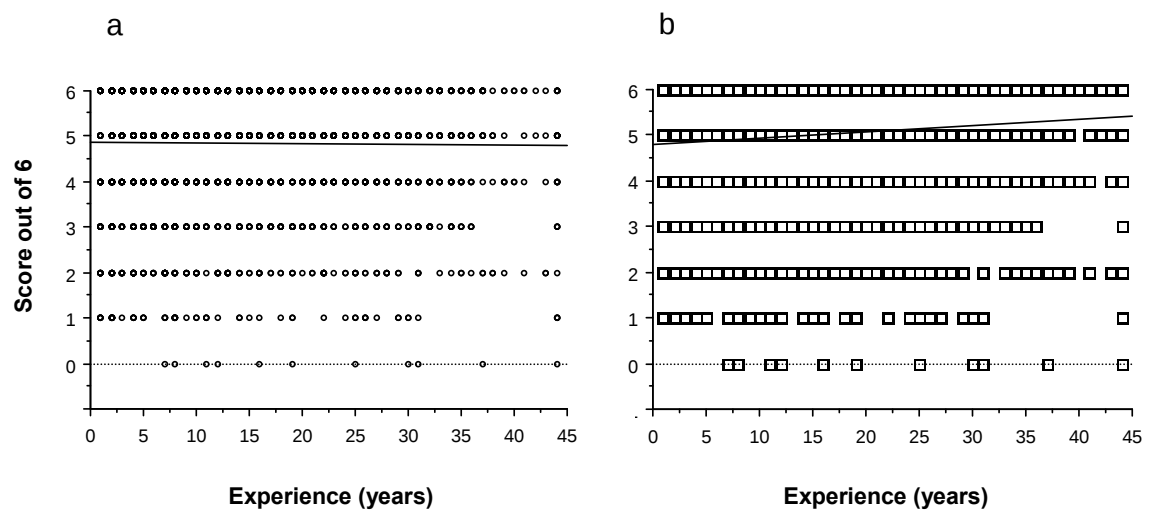


Figure 17: A) Regression plot showing the absence of a statistically significant relationship between score in the multiple choice questionnaire and the amount of clinical experience ($F = 0.32$, $R^2 = 1.04 \times 10^{-4}$, $p = 0.572$). B) When hospital doctors' performances are analysed in isolation, a strong relationship is seen ($F = 18.83$, $R^2 = 0.01$, $p = <0.001$).

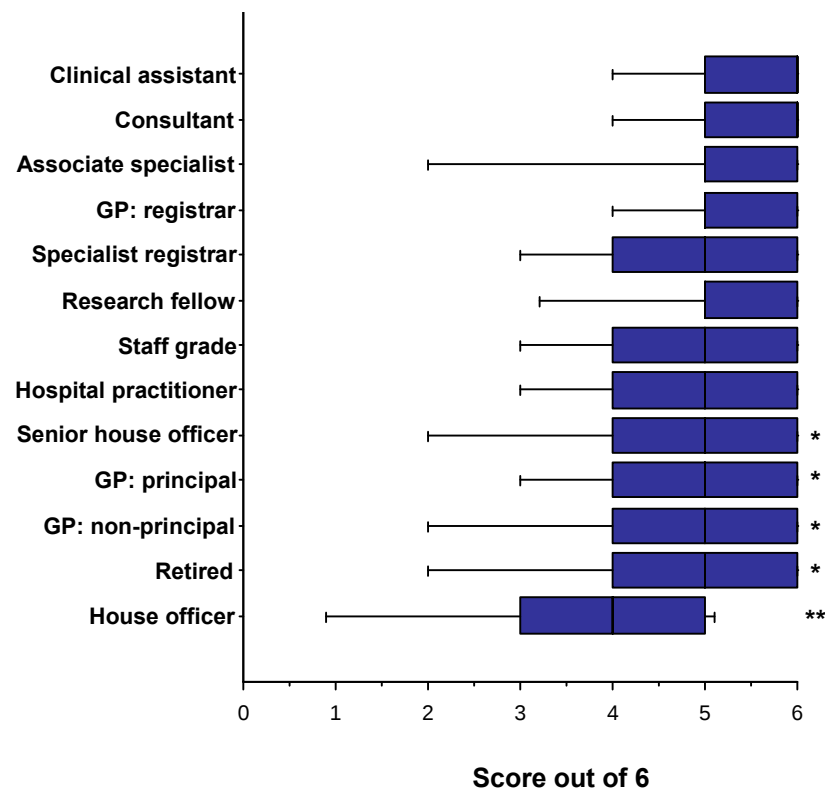


Figure 18: Box and whisker plot of the performance of different grades of doctors in the multiple choice questionnaire. Exact p values cited in table 7.

Grade	Description	n	z value when compared to clinical assistant	p value when compared to clinical assistant
Clinical assistant	Career grade, works under supervision of consultant	16		
Consultant	Works unsupervised and independently, mainly in hospitals	704	-0.46	0.647
Associate specialist	Career grade, works semi-independently but under supervision of consultant	44	-1.05	0.292
GP registrar	Training for position in general practice	65	-1.22	0.222
Specialist registrar	Training to be a consultant	668	-1.30	0.194
Clinical research fellow	Trainee in research position	17	-1.21	0.225
Staff grade	Career grade, works under supervision of consultant	95	-1.57	0.116
Hospital practitioner	Career grade, works under supervision of consultant	22	-1.55	0.121
Senior house officer	Training to be a specialist registrar or career grade	362	-2.11	0.035
GP: principal	Works independently in general practice	730	-2.31	0.021
GP: non-principal	Works semi-independently in general practice under supervision of GP principal	221	-2.42	0.016
Retired		43	-2.20	0.028
House officer	First year in clinical practice, typically in hospital	44	-3.03	0.002

Table 7: Comparison of performance of doctors of different grades in the multiple choice questionnaire. Includes brief description of each grade to indicate seniority to those that may not be familiar with the training system in the UK. Groups compared using Mann-Whitney U test.

Contingency tables were constructed to ensure that the relationships between doctors' performance in the MCQ and their grade, experience and medical school were independent. There was no relationship between doctors' grades and medical school (contingency coefficient 0.476, Cramer's V 0.140). Significant

differences were seen between medical school attended and length of experience, accounted for by the inclusion of newly-established medical schools and the fact that participants from a handful of medical schools had significantly more or less experience. Excluding these medical schools from the analysis reduced the strength of the statistical relationship between medical school and performance, but it remained highly significant ($H = 61.6$, $p < 0.0001$).

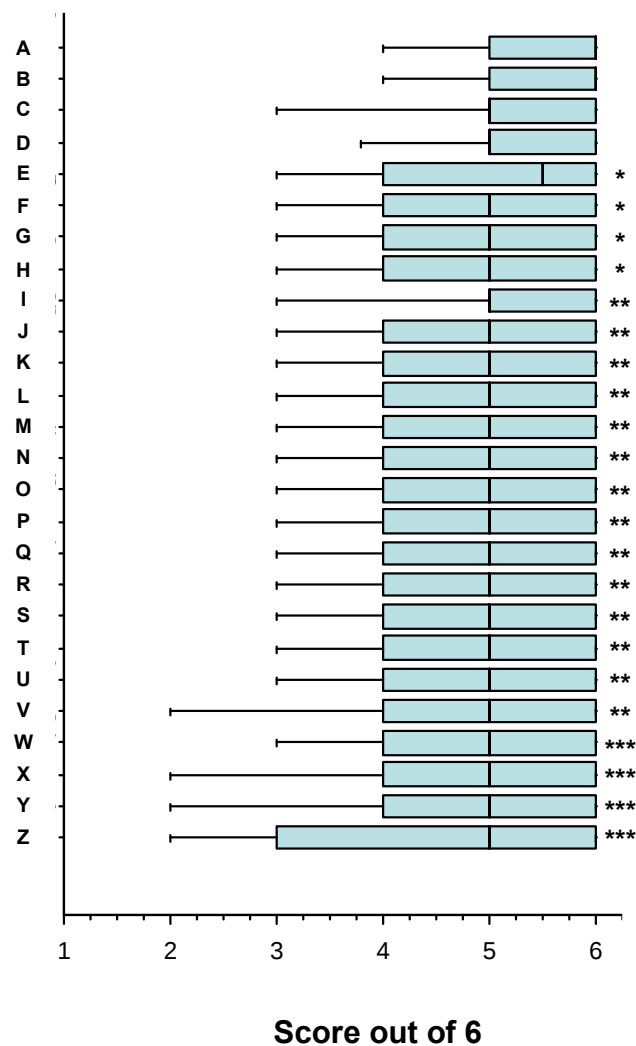


Figure 19: Box and whisker plot showing significant differences in the performance of graduates of different medical schools in the multiple choice questionnaire ($H = 70.9$, $p < 0.0001$). Further analysis using Mann-Whitney U test. * $p > 0.01 < 0.05$, ** $p > 0.001 < 0.01$, * $p < 0.001$. Schools ranked by MCQ score, significance values cited reflect performance compared to medical school A.**

Discussion

The results show that a substantial number of doctors do not understand different means of expressing the concentration of drugs in solution, with concentrations expressed as percentages causing particular problems. Some made errors by factors of ten or more. Making an accurate conversion into mass per unit volume is essential when calculating the correct volume of drug to give.

The refinement of the questions in this study to include clinically relevant scenarios goes further than the pilot study in demonstrating how this confusion might translate into clinical errors. Most doctors are familiar with adrenaline and lidocaine, and fewer would have administered the wrong volume than calculated the concentration incorrectly, implying that doctors know what is “about the right amount”. This approach did not work with atropine. Unsurprisingly the vast majority calculated the concentration in milligrams per millilitre correctly. However, many would have still given the wrong volume, perhaps because atropine is a less familiar drug, or because a conversion from micrograms to milligrams was required.

There were also clear differences in the performances of doctors from different specialties. Despite the large number of respondents, some of the smaller specialties were represented by just a handful of participants with 11 specialties attracting less than ten participants. Immunologists and audiologists as specialties scored six out of six, but they only had two and one participant respectively. Taking into account the specialties with 50 or more participants, anaesthetists performed best, a finding that concurs with that of Rolfe and Harper (Rolfe and Harper, 1995). General practitioners were the biggest group, and unsurprisingly they performed relatively poorly as they would very rarely need to administer drug solutions. Generally, the more removed from acute medical emergencies a specialty is, the poorer the result: psychiatry, dermatology and rheumatology featured amongst the bottom ten. Perhaps the most surprising finding was that paediatricians did not perform better. It might be imagined that weight based calculations would be a familiar part of their practice and that they should perform well. It is hard to explain why they did not, apart from the possibility that a large

number of paediatric senior house officers may be training to be general practitioners.

Although it can be demonstrated that better drug administration teaching benefits medical students (Wheeler et al., 2004b; Degnan et al., 2006; Wheeler et al., 2006), doctors clearly require education too. These results show that competence in and understanding of drug administration comes with experience, at least in hospital doctors. The mechanism by which this experience is gained is not clear, it may be by 'osmosis', or by trial and error. Thus, two groups of doctors have been identified that might benefit from further drug administration training. House officers and senior house officers are trainee doctors with clinical experience that generally ranges from novice to 3 or 4 years. In the UK, junior training grades are currently being combined into a foundation training programme, which is meant to offer improved training and educational opportunities (Neville, 2003). The foundation years would be an appropriate time to reinforce teaching about drug administration teaching should be reinforced in the foundation years, together with the concepts of medical error in general (Rosebraugh et al., 2001). The second group of doctors comprises mainly those working in general practice. These senior doctors are unlikely to encounter the clinical scenarios that were presented or to need to administer adrenaline, lidocaine or atropine. Infrequent users of these drugs, however, seem more likely to be confused by the way that their strengths are expressed, reinforcing the argument for ampoule labels to be standardised to mass concentration.

Significant differences were found between graduates of different medical schools but several possible confounding factors must be borne in mind such as the reorganisation and merger of London medical schools in the early 1990s (Dickson, 1993), the necessity of grouping graduates from outside the UK together, and the move by some medical schools from traditional pre-clinical and clinical to integrated courses over the past 20 – 30 years. These confounding factors mean that the data are difficult to interpret, but they still serve to illustrate that all medical schools should ensure that drug administration skills are properly taught.

Despite criticism of questionnaire-based research the alternative – observational studies in the workplace – would be cumbersome, time consuming, expensive, and inevitably concentrate on acute hospital specialties. This study reached doctors working in the community, those with little patient contact, and those who administer drug solutions rarely – exactly those for whom volume calculation should be as simple as possible. A response rate of 24.6% might be perceived as low. Using online questionnaires for clinical research is a relatively new idea and it is not yet clear what an “adequate” response rate might be. The quality of the sample is more important than the response rate. This survey attracted a group of participants that was highly representative of the population of doctors in the UK (Sang, 2003).

Converting ratios or percentages to mass per unit volume is essentially a superfluous step in the calculation of the correct volume to administer. These data show that this extra step increases the chance of error. It is clear from the analysis of the causes of human error and the principles of safe-system design developed in the chemical, nuclear and aviation industries that reducing the number of actions required to complete a process reduces risk of error and hence improves safety (Sagan, 1993; Takano and Reason, 1999; Reason, 2000). This would appear to be a strong argument that labelling should be standardised so that concentrations of drugs in solution are expressed solely as mass per unit volume. This change would involve little or no cost to manufacturers, can only improve patient safety, and should be instituted forthwith.

Potential interventions to reduce dose errors

Clearly questionnaire based studies carry insufficient weight to effect a change in ampoule labelling policy. The publication of four studies since 1983, and these results in 2004 and 2007 (Wheeler et al., 2004a; Wheeler et al., 2007), stimulated two brief episodes of correspondence in 1995 and 2004 (Baldwin, 1995; Cohen, 1995; Nunn, 1995; Ghosh and Ghosh, 2004; Hillier and Kelly, 2004), but regulatory authorities have not shown any interest. None has ruled to remove

ratios and percentages from ampoules, although Abbott has unilaterally chosen to present the new local anaesthetic Chirocaine™ (levobupivacaine) as mass concentration only. A different approach is needed to establish whether labelling ampoules with mass concentration only can be more closely correlated with an improvement in doctors' clinical performance or even patient outcome. This study will be described in detail in Chapter 6.

The magnitude of the difficulties doctors encountered calculating the correct volume of atropine was surprising, as this question had been included as a control to show that mass concentration was a superior means of ampoule labelling. The questionnaire format cannot explain why question 6 was answered so poorly, but is most likely to be due to the requirement to convert micrograms to milligrams. This cannot be remedied by improved labelling, but requires teaching and reinforcement during undergraduate and postgraduate training (Scobie et al., 2003; Wheeler et al., 2004b). As pharmacology teaching involves ever more molecular and cell biology, perhaps the more mundane topics of drug preparation and administration are being neglected. The next chapter will examine the impact of more intensive drug administration teaching on medical students' drug administration skills.

CHAPTER 5

THE INFLUENCE OF IMPROVED TEACHING ON ACADEMIC UNDERSTANDING OF DRUG ADMINISTRATION TOPICS

The need for better drug administration teaching

In 2003 the General Medical Council of the United Kingdom made recommendations on undergraduate medical education that specify that students should learn the “Effective and safe use of medicines (side effects, interactions, antibiotic resistance, genetic factors)” and be able to “Work out drug dosage and record the outcome accurately” (Anon, 2003). Acquisition of drug administration skills is mentioned in the curriculum at the University of Cambridge, but judging by the findings reported in Chapter 3 and published in 2004 (Wheeler et al., 2004b) it would appear that formal teaching of the topic was completely overlooked.

This is perhaps typical of most medical schools. A survey of the heads of clinical pharmacology at all 27 medical schools in the United Kingdom in 1993 found that barely a quarter included a formal lecture session about drug administration in their course, with a similar proportion asking the students to record their experience on a self completed “check list” of procedures (Teahon and Bateman, 1993). The majority simply expected the students to pick up the skills during clinical attachments. One medical school gave no teaching to undergraduates at all, stating “We believe this and other practical procedures should be taught to pre-registration House Officers”.

There is evidence that students benefit from additional practical training sessions in drug administration given by a pharmacist (Scobie et al., 2003). Two teams of pharmacists at two UK teaching hospitals recruited 40 volunteer final year medical students, half of whom were randomised to receive additional drug administration teaching. The teaching comprised five practical exercises covering seven skills through which students rotated in small groups, and resulted in

significantly improved performance in a nine-station objective structured practical examination (OSPE) one month later. Interestingly, one of the greatest improvements was in preparation of intravenous drugs, but no improvement was seen in dose calculation. Barely half of the students reported prior experience of drug preparation or having received any teaching about the matter. When seeking feedback about the value of the teaching one student's comment was telling:

“...there is no incentive to learn these things at ward level because they won't help us to pass Finals...”

This chapter will describe how improved drug administration teaching session has been incorporated into the anaesthesia and perioperative medicine attachment in Cambridge, to address the problem of students being expected to absorb practical skills by osmosis during the course when clearly many miss out.

Structure of the Medicine course at Cambridge

The University of Cambridge retains a traditional course structure for medicine, divided into pre-clinical and clinical phases. The pre-clinical course lasts three years: two years of pre-clinical basic science teaching and a final year in which students may study another subject. Essentially, this can be any subject offered by the University but generally is one of the natural sciences. After final examinations the students are awarded a BA degree and move on to the clinical course. The pre-clinical and clinical medicine courses are completely distinct: only half the graduates remain in Cambridge for their clinical studies, the remainder leaves to study elsewhere, generally Oxford or London.

Until 2006, the clinical course lasted 2½ years. Students attended the anaesthesia and perioperative medicine attachment in the nine months of their clinical course, having completed their training in all the major specialties including surgery, medicine, obstetrics and gynaecology and pathology. There are approximately 130 students in each year, who cannot be accommodated at once, so the year is divided into groups of roughly 10 – 12 students who rotate through a series of

attachments every fortnight for nine months before the Final examinations. One of these attachments is anaesthesia and perioperative medicine. At the end of the course, after three weeks of revision lectures, the students sit the Final MB examination, consisting of written papers, an OSPE, and clinical and viva voce examinations. Those that pass attain provisional registration as a Medical Practitioner under the Medical Act 1983.

Structure of the anaesthesia and peri-operative medicine attachment

The attachment lasts two weeks, but once weekends and occasional lecture days are accounted for, it may be as short as seven days. The first day is spent at the teaching centre, Addenbrooke's Hospital in Cambridge, where the students receive four lectures and a brief refresher about airway and cannulation skills. Thereafter students are further divided into smaller groups, with some remaining in Addenbrooke's and the rest attending local district general hospitals as far afield as Bedford, King's Lynn, Luton or Peterborough for their practical experience. Students are assessed by means of a case presentation and a negatively-marked online multiple choice examination (Wheeler et al., 2003).

Students take the examination online from any computer with Internet access at a convenient time on the last day of the attachment. This system has several advantages that expedite course administration, but also allows data about all aspects of the questions and students' answers to be collected but necessarily contains safeguards to prevent collaboration, collusion or the use of crib sheets or books (Ercole et al., 2002). Students must pass the anaesthesia and peri-operative medicine attachment before they can proceed to the Final MB examination.

Additional online drug administration teaching

Having established the need for better drug administration teaching, the attachment structure meant that there were several practical difficulties in ensuring that all students had the opportunity to receive it. A two pronged approach was chosen. A brief didactic session was introduced during the first lecture day, augmented by the additional online teaching module that had been written for the Doctors.net Continuing Medical Education foundation skills module (Appendix 1). The module was transferred on to the Clinical School's servers that host the ERWeb (Wheeler et al., 2003) allowing data to be collected about which students had accessed the module and when. All students were invited by email to undertake the module as a means of guaranteeing a consistent level of teaching despite their widespread distribution throughout the region. Although the importance of drug administration skills and the likelihood of formal assessment in the topic were stressed in the invitation, the completion of the module was not compulsory.

Assessment of the efficacy of the online teaching module

The efforts to improve drug administration teaching were driven by the extent of the students' deficiencies in drug administration skills documented herein, and the grave clinical consequences of medication errors in general. Poor understanding of drug administration has been consistently identified as one of the main causes of drug error. Better teaching is therefore a key intervention, and the research presented in the following chapters explores whether the online module was effective in improving students' written and practical drug administration skills by assessing whether it:

- a) improved the academic performance of students in written tests of drug administration skills,
- b) improved the performance of students in a drug administration OSPE,
- c) improved the performance of students in a simulated critical incident scenario.

The use of written tests to assess the efficacy of the online module

Methods

All 130 final year medical students in the University of Cambridge from the 2002 intake were invited to participate in additional online drug administration teaching during the anaesthesia and peri-operative medicine attachment in 2004. The respondents' identities and the number of web pages of the teaching material they viewed were recorded. The latter was used as a surrogate of the amount of time a student spent looking at the module. To test the short term efficacy of the module, the six multiple choice questions from figure 11 (page 71) were incorporated into the online negatively-marked anaesthesia examination taken two weeks later. All students' answers in all the questions in this examination were recorded, allowing performance in the drug administration questions to be compared with overall performance to control for some students' greater academic ability and / or keenness. Further data were collected about students' performance in the Final MB examination six months later as a second indicator of ability or keenness. As a result of the negative marking scheme, the probability of giving a correct answer was calculated for each student to allow later statistical modelling. Data were analysed as described in Chapter 4, but the further statistical modelling was performed with R (www.r-project.org) and with the kind assistance of Dr Raymond Salvador of the Wolfson Brain Imaging Centre, University of Cambridge. The study protocol was approved by the local ethics and research committees.

Results

Sixty-eight students (52.3%) tackled the online module, viewing on average 39 web pages (range 1 – 187, median 26, interquartile range 69). The marking structures and students' results in each of the examinations are shown in Table 8, which are represented in figure 20 having been divided into quartile groups based upon the number of web pages of the module viewed.

	Mean score	Median score	Range	Interquartile range	Examination type
Drug administration MCQs in anaesthesia examination	3.95	4	-4 – +6	4	Negatively-marked MCQs
Anaesthesia examination overall	66.7%	68.0%	31 – 90%	17.0%	Negatively-marked MCQs
Finals overall	182	182	176 – 191	5.5	Close marked written, oral and clinical

Table 8: A summary of marks obtained by students in the drug administration questions of the anaesthesia examination, the anaesthesia examination as a whole, and the Final MB examination. Abbreviation used: MCQ – multiple choice question.

The use of objective structured practical examination to assess the efficacy of the online module

Methods

All students sit an OSPE as part of the Final MB examination. This is held up to six months after the anaesthesia and peri-operative medicine attachment. The OSPE consists of 20 stations that test a variety of practical skills. These include communication skills, practical procedures such as urethral catheterisation or lumbar puncture, and for the purposes of this study two drug administration questions were incorporated. The students' marks in these drug administration questions were recorded. The marks given for each station were converted into a percentage.

Results

The students' results in the OSPE and Final MB examinations are shown in Table 9, which are represented in figure 21 having again been divided into quartile groups based upon the number of web pages of the module viewed.

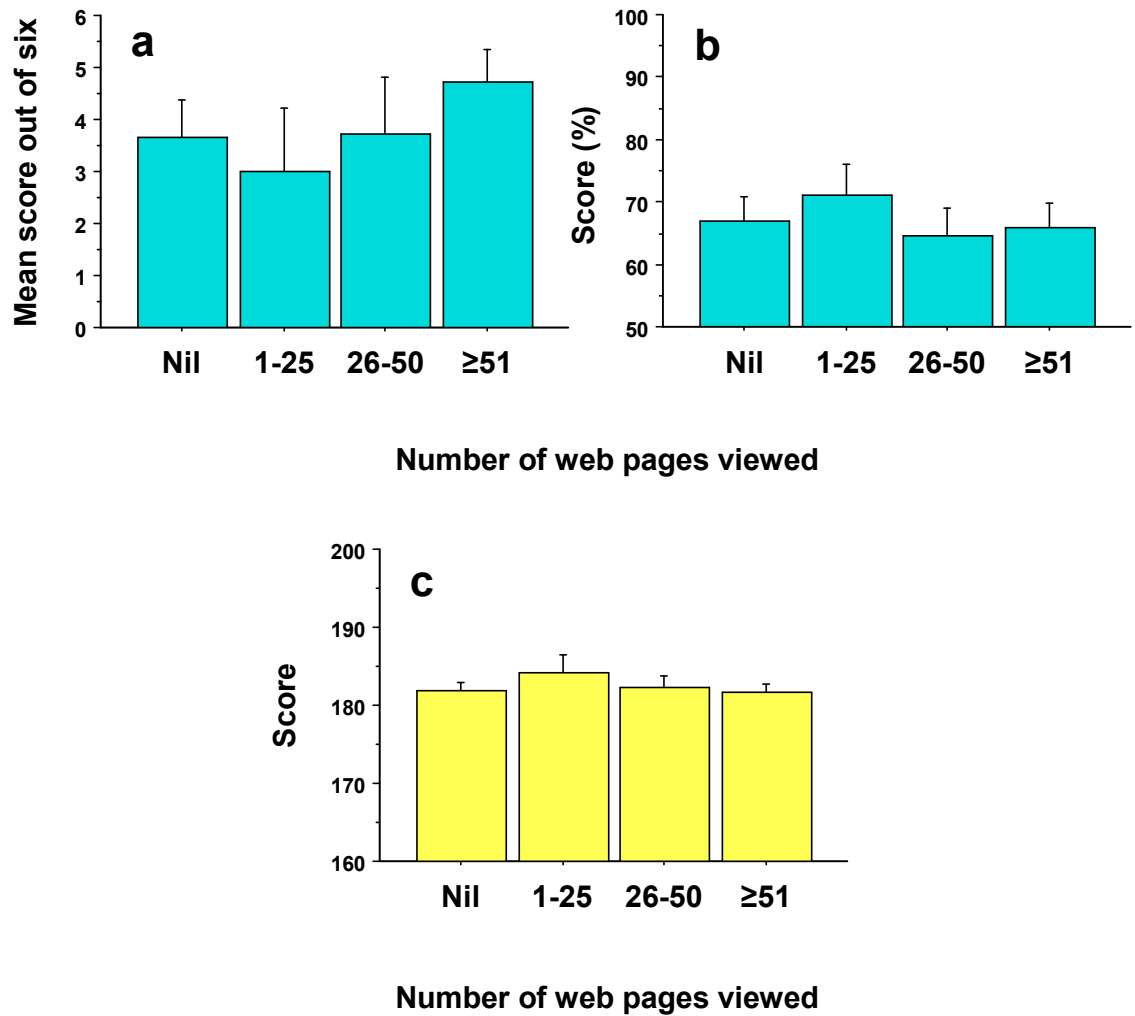


Figure 20: Graphs to show the students' scores A) in the drug administration questions of the end of attachment anaesthesia MCQ examination B) overall in the end of attachment anaesthesia MCQ examination C) in the Final MB examinations. Students were divided into quartiles by the number of web pages viewed, shown on the x-axes. Error bars represent 95% confidence intervals. For further statistical analysis see Results.

	Mean score	Median score	Range	Interquartile range	Examination type
OSPE intravenous drug administration	80.2%	82.5%	35 – 100%	20.0%	OSPE. Mark out of 20 converted to percentage.
OSPE dose calculation	77.9%	90.0%	0 – 100%	45.0%	OSPE. Mark out of 15 converted to percentage.
OSPE overall	84.7%	85.0%	55.0 – 94.0%	6.0%	OSPE. Accumulated percentage scores at 20 stations.
Final MB examination	182	182	176 – 191	5.5	Close marked written, oral and clinical

Table 9: A summary of marks obtained by students in drug administration questions and overall examinations and an explanation of the format of each examination. Abbreviations used: MCQ – multiple choice question, OSPE – objective structured practical examination.

Statistical modelling of results

The students were not randomised to undertake the online module, for reasons that are examined in the Discussion below (page 105). For this reason, the statistical analysis of the data was considerably more complex than for a simple randomised study, because of potentially confounding factors. For example, it would not be unreasonable to argue that students that had taken the extra time to study the online module were more keen than those who did not, and thus likely to be more successful generally in all written assessments. This is why more general data about students' performances in other examinations were collected, and used in the statistical analysis. This is divided into several steps that follow an iterative, deductive logic.

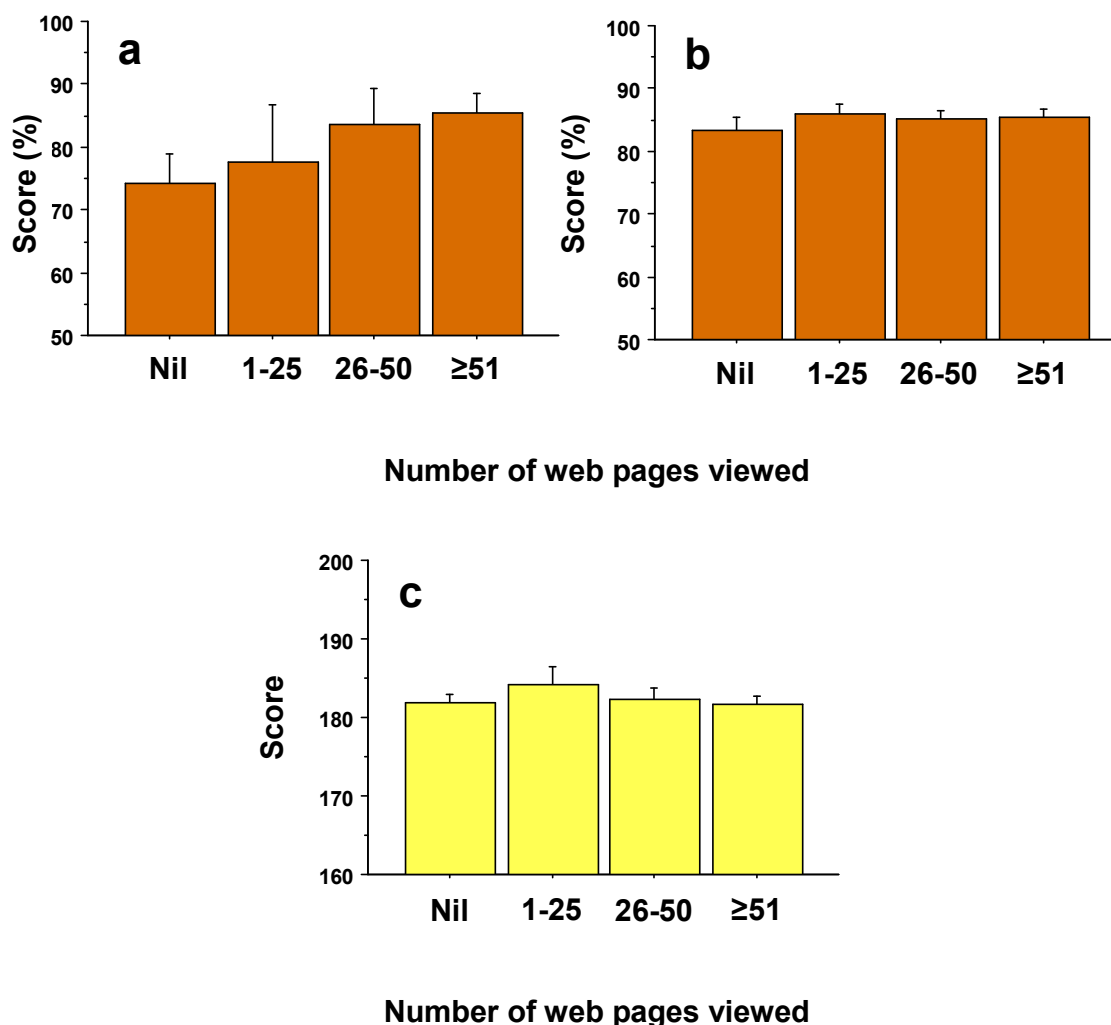


Figure 21: Graphs to show the students' scores a) in the drug administration questions in the OSPE b) overall in all 20 stations of the OSPE and c) in the Final MB examination. Students were divided into quartiles by the number of web pages viewed, shown on the x-axes. Error bars represent 95% confidence intervals. For further statistical analysis see Results.

Construction of individual models with a single independent variable

There are two variables that may explain any change in the students' scores in the six drug administration questions of the anaesthesia examination, although these

Students' academic ability could also explain better performance in the drug administration questions. To assess this, the marks in the drug administration questions were subtracted from the total marks in the anaesthesia examination to give the total mark for the rest of questions, used as a surrogate of general ability and / or willingness to learn. Fitting these parameters into a second GLMM also shows a positive relationship of the same strength (figure 23, $z = 3.22$, $p = 0.001$), suggesting that academic ability also plays a role.

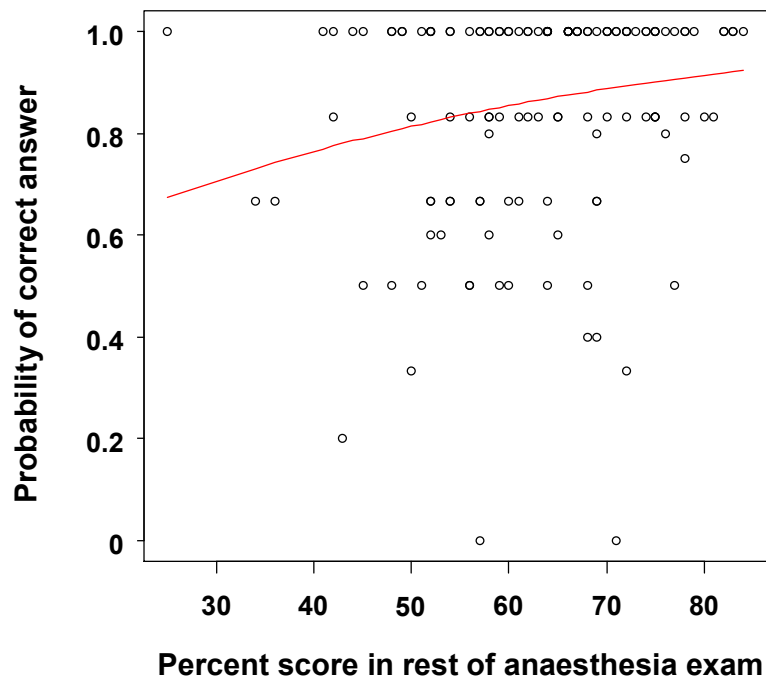


Figure 23: GLMM 2 – The **red** line represents the best fit linear regression curve showing a positive relationship between the probability of a correct answer in the drug administration questions and performance in the rest of the anaesthesia examination ($z = 3.22$, $p = 0.001$).

The relationship between the two variables fitted separately

Finding positive relationships between both variables and performance in the six drug administration questions raises the possibility that they are not independent and are confounding each other. The more able and enthusiastic students may have taken the online module more seriously, falsely overestimating its value. If the module was compulsory then an average or poorly performing student would be expected to have a worse performance than that predicted by the first model.

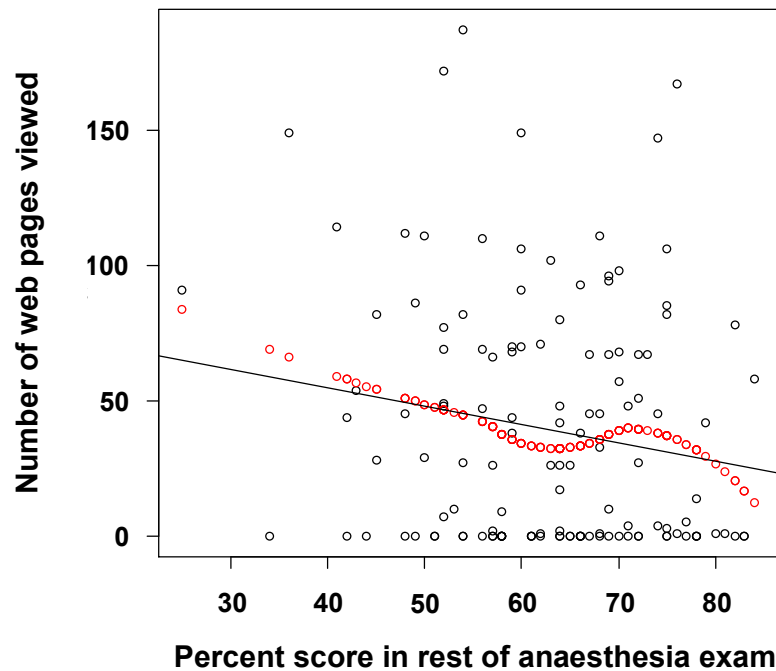


Figure 24: The negative relationship between the probability of a correct answer in the general questions of the anaesthesia examination and the number of web pages of the online module viewed. The black line represents the result of simple linear regression, the red dots are values given by a local regression (LOESS) algorithm (see Appendix 4).

Surprisingly, plotting the number of web pages viewed against the scores in the general questions of the anaesthesia examination reveals a negative relationship, suggesting that those *least* likely to succeed in the anaesthesia examination spent *longest* studying the online module (figure 24).

There are two plausible explanations for the findings so far. First, less academically able students may prefer to study using the computer over other means. In this case, the effect of the online module on performance in the drug administration questions, as measured in the first fitted model, would be underestimated. Alternatively, students may have spent time studying the online module at the expense of the rest of the curriculum (time being a limited resource for the students) and hence did poorly in the general questions in the anaesthesia examination.

Therefore Final MB examination marks were substituted for performance in the general questions of the anaesthesia examination as the indicator of overall academic ability, as performance in this examination could not realistically have been affected by studying the online module. This plot (figure 25) shows a negative relationship between the number of web pages viewed and the mark in the Final MB examination, supporting the (first) explanation that less capable individuals spent more time studying the interactive module.

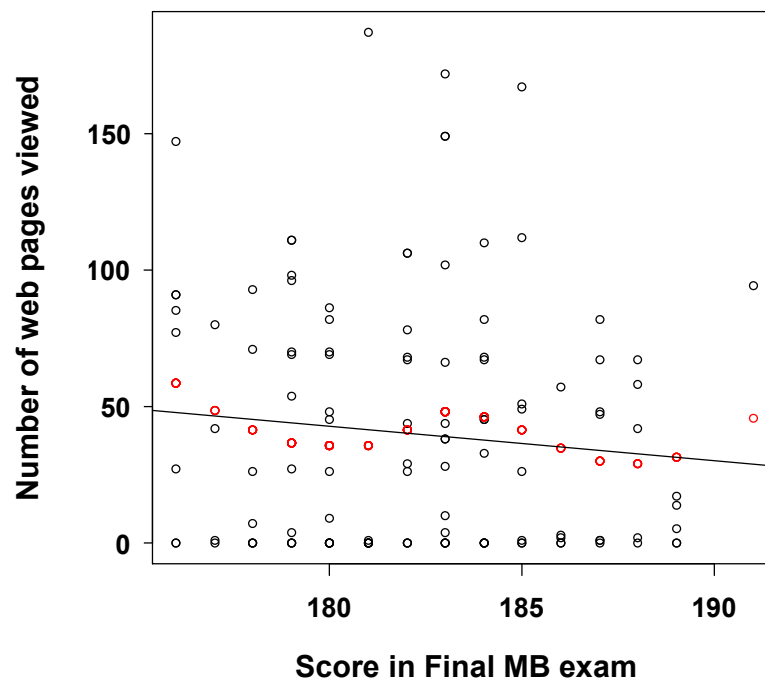


Figure 25: The negative relationship between the number of web pages of the online module viewed and the score in the Final MB examination. The black line represents the result of simple linear regression, the red dots are values given by a local regression (LOESS) algorithm (see Appendix 4).

Does the online module influence practical performance up to six months later?

Further GLMMs were fitted with the results from the two drug administration stations in the OSPE rather than the performance in the anaesthesia examination. To model the OSPE station results in the same way it was assumed that their mean was a binomial with $n = 100$. Although this interfered with some of the

outputs of the statistical analyses, the estimates of the coefficients for web pages viewed remain comparable.

A third GLMM examining the relationship between the number of web pages viewed and performance in the OSPE stations reveals a positive relationship, as shown by the green line in figure 26. For comparison, the red line shows the result of GLMM1 from figure 22, which represents the short term effect of the module on knowledge of drug administration skills.

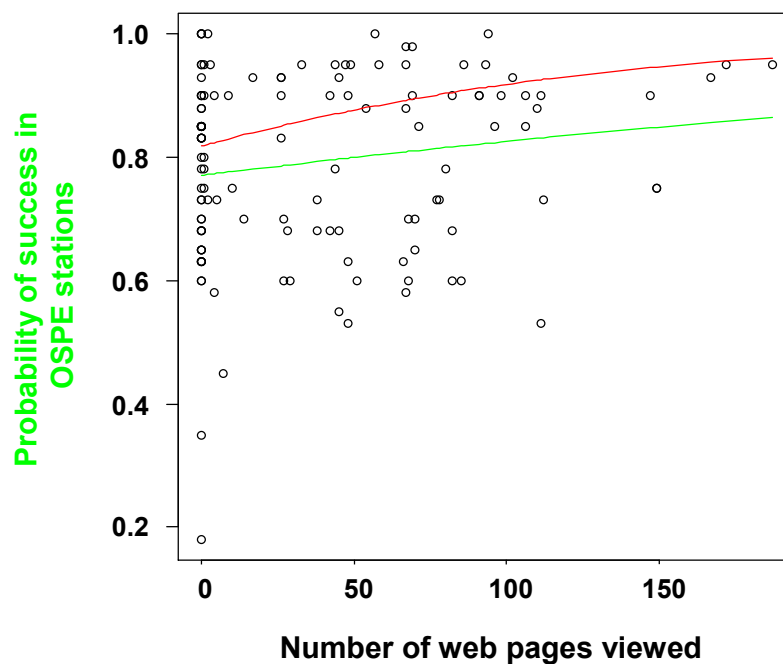


Figure 26: GLMM 3 – Scatter plot of the averaged OSPE value (ranked from 0-1) in green viewed with the line of GLMM1 (in red) from figure 22.

As the green line is clearly below the red line, the probability of success in the two OSPE stations was lower than in the drug administration questions of the anaesthesia examination. This may be because the OSPE was harder than the drug administration multiple choice questions, that the OSPEs do not usually lead to 100% scores, or that individuals' knowledge of the subject was declining. Notably the gradient of the red line in figure 26 is steeper than the green line; in the log odds scale this is translated to a coefficient (0.0091) greater than that of

GLMM3 (0.0034) suggesting that although knowledge acquired through the course is still present, it has much less weight.

Discussion

After correcting for potential confounding factors, the positive correlation between students' performance in the drug administration questions and the number of web pages viewed suggests that the online teaching material had a positive influence on their knowledge of drug administration that waned over time.

A potential criticism of this study is that the students were invited to participate in additional teaching rather than being randomised. The possible confounding factor of keener students being more likely to undertake the online module was taken into account by recording students' overall examination marks as indices of general ability. These analyses perhaps surprisingly showed that the *less* academic students spent more time on the teaching and gained most benefit from it.

There are several arguments in favour of inviting students rather than randomising them. First, medical students are notoriously competitive and worry constantly about their performance in assessments and examinations. They can be very resourceful and frequently share information about teaching and learning, so many of those randomised not to view the additional teaching may have managed to do so. Second, by incorporating drug administration questions into later examinations, it was possible to assess long-term retention of information. These examinations are integral to students' progress through medical school and randomisation would have put half the students at a disadvantage. In this way, the study was conducted without alerting the students to any interest in their long-term knowledge of drug dose calculation. Inevitably most students would have revised the topic had they known, introducing a major confounding factor. The chosen study design more accurately reflects the realities of teaching medical students, was more equitable and yielded data that could not have been obtained

within the constraints of a rigid randomised trial. For example, a randomised trial would not have shown that only about half of students are likely to participate in voluntary online teaching. One disadvantage was that the statistical analysis was much more complex: interpreting the results from an observational study will always have an exploratory nature, and some of the variables used were surrogates for the real factors of interest.

The data presented in Chapter 3 showed students' poor understanding of parenteral drug administration, with knowledge seemingly absorbed by osmosis rather than as a consequence of formal teaching (Wheeler et al., 2004b). As the clinical pharmacology curriculum evolves to encompass cell and molecular biology, drug administration is at risk of being neglected. This study shows that an online teaching module can improve some students' drug administration knowledge, but that the offer of additional teaching is only taken up by roughly half. For topics about which students tend to lack knowledge or tend to be overlooked, online teaching can complement classroom teaching.

Drug administration skills may seem basic or mundane but it is vital for patient safety that they are properly taught and reinforced at medical school. Doctors working in all clinical disciplines involved in drug application should collaborate to teach and reinforce these skills throughout medical school so that the knowledge may be retained better. The arithmetic involved in drug dose calculation is simple and all medical students and doctors should be capable of answering the six drug administration questions correctly. The fact that they cannot reflects the human tendency to make slips and errors (Reason, 1990) and strengthens the argument for improving drug labelling (Wheeler and Wheeler, 2004c).

For topics that can be overlooked, online teaching may be able to plug gaps in students' knowledge. However, online modules must be engaging, useful and educational – rather than lecture notes simply transferred to a web page – to ensure that students are motivated to access them. The data presented in this chapter suggest that the module is effective, but the statistical analysis proved to be complex. Whilst this may be a valid way of assessing the educational value of

a teaching resource, it cannot be argued from these findings that the module improves clinical performance rather than just academic performance. A further study was conducted to assess the impact of the online module on students' performances in simulated critical incident scenarios.

CHAPTER 6

THE INFLUENCE OF IMPROVED TEACHING ON MEDICAL STUDENTS' CLINICAL DRUG ADMINISTRATION SKILLS

Measuring clinical performance using high fidelity simulation

The evidence that the online module improves academic performance in written tests is encouraging, but it is not possible to extrapolate these findings to say that the module improves patient safety. However it must be hoped that a better understanding of prescribing and drug administration would benefit the patients for whom these students will be responsible once they have qualified.

To assess whether the module might also improve clinical skills, a study was devised that examined the influence of the module upon students' performances in a simulated critical incident scenario. Medical students are not permitted to prescribe or administer drugs to patients unless under strict supervision, therefore the high fidelity patient simulator is the ideal environment in which to test the impact of the additional teaching. Use of the simulator allowed the competence with which the medical students were able to prescribe the correct dose of drug to be assessed, and also provided an ideal opportunity to identify what aspect of drug administration the students found difficult and at what point problems were encountered.

A mannequin connected to a computer and placed in a realistic environment such as an operating theatre with people acting the roles of the staff allows situations closely resembling that of the real working environment to be created. These complex machines have been called 'full scale' (Seropian, 2003), 'realistic' (Seropian, 2003; Wong et al., 2004) and 'high fidelity' (Schwid, 2000) simulators.

The most common use of simulators is for teaching and training. In a recent worldwide survey, the majority of the respondents (77–85%) indicated that they

were using the simulator for teaching purposes (Morgan and Cleave-Hogg, 2002). There are a number of reasons for their popularity in being used for training in anaesthesia (Gaba, 2000):

1. They simulate a high degree of reality;
2. No risk to a real patient;
3. Predictable, programmable, and reproducible scenarios presented;
4. Repeated assessments are possible;
5. Allows for practice on rare clinical scenarios;
6. Videotaping allows for review;
7. Simulation can be stopped or restarted for teaching.

One of the seminal uses of high fidelity simulation in anaesthesia is in training and rehearsing for crisis management. Studies in error evolution and critical incidents in anaesthesia have shown that human error is a major contributor (up to 80%) (Cooper et al., 1989; Fletcher et al., 2002). Also many life-threatening anaesthetic emergencies such as malignant hyperthermia have an incidence of less than one in 10 000, therefore the opportunity to encounter them in actual clinical practice may not occur during the course of an anaesthetist's career (Chopra et al., 1990). Moreover, the traditional training of anaesthetists does not address teaching crisis management in a systematic way (Howard et al., 1992). Drawing from the experiences of the aviation industry, Gaba noted that in order to be effective, these skills must be actively taught rather than acquired through reading or by *ad hoc* bases (Gaba, 2000). The simulator allows the opportunity for repeated practice, which has been shown to be a crucial factor in developing expertise (Issenberg et al., 1999). As a result, Anesthesia Crisis Resource Management (ACRM) courses analogous to courses in Crew (Cockpit) Resource Management (CRM) conducted in commercial and military aviation have been developed to address these training issues (Howard et al., 1992).

The success of the use of the simulator for the ACRM has resulted in a broadening of simulator use in anaesthesia, and now some centres are using simulation for medical student teaching (Morgan and Cleave-Hogg, 2002). High fidelity patient simulation has been used to demonstrate basic airway skills, principles of

cardiopulmonary physiology, and to provide an introduction to the practice of anaesthesia, as well as aspects of critical care (Morgan and Cleave-Hogg, 2002). The medical student may often be relegated to the position of being an observer in many clinical situations due to issues of patient safety. The simulator allows for simulated scenarios to be demonstrated and for the medical student to actively participate without patient harm.

The METI Human Patient Simulator (HPS) high fidelity patient simulator consists of an adult or paediatric mannequin supported by a computer controlled gas module that physically simulates the uptake and release of gases and vapours (Cumin and Merry, 2007). Hydraulic pumps driving flexible tubing mimic pulsatile arteries and in addition heart sounds, breath sounds and even pupillary reactions can be created and manipulated. Computerised algorithms control the mannequin's response to physiological insults and drugs, which can be further tailored to the operator's requirements. This equipment was installed at Addenbrooke's Hospital in 2004 under the aegis of the Postgraduate Medical Centre.

High fidelity simulation therefore offered the ideal opportunity to examine to what extent the online teaching module improved medical students' practical, clinical skills in drug administration rather than academic knowledge. To avoid the previous complications associated with inviting students to view the module, the study was conducted as a randomised, blinded and controlled trial. Students undertook a simulated critical incident scenario having previously been randomised into two groups. The first group were contacted via the ERWeb seven days before their appointment with an invitation to view the module. The second group undertook the module without the prior opportunity to view the module, but were permitted to view it afterwards. The online module was not compulsory, however.

Methods

Permission to conduct the study was gained from the local ethics committee. Final year medical students from the 2003 intake consented to undergo one 15 minute session in a high fidelity patient simulator (METI HPS, Sarasota, FL, USA). Before the appointment was offered, the students were randomised into two groups. One group was invited to undergo the online teaching module within the week before their session, although this teaching was not compulsory. The second group was referred to the teaching module after their simulator appointment, so as not to deprive these students of the opportunity to learn essential clinical skills. In this way, each student's performance in the simulator could be used to assess the impact of the additional teaching upon his or her drug administration skills. Although the teaching module does not include the exact drug doses relevant to the scenario, it teaches the generic skills required to convert ratios and percentages to mass concentration (Appendix 1).

Critical incident scenario for medical students

The candidate was given the role of a recently qualified hospital doctor working in the emergency medical admissions unit. A senior nurse, played by one of the simulator centre staff, was available to assist them. The students were asked to assess an elderly man who had tripped and fallen at home, sustaining a pretibial laceration. The patient was receiving antibiotics for a pulmonary infection, but is allergic to penicillin. Students were asked to calculate an appropriate volume of 1% lidocaine with which to suture the laceration, on the basis of his weight (60 kg) and the maximum safe dose of lidocaine (200 mg or 3 mg.kg⁻¹). Whilst the candidate prepared the suturing equipment, the nurse (played by Louise Murray) gave the patient intravenous penicillin that had been erroneously prescribed earlier by a more senior doctor, resulting in acute anaphylaxis. The adrenaline available was presented in a 1 mL ampoule labelled 1:1 000 adrenaline. Hence the student needed to make the conversions from 1% to 10 mg.mL⁻¹ and 1:1 000 to 1 mg.mL⁻¹ whilst under pressure.

Interventions were made to help the candidate when appropriate. For example, the nurse told candidates the maximum safe dose of lidocaine if they did not know it, or referred those unfamiliar with the treatment of anaphylaxis to a protocol that specified a 0.5 mg intramuscular dose of adrenaline but did not mention ratios (Appendix 2). All students were given access to the current edition of the British National Formulary (BNF, 2006) and other emergency protocols that would normally be available to them in an acute referral department. At the end of the scenario candidates underwent a five minute debriefing.

Audiovisual recordings of the scenarios were made. Investigators blinded to each student's randomisation status subsequently scored each drug administration episode using the criteria shown in Table 10. A total score was calculated for each student by simple addition of each of his or her scores. This allowed the impact of the teaching upon the administration of each drug and each student's overall performance to be examined.

Score	Definition
3	Student knows drug dose and makes calculation without assistance
2	Student does not know dose, but makes calculation after consulting protocol
1	Student does not know dose and requires help with calculation
0	Student gives incorrect answer or runs out of time

Table 10: The system used to score each student's drug administration episode in the simulated critical incident scenario.

Statistical considerations

Power analysis suggested that 24 participants would be required in each arm of the study to achieve a significance level of 5% and study power of 80%. Randomisation was performed using an on-line research randomiser (<http://www.randomizer.org>). Data were analysed using non-parametric statistical tests, as the rating scale of the student's performance was nominal. Fisher's exact test (Appendix 4) was carried out using Statview to compare groups and determine the statistical significance of all data.

Results

Appointments were offered to 48 students and 44 (92%) attended. Twenty of the students who participated in the study were directed to the on-line teaching module before their appointment but only 9 students (45%) undertook it. Therefore 35 students undertook the scenario without first seeing the on-line module (Figure 27).

Ability of medical students to prescribe lidocaine under simulated conditions

Figure 28 shows the number of students that attained a particular score for administration of lidocaine depending on whether they had undertaken the online module. Only one of the 44 students scored 3. This student knew the safe dose of lidocaine and that a 1% solution contains 10 mg.mL^{-1} , so calculated the correct volume to give without any external help. This student was subsequently found to have studied the teaching module.

From the remaining eight students who looked at the teaching module, six scored 2. They did not know the safe dose of lidocaine, but having been told this by the assisting nurse converted the percentage to mass concentration correctly and worked out the correct volume. The other two students scored 1 as they had to be

told that 1% lidocaine equates to 10 mg.mL^{-1} by their assistant before working out the correct volume.

The scores of the students who did not view the online module before their appointment are skewed to the right of the graph in Figure 28 with 51.4% of the

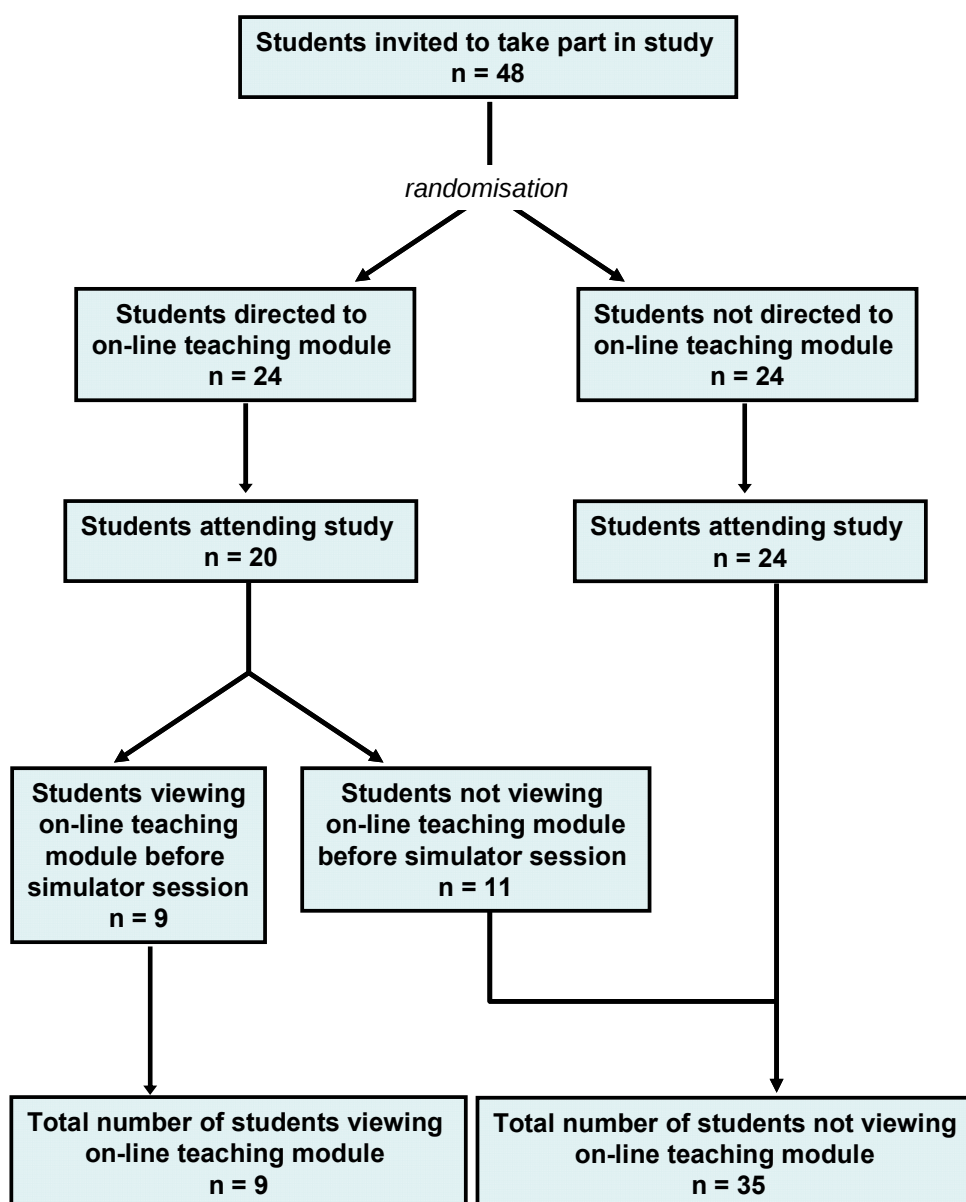


Figure 27: Schematic representation of the number of students who took part in the study.

students (18/35) scoring 0. These students were either unsuccessful in completing the calculation or came up with the wrong volume of lidocaine. Nonetheless several students who did not look at the extra teaching did fare better with nine scoring 1 and eight scoring 2.

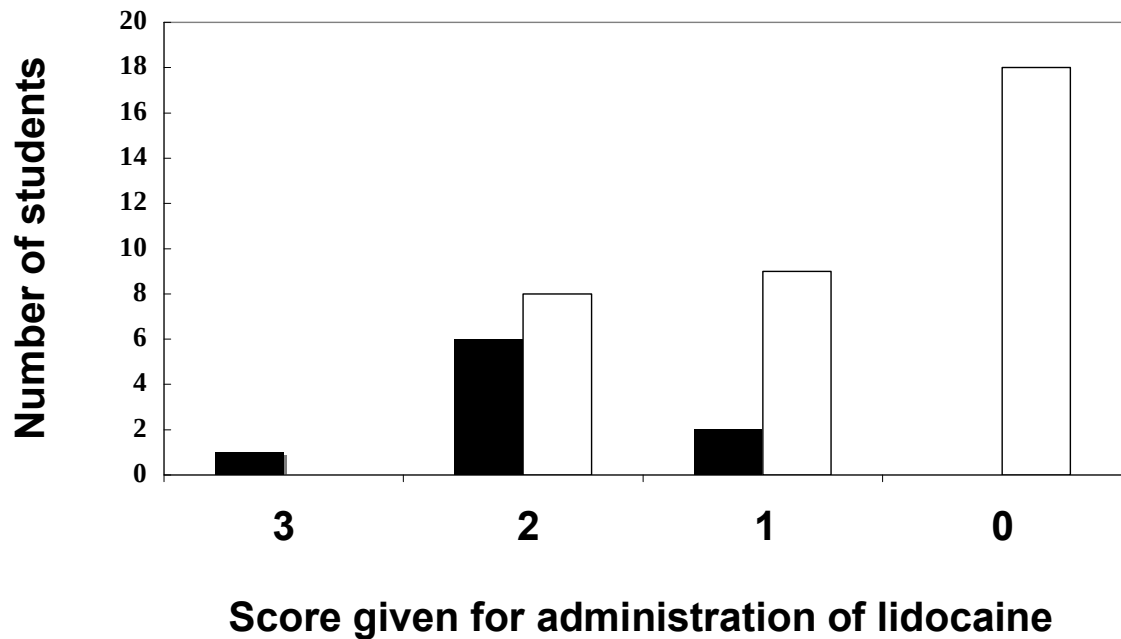


Figure 28: Bar chart to show the distribution of the students' scores for the administration of lidocaine in the simulated emergency scenario. Black bars represent students that had undertaken the online teaching and white bars represent those that did not.

Administration of adrenaline by medical students under simulated conditions

Figure 29 shows the distribution of student scores for the prescription of adrenaline depending on whether the additional teaching had been undertaken. All students who had consulted the teaching module scored either 2 or 3 (five and four students respectively). Although all nine students asked for 0.5 mL of 1 in 1 000 adrenaline and were aware that this was equivalent to 0.5 mg of adrenaline, those students scoring 2 had needed to consult the anaphylaxis

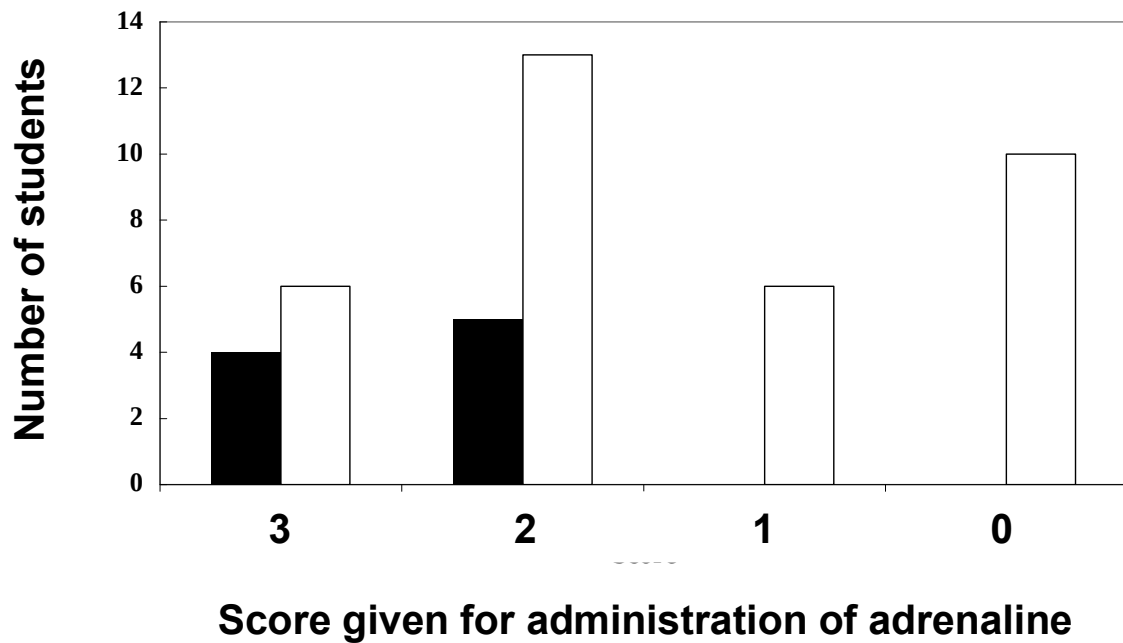


Figure 29: Bar chart to show the distribution of the students' scores for the administration of adrenaline in the simulated emergency scenario. Black bars represent students that had undertaken the online teaching and white bars represent those that did not.

protocol. None of the students who had undertaken the teaching module scored 1 or 0.

Whilst all the students viewing the online teaching scored either 3 or 2, of the 35 students who did not complete the teaching module, six scored 3 and thirteen scored 2 (54.3% combined); the remaining sixteen scored 1 or 0. Six students were only able to calculate the correct volume after being told how to convert a ratio to mass concentration (score 1), and ten could not complete the calculation or gave an incorrect answer even with the aid of the protocol and scored 0.

Influence of the teaching module on students' ability to calculate drug doses

The above data were analysed to determine the influence of the teaching module on the administration of lidocaine and adrenaline. For these analyses, the students invited to view the module before the scenario were compared against those attending the scenario first. In essence, the test compares the effect of being

invited to view the module on clinical performance, but in reality corrects for any lack of enthusiasm that may have existed amongst the 11 who did not take up the invitation. Despite this adjustment, the teaching module significantly improved the administration of lidocaine (χ^2 $p = 0.005$) and adrenaline (χ^2 $p = 0.0002$, Fisher's exact test). The influence of the teaching upon each student's overall performance was also examined using the sum of the scores for each drug administration episode. This analysis also revealed a statistically significant benefit (χ^2 $p = 0.0007$). The magnitude of the improvement is shown in Figure 30.

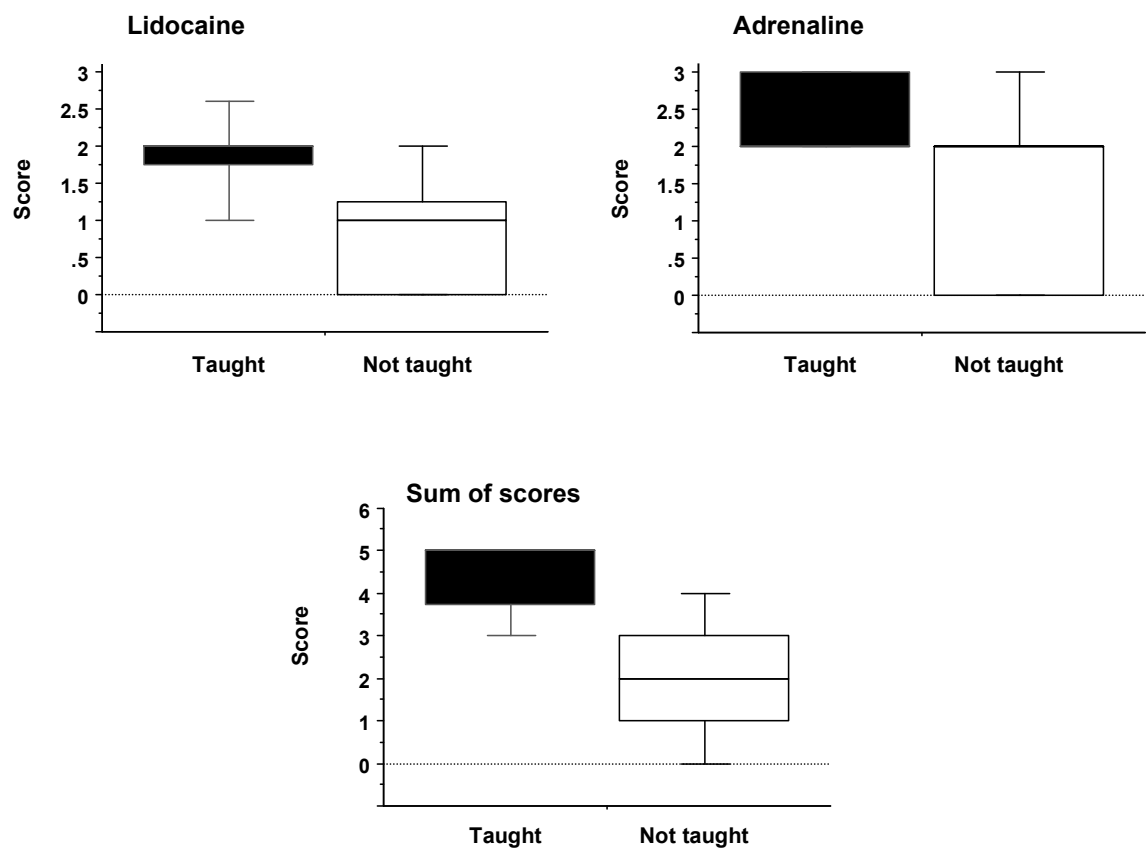


Figure 30: Box and whisker plots showing the median and interquartile range of scores obtained by the students for the administration of lidocaine, adrenaline and both drugs in the simulated critical incident scenario. The black boxes represent students that had undertaken the online teaching and the white boxes represent those that did not.

Discussion

Having previously shown that medical students' knowledge of drug doses and calculations is improved after viewing web-based teaching modules, this study examined whether such teaching could also improve students' drug administration skills in more stressful and realistic conditions. In the scenario described above, the students were expected to calculate the correct volume of drugs to give patients, whilst also taking a history, examining the patient and preparing for a practical procedure.

The results show that medical students' ability to prescribe the correct dose of a drug under simulated conditions was significantly improved if they had previously viewed the additional web-based educational material. Those students who viewed the teaching module before attending the simulator centre performed significantly better than those that did not view it, or who were not directed to it before their session (Figure 30). The magnitude of the improvement was sufficient to show a highly statistically significant benefit despite the fact that not all students randomised to receive additional teaching actually undertook it. Only 45% of the students directed to the website viewed the material, once again a disappointingly low proportion but similar to the study conducted in the previous year's intake and reported in Chapter 5 (Wheeler et al., 2006). This suggests that online teaching is only likely to reach half the intended audience at best. In contrast, the medical students were very enthusiastic about partaking in a simulator session, with 92% attending. Feedback was also very positive with several students asking for further appointments.

Figure 27 shows that although 24 students were invited to the simulator and directed towards the teaching module, only 20 attended. However, all 24 students invited to the simulator but not directed towards the teaching module attended. It could be argued that the module actively discouraged some students from attending. Using the principles of intention to treat (or, in this case, 'intention to attend') all four of these students might have viewed the module, but all four might have scored 0 if they had attended the simulator. If the data are reanalysed to take this 'worst case scenario' into account, the influence of the module upon

the students' ability to administer lidocaine accurately is no longer significant (χ^2 $p = 0.123$). This reflects the fact that the calculations involving lidocaine presented the greatest difficulties, and that the module was probably less effective in resolving them. The magnitude of improvement seen in the administration of adrenaline was sufficiently great for the module's influence on both adrenaline administration and sum of scores to remain statistically significant (χ^2 $p = 0.004$ and 0.010 , respectively).

Use of the simulator allowed all the steps taken by the medical students in the drug calculations to be examined. In contrast, the multiple choice questionnaire format used previously (Wheeler et al., 2004b; Wheeler et al., 2004a; Wheeler et al., 2006; Wheeler et al., 2007) can only establish correct *versus* incorrect answers, cannot account for those who guess correctly, and gives no information about *why* a particular answer was given. The simulated critical incident scenarios were ideally suited to answering these questions, and provided valuable insights into the problems and confusion encountered by the students whilst under pressure. For example the vast majority of students did not know the maximal safe dose of lidocaine, or even that the dose could be calculated according to the patient's weight. In the pilot study reported in Chapter 3, 25.6% of final year students from the 2001 intake had answered this question correctly in a multiple choice questionnaire – but with five possible answers approximately 20% could have given the correct answer by guessing (Wheeler et al., 2004b). Guessing in a simulated scenario is far more obvious, indeed wildly differing suggestions were made as to the appropriate volume of lidocaine (“1 ampoule”, “2 vials”, “4 – 5 mL”, “50 mL”). It is hoped that students are happier to guess under simulated conditions rather than in “real life”.

A substantial number of the medical students were also confused by expressing the strength of the lidocaine solution as a percentage. Some thought that a 1% solution was equivalent to 1 g in 1 000 mL and others thought that it was 1 mg.mL^{-1} , leading to order of magnitude errors. Many gave up on the calculation or sought refuge in the BNF, and were so shocked to find that it does not contain the answer that they gave up. Several students who had been struggling with the

lidocaine calculation completed it quickly and correctly once they were made aware that a 1% solution is equivalent to 10 mg.mL⁻¹.

The students seemed to fare slightly better when it came to giving adrenaline (Figure 29). Only 22.7% scored 0 when calculating the correct dose, as opposed to 40.9% of students who could not calculate the correct volume of lidocaine. This may be because the dose of adrenaline recommended in the adult anaphylaxis protocol is independent of the patient's weight, or because the students are more familiar with the protocol. However, students were still prone to making errors when converting the ratio to mass concentration. Many of those that successfully did so took several minutes, resulting in an unsatisfactory delay in the treatment of the anaphylactic shock. These observations add further weight to the argument that expressing the strength of drug solutions as mass concentration instead of percentages or ratios may help improve the accuracy and efficiency of drug administration and reduce the possibility of dosing errors (Kelly and Henderson, 1983; Scrimshire, 1989; Rolfe and Harper, 1995; Wheeler and Wheeler, 2004c).

That the additional teaching significantly improves medical students' performance in simulated critical incident scenarios as well as written tests is very encouraging. As well as being statistically significant, it is also clinically significant. It can be argued that a rating of 2 for a drug administration episode is an acceptable standard – namely that if a student did not know the dose, they made the dose calculation correctly after consultation with a protocol. In light of the large reduction in the number of 1 or 0 ratings per drug administration episode when students have received additional teaching, this should result in a clinically significant benefit in real life situations hence improving patient safety. It is important to recognise that the improvements observed in this study are in the short term only, and follow up studies would be required to examine whether the effect was sustained. Also, making a connection between improved simulator performance and reduction in harm to patients is a surrogate outcome measure; substantial further improvements are needed and online teaching alone is clearly not the answer.

During the debriefings, the candidates expressed high levels of satisfaction with simulated scenarios and reported difficulty gaining ‘hands on’ experience of medical emergencies. Even though the simulator was being used as a research tool, it appeared to the students to be an engaging and exciting teaching experience in itself. High fidelity patient simulators are not widely available, and are expensive to establish and run (Kurrek and Devitt, 1997). Providing simulated scenarios for 44 medical students required a substantial commitment of time and personnel – the latter reflected in Acknowledgements (page 3). These constraints mean that in the University of Cambridge – and I suspect most others – it takes a great deal of effort and substantial funding to offer regular simulator teaching sessions to clinical medical students. Instead, perhaps it should be asked whether modern medical school curricula expose today’s students to fewer practical procedures and medical emergencies than their predecessors, and if so address the causes.

CHAPTER 7

THE EDUCATIONAL VALUE OF A SIMULATED CRITICAL INCIDENT SCENARIO

Does a session in the simulator have an intrinsic educational value?

Online teaching of drug administration skills has some benefit, but reaches at best only half the students and its effects wane over time. There was an improvement in the students' clinical performance in the simulated critical incident scenarios, but these took place within one week of viewing the module. As the students leave Cambridge having qualified it has not proved possible to invite enough back for a second appointment to examine whether the improvement in drug administration skills is sustained. In stark contrast to the online module, 92% attended the simulated scenario and there was a great deal of positive feedback. It therefore seemed worthwhile to investigate whether the simulator session might have its own intrinsic educational value, and how this might compare with the online module.

As well as students enrolled in the study already reported, other students from the same intake had attended the simulator centre and had taken part in other critical incident scenarios. In total, 72 out of the 130 students in the year attended the simulator centre in 2005. Amongst those who did not or could not attend the simulator, some had viewed the online module and some had not. Therefore each student could be assigned to one of four groups according to Table 11.

The randomised study had not been designed to assess the educational value of a single simulated emergency scenario. A minority of the students in the year group had participated, whilst others had received simulator training but were not enrolled in the trial. All students should have attended the lectures at the start of the anaesthesia and peri-operative medicine course, when they would have been formally taught drug administration skills. Also, all would have been invited to view the online teaching module, and data continued to be collected about which

Group	Teaching	<i>n</i>
A	Formal lecture only	41
B	Formal lecture and viewed online module	13
C	Formal lecture and attended patient simulator	41
D	Formal lecture, viewed online module and attended patient simulator	34

Table 11: The division of students into four groups on the basis of the intensity of their drug administration teaching, and the numbers in each group.

students had viewed the teaching and when. The drug administration skills of these students were also formally assessed in an OSPE station 6 – 9 months later. By recording the students' performances in this station, it could be established whether undertaking a simulated critical incident scenario or viewing the online module predicted a good performance in the OSPE, giving an indication of the relative importance of both teaching methods in the medium term retention of drug administration skills. Once again a potential confounding factor was that students who performed well in the simulator might reasonably be expected to perform well generally. To correct for this, comparison data were also collected from four unrelated OSPEs concerning suturing, the control of haemorrhage, male catheterisation and nasogastric tubes.

Methods

All students from the 2003 intake of the clinical medicine course were included in the study. Six to nine months before Final MB, the majority were offered an appointment in the high fidelity patient simulator. Students took part in one of three scenarios that required the calculation of two drug doses on the basis of the patient's weight and understanding of how to convert ratios or percentages to mass concentration. One of the scenarios was used exclusively for the study described above and reported in *Anaesthesia* in December 2006 (Degnan et al., 2006) and was described in detail on page 112. The second scenario required students to manage an elderly man with partially treated anaphylaxis caused by a

bee sting, who later became bradycardic as a result of an inferior myocardial infarction. The third scenario concerned the pharmacological and electrical cardioversion of a hypotensive patient with a ventricular tachyarrhythmia. Each scenario required the students to perform two of three tasks: calculate the volume of a solution expressed as a ratio, calculate the volume of a solution expressed as a percentage, and / or perform a microgram to milligram conversion.

The drug administration episodes were again graded according to the criteria in table 10. The sum of the scores was also calculated for each student. All students received formal teaching about drug dose calculation as part of the core lecture curriculum in the anaesthesia and peri-operative medicine attachment. Additionally, all students were able to access the supplementary online teaching module about drug administration from the specialty home page (Wheeler et al., 2003), but this teaching was not compulsory. The existence and value of the teaching module was stressed to students invited to the simulator. The students were thus divided into four groups on the basis of the intensity of the drug administration teaching they received (table 11, and see results).

All students undertook a question about drug administration as part of the OSPE element of the Final MB examination between 6 – 9 months later. This concerned the prescription of an aminophylline loading dose and infusion for a 50 kg woman admitted with acute severe asthma. The skills required to successfully complete this task had been taught in the formal lecture and online module, and had been required in the simulated scenario. Students were marked on criteria such as writing legibly, correctly calculating the loading and maintenance doses, and choosing the correct diluent, final volume, and infusion rate. The score out of 20 was converted to a percentage. The scores in four other, unrelated OSPEs were also recorded, for future comparison. As some OSPE stations were higher scoring than others, each student's score was divided by the mean score for that station to create a performance index, where a result of 1 meant that a student's OSPE station equalled the mean. An index score of less than 1 meant that the student's OSPE station score was below average, and greater than 1 meant that the score was above average. This technique was also used for the four unrelated OSPE stations.

Statistical analysis

None of the datasets were found to be normally distributed. They were subject to non-parametric testing using the Kruskal-Wallis test. The H statistic and p value are quoted in the figures and text. These data are represented in box and whisker plots that show the median, interquartile range and 10th – 90th centiles. Where appropriate, further comparisons between groups were made using the Mann-Whitney U test or the paired t test (Appendix 4).

Results

Of 129 students, 75 (58.1%) were invited to undertake a simulated emergency scenario and 72 (55.8%) attended. The attendance rate of those invited was therefore 96.0%. Of the 75 students reminded to view the online teaching module, 47 (54.7%) did so. Of the 54 students not invited to the simulator and who were not actively reminded to view the teaching module, 13 (24.1%) spontaneously followed the link from the anaesthesia and peri-operative medicine ERWeb page.

Does performance in the simulated scenario predict performance in the final OSPE?

A positive relationship between performance in the drug administration OSPE station and performance in the simulated scenario was evident. When students' drug administration OSPE station scores corrected for the mean are plotted against simulator performance the general trend towards improvement can be seen (figure 31), which proves to be statistically significant ($H = 13.0$, $p = 0.042$). Those scoring 1 performed worst in the final OSPE according to the Kruskal-Wallis rank of means. Those scoring 3, 5 or 6 performed significantly better than these students in the final OSPE ($p = 0.033$, 0.014 and 0.006 respectively). The positive effect was specific to drug administration. When performance in the simulator was plotted against that in the unrelated OSPE stations, no significant ratio was seen (figure 32, $H = 5.66$, $p = 0.462$), showing that the effect was not confounded by differences in students' general ability.

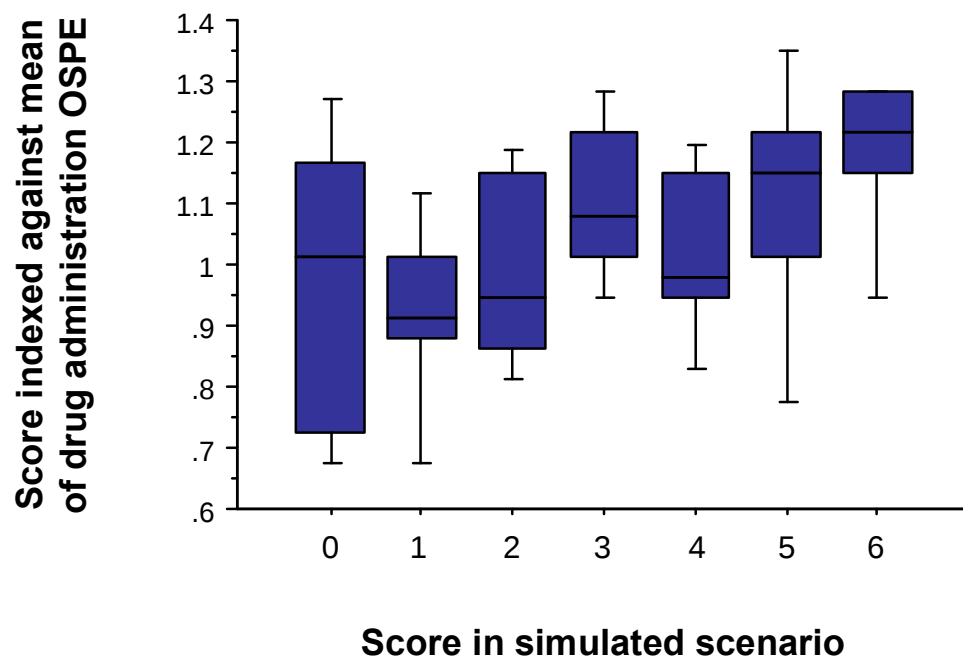


Figure 31: A plot of the performance in the simulated critical incident scenario against the index of students' marks in the drug administration OSPE corrected against the mean score for that station.

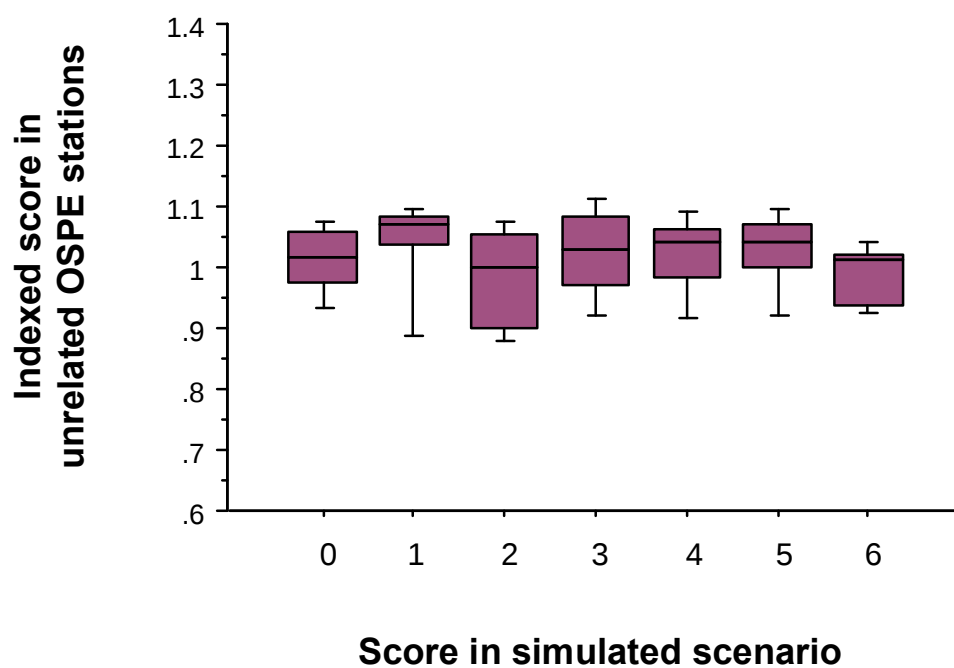


Figure 32: A plot of simulator performance against the indexed mean of the marks obtained in the four unrelated OSPEs.

Do those viewing online teaching and/or attending the simulator do better in the drug administration OSPE?

A similar trend of a positive relationship between the intensity of drug administration defined by the teaching group A – D and OSPE drug administration station performance was found (figure 33), which again was statistically significant ($H = 11.0$, $p = 0.012$). Those attending the simulator and viewing the online teaching in addition to the formal lecture (i.e. those in group D) performed significantly better than those students that did not attend the simulator (Group A, $p = 0.002$ and Group B, $p = 0.038$). Although those in group C, who only attended the patient simulator, appear to perform better than those who only attended the lecture the magnitude of the difference was not statistically significant ($p = 0.108$ when compared to Group A). A plot of the mean scores of the four unrelated OSPEs against simulator performance (figure 34) again shows no relationship ($H = 3.49$, $p = 0.322$).

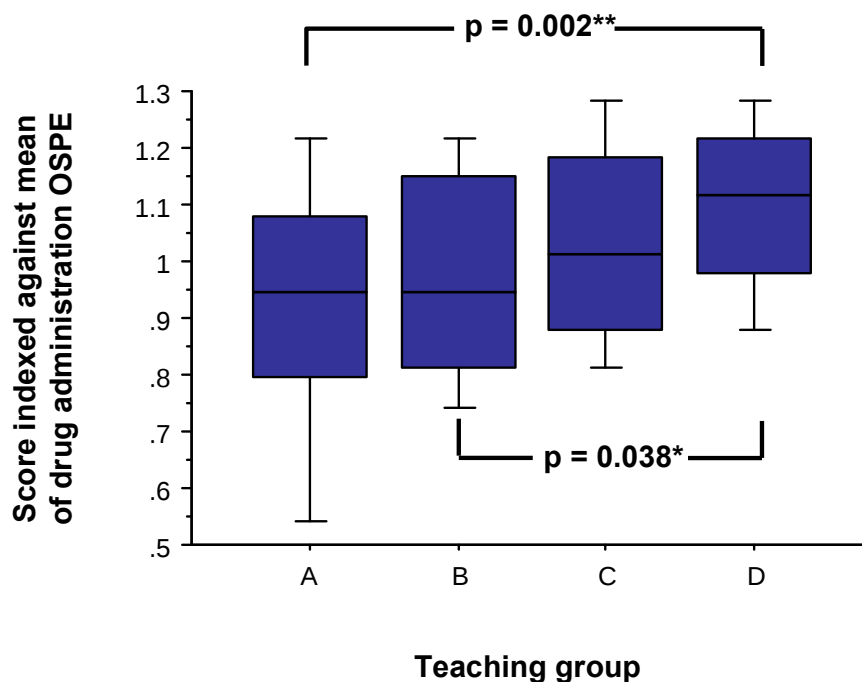


Figure 33: A plot of the intensity of drug administration teaching (table 11) against the index of students' marks in the drug administration OSPE corrected against the mean score for that station.

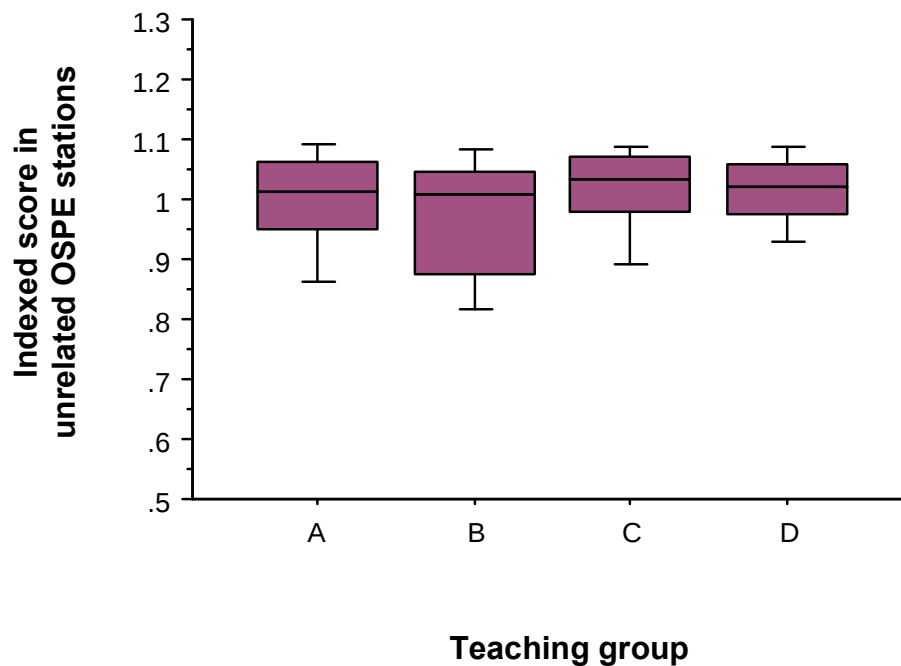


Figure 34: A plot of the intensity of drug administration teaching (table 11) against the indexed mean of the marks obtained in the four unrelated OSPEs.

Discussion

These results show that an intensive approach to the teaching of drug administration skills improves medical students' knowledge in the medium term. Students who viewed the online drug administration teaching module *and* attended a simulated critical incident scenario in which drug administration skills were tested fared significantly better in an OSPE 6 – 9 months later than those who received standard teaching and those who had viewed the module alone. Significant differences were not seen between all groups; however figure 31 shows a trend of improvement as teaching became more intensive. The power of this study was not adequate to show differences between all groups, but the sample size was limited by the number of students in the year group. It could be argued that students more likely to attend additional teaching sessions are keener,

and hence more likely to do well generally. The effect seen here appears to be specific to drug administration, as there was no relationship between intensity of drug administration teaching and performance in four unrelated OSPEs.

A good performance in the simulated critical incident scenarios also predicted a good performance in the later drug administration OSPE. This may not be surprising, it is still worthy of comment as it helps to validate simulation against another widely accepted practical test. The value of simulation has a narrow evidence base, with no studies in medicine, aviation or any other industry to show that simulation reduces morbidity and mortality – yet the high staff requirements and capital expenditure required to maintain a high fidelity simulation centre require justification. The finding that performance in the simulator positively correlates with performance in other tests of practical ability suggests a potential use for simulation in providing a structured and reproducible means of identifying students who may require extra help learning practical skills. Again, these observations were specific to drug administration skills with no correlation with performance in the unrelated OSPEs, so it is important to stress that scenarios must be carefully tailored to the skill or skills of interest.

A limitation of this study is that the division of students into the teaching groups described in table 11 occurred by serendipity rather than randomisation. The financial realities of running a simulation centre meant that students had to fit in around paying users, so there was not time to offer all students an appointment. Also, it was neither possible nor desirable to randomise (and thus in practice compel) students to undertake the online teaching module. This may have introduced bias into the study although one should not be hasty about the nature of the bias, considering that less able students were more likely to view the online module and gained most from it. It would be a pity to ignore these findings simply because it was not a double blind randomised controlled trial, when in fact it accurately reflects the realities of organising the clinical medical course. It has not been possible to follow up beyond qualification to see whether drug administration skills are retained for more than nine months. It can only be speculated whether more time in the simulator would further improve the level of

practical skills and their retention; at present the resources are not available to conduct such a study.

As well as appearing to have a positive influence on the acquisition of drug administration skills, these results reveal a lot more about the role of online teaching and simulation in medical education. First, the findings reinforce those of earlier, namely that online teaching is at best viewed by about half of the students. Only 47 students (36.4%) chose to follow the link of their own accord despite it being prominently positioned on the attachment webpage that the students consulted when organising their attachment. When actively reminded about the module, only 34 out of 75 (45.3%) chose to view it, however those doing so reported that it was useful. There is clearly a problem engaging students in online teaching that must either be addressed or accepted as an unavoidable limitation of the technique. In contrast, despite nervousness and misgivings about their potential performance, 96% attended the high fidelity patient simulator. High fidelity simulation is not used routinely for medical student teaching in the University of Cambridge so it may possess a certain novelty value, but despite this it clearly enthused the students.

So should all medical students be offered comprehensive simulator-based training in order to teach all aspects of practical skills, the recognition and management of the critically ill and medical emergencies? Clearly this would have enormous cost implications, but it is worrying that medical students found the simulator more engaging than being involved in real medical emergencies on the wards. Do today's students find it more difficult to get involved, and as a consequence do they lack the practical and clinical skills of their predecessors? If so, why, and what can be done about it? Simulation provides a safe learning environment in which students can learn and make mistakes without consequences, but at best can only complement traditional clinical teaching.

The finding that the drug administration skills the students were taught are retained in the medium term is encouraging, as the randomised study of the influence of the online module on simulator performance presented in Chapter 6 examined short term improvements only (Degnan et al., 2006). The results would

also appear to be clinically significant, in that those students who received the most intensive teaching were more likely to pass the drug administration OSPE station, implying that they had achieved the level of competence expected of a junior doctor. However, a substantial minority did not meet this standard, and the findings presented in Chapter 4 show that many doctors do not meet a clinically acceptable standard either.

Generally, it seems reasonable to conclude that only the most intensive drug administration teaching can improve some medical students' performance to a clinically acceptable standard. The intensity of the teaching is draining on resources, and probably could not be sustained outside a separately funded research programme. Therefore better education cannot be the only solution, the problem of labelling drug solutions as ratios and percentages must also be addressed.

CHAPTER 8

A RANDOMISED TRIAL OF DIFFERENT AMPOULE LABELS IN A SIMULATED CRITICAL INCIDENT SCENARIO

Simulation as a research tool for doctors

The interventions described in previous chapters have concentrated on better drug administration education specifically for medical students. The evidence shows that more intensive teaching improves both academic and clinical performance in tests of drug administration topics.

Knowledge about drug administration is not the only intervention suggested by the survey data presented in Chapter 4. Removing ratios and percentages from the ampoule labels of drug solutions would also appear to be a necessary and fundamental change that could improve patient safety.

Most doctors are likely to have used local anaesthetics and catecholamine solutions at some stage during their career. They may have developed prescribing or administration habits that make them liable to making dose errors when using drug solutions when managing a patient, whereas medical students will not have. Doctors are therefore the best group in which to assess the influence of ampoule labels on drug administration. A randomised, blinded, controlled trial was designed to test the hypothesis that doctors using ampoules labelled as mass concentration were more likely to administer the correct drug dose in a more timely fashion than those using ampoules labelled only with a ratio. High fidelity simulation was again used as a research tool.

During the simulated anaphylaxis scenarios undertaken by the medical students it had become clear that many had memorised the dose of adrenaline used in the management protocol as 0.5 mL of 1 in 1 000 adrenaline without knowing how many milligrams this is. If this also applied to doctors, an adult anaphylaxis

scenario would be unlikely to be able to detect a difference between the groups of doctors using ampoules labelled with mass concentration *versus* ampoules labelled with ratios. Indeed, it could even result in a more favourable outcome for those using ratio labelled ampoules. Therefore a simulated scenario was chosen that involved the management of a 5 year old with acute anaphylaxis to peanut butter. Few doctors would be familiar with the dose of adrenaline required, especially if they did not have a substantial paediatric practice. They would be likely to consult a protocol, and if the protocol only stated the dose in milligrams (0.12 mg) then the doctor would need to make a calculation that would make it clear if they understood how to convert between the different units of measure.

To summarise, this randomised, blinded, controlled study examined the impact of ampoule labelling practices on doctors' clinical performance in a simulated critical incident. The scenario required the acute management of a child with anaphylaxis in a rural location; the only ampoule of adrenaline available was labelled either as 1 mg in 1 mL or 1 mL of 1:1 000. The quantity of adrenaline administered and the time taken to give it were recorded.

Methods

Conduct of the study was granted ethical approval. Doctors without a substantial paediatric practice undertook a scenario in the high fidelity patient simulator (METI Human Patient Simulator).

Briefing

The participant was briefed as follows: 'You are at a small rural hospital conducting an outreach clinic. The hospital has some inpatient beds for rehabilitation and an adult minor injuries unit, but no resident doctor. You are the only doctor in the hospital at the moment. You have been called to the minor injuries unit to review Jack, a 5 year old brought in after eating peanut butter whilst unsupervised. He is known to have a peanut allergy. Please begin the immediate management of Jack'.

Scenario

Jack develops acute anaphylaxis severe enough to warrant a dose of 0.12 mg intramuscular adrenaline, according to the local protocol, as well as other treatments (Chamberlain, 1999). The participant is given an ampoule of adrenaline labelled either as 1 mg in 1 mL or 1 mL of 1:1 000, having been randomised to the mass concentration or ratio group earlier. He or she needed to calculate the correct volume to administer (0.12 mL). The protocol provided (figure 35) stated only that the dose required was 0.12 mg without referring to ratios or volumes. A nurse played by Louise Murray was the only help available, but a formulary, calculator, paper and pencil were provided. The nurse told those requesting other adrenaline presentations that they were not stocked in the unit.

Data collection

Audiovisual recordings of the scenarios were made. Investigators blinded to each candidate's randomisation status subsequently recorded the time taken for the adrenaline to be given, and scored the dose administered using the criteria shown in Table 12.

Statistical considerations

Power analysis suggested that 14 participants would be required in each arm of the study to achieve a significance level of 5% and study power of 80%. Randomisation was performed on-line (<http://www.randomizer.org>). Groups were compared and the statistical significance of data determined with Statview. The unpaired t test was used to analyse the time taken for adrenaline administration, and the χ^2 test employed to analyse the nominal dose administration data.

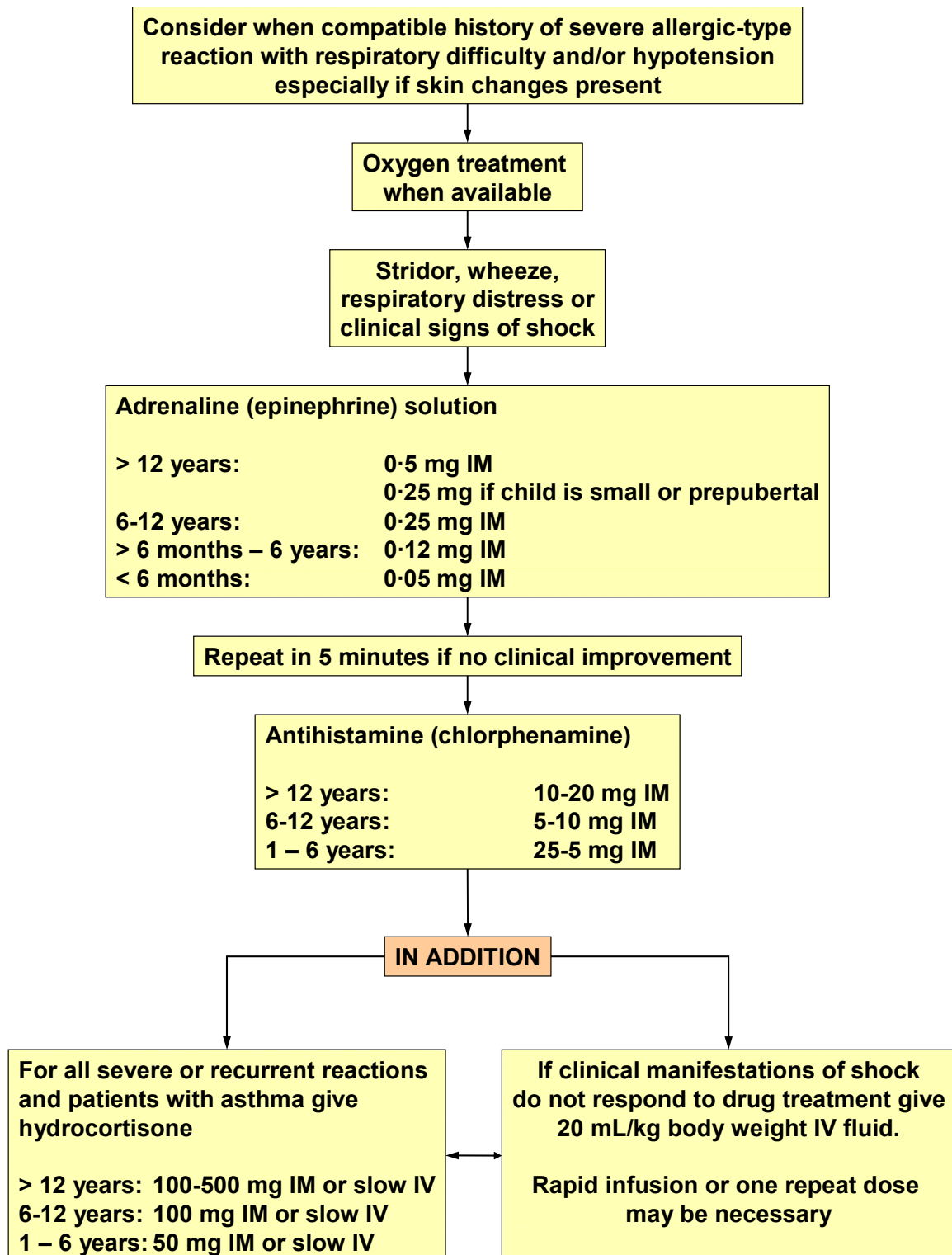


Figure 35: The protocol presented to doctors undertaking the paediatric anaphylaxis scenario. Note the absence of ratios in the protocol. Based on the Resuscitation Council (UK) guidelines (Chamberlain, 1999).

Results

Twenty-eight doctors attended a session, gave consent to participate and were randomised; 14 to the mass concentration group and 14 to the ratio group. All candidates completed their scenario. There were no differences between the groups on the basis of age, seniority, specialty or gender (data not shown).

Dose of adrenaline administered

There were highly significant differences between the doses administered by each group (χ^2 $p = 0.009$). Eleven of the 14 participants (78.6%) in the mass concentration group calculated a dose within 10% of that given in the protocol, two (14.3%) were incorrect by >10% but <50%, whilst one (7.1%) gave a dose that was incorrect by >50% (table 12, figure 36). In contrast, only two (14.3%) of those in the ratio group calculated a dose within 10% of the protocol, six (42.9%) were wrong by >10% but <50% and six (42.9%) were wrong by >50%. All doctors scoring 0 or 1 gave too much adrenaline, some giving as much as 1 mg (data not shown).

Time taken to administer adrenaline

Doctors using ampoules labelled with mass concentration were able to calculate and administer their chosen dose more quickly than those receiving adrenaline labelled as 1:1 000 (figure 37). The mean time taken to administer adrenaline for the mass concentration group was 46 s (range 12 – 135 s, interquartile range 38 s) compared to 140 s (range 76 – 244 s, interquartile range 59 s) for the ratio group ($p < 0.0001$).

Score	Definition
2	Dose given is within 10% of a recognised protocol
1	Dose given differs from that of a recognised protocol by >10% but <50%
0	Dose given differs from that of a recognised protocol by >50%

Table 12. The system used to score each dose administration episode.

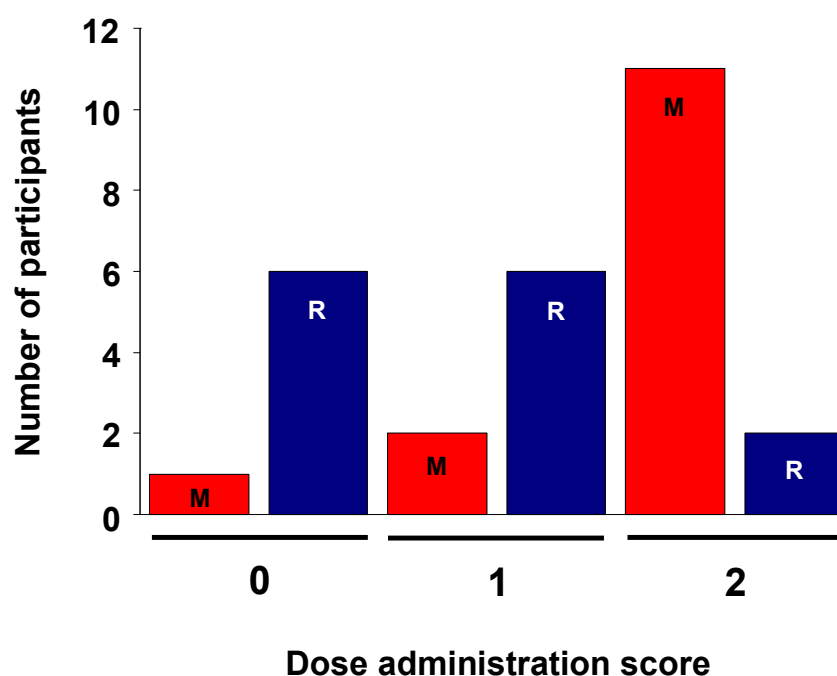


Figure 36: Graph to show the distribution of the dose administration episodes. **Red** bars (M) represent the group that received ampoules labelled with mass concentration. **Navy** bars (R) represent the group that received ampoules labelled with a ratio.

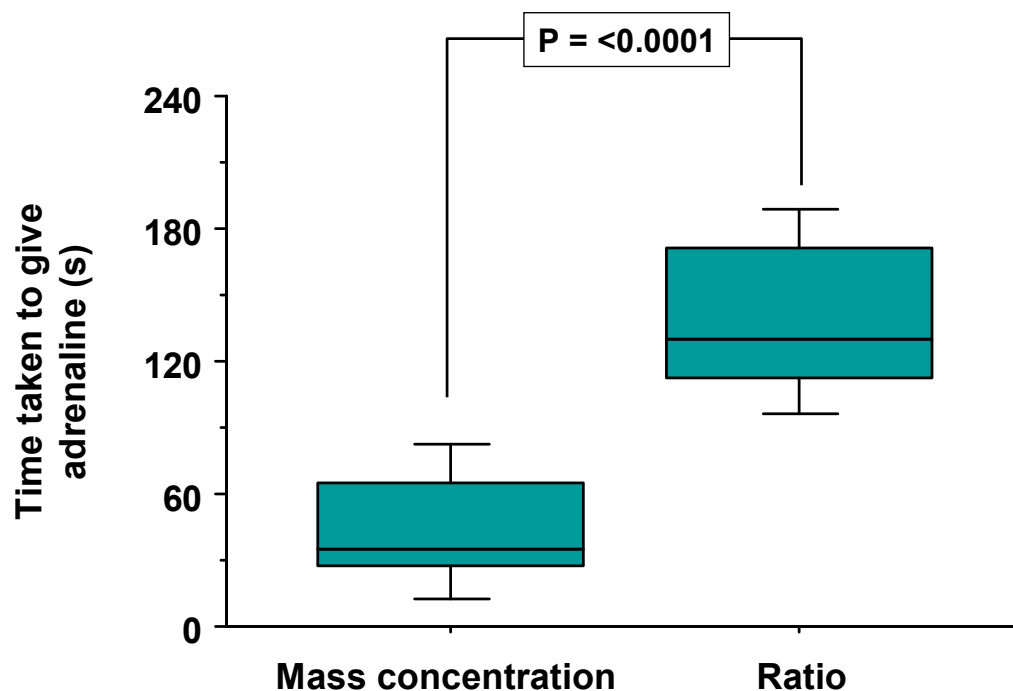


Figure 37: Box and whisker plots showing the median, interquartile range and 10th to 90th centiles of the time taken to administer the adrenaline dose in the simulated emergency scenario.

Discussion

Any doctor could be called upon to manage a patient with acute life-threatening anaphylaxis, whatever their specialty. This study shows that doctors are likely to give the wrong dose of adrenaline – and take longer to do so – when the strength of adrenaline is expressed as a ratio. These differences are clinically as well as statistically significant: the difference in the mean time taken to administer the adrenaline was more than 1½ minutes, and 11 out of 14 in the mass concentration group gave a dose within 10% of that recommended compared to 2 out of 14 in the ratio group. The consequences of a delay in treatment or an overdose of adrenaline in an isolated situation are potentially catastrophic.

I believe that many doctors know that the intramuscular dose of adrenaline for an adult in anaphylaxis is 0.5 mL of a 1:1 000 solution without knowing how many

milligrams this is (Wheeler et al., 2004a). A paediatric case was chosen as the participants – who were not paediatricians – would be likely to consult a protocol and make a calculation. In reality, adrenaline ampoules are labelled using both systems, but our study design allowed the value of the ratio to be examined in isolation and found that it causes substantial confusion that is likely to result in patient harm.

The survey and questionnaire evidence that doctors, nurses and medical students find different means of expressing the concentrations of drugs confusing has clearly had insufficient impact to influence labelling policy. Multiple choice questionnaires cannot account for guessing, and give no information about *why* a particular answer is given. The use of simulation revealed the steps in the calculation that caused difficulty (namely arithmetic and lack of understanding of ratios) and added degrees of realism and pressure that more accurately reflect reality whilst eliminating many of the variables and practical and ethical difficulties of conducting such a study in patients.

There is no international standard for the labeling of drug solutions. The World Health Organization states that the packaging should state the name, strength, quantity and physical description or identification of the medicinal product, that the labels should permit the identification of each active ingredient, and give the dosage form (WHO, 2002). It defers responsibility for the exact means of expressing this information to national regulatory bodies. The European Union Directive 92/27/EEC gives more explicit advice on labeling (European Union, 1992). It states that an ampoule label should include a statement of the active ingredients expressed qualitatively and quantitatively, the pharmaceutical form, and the contents by weight, by volume or by number of doses but does not mention ratios. No regulatory authority has ruled to remove ratios from ampoules, but an analogous change has recently occurred with the new local anesthetic levobupivacaine (ChirocaineTM, Abbott Laboratories, IL, USA). The concentrations of local anaesthetics are traditionally expressed as percentages, which can be even more confusing than ratios (Wheeler et al., 2004b; Wheeler et al., 2004a; Wheeler et al., 2007). However, levobupivacaine is presented in

ampoules labeled with mass concentration only; notably there have been no reports in the literature of dose errors since this change was made.

Whilst ratios and percentages were once useful when drug doses were expressed in Imperial units, they are now outdated and should not be used to express the concentration of drug solutions on ampoules even when there is dual labelling. However using mass concentration exclusively is not the answer, as conversions between milligrams, mols and micrograms also cause difficulties (Lesar, 2002; Stratta et al., 2006), and the concentrations of some drugs such as insulin and heparin are more conveniently expressed in international units. A better solution is for pharmacopoeias and formularies to express the concentration of each drug in one way only, and for this to be reproduced on ampoule labels.

CHAPTER 9

THE INFLUENCE OF AMPOULE LABELLING ON THE PREPARATION OF DRUG INFUSIONS

Intravenous drug infusions

Administering drugs by intravenous infusion is a mainstay in the practice of critical care and perioperative medicine. Like all drug administration episodes, errors may be made when infusions are given.

The recent multinational Sentinel Events Evaluation (SEE) study in intensive care units (ICUs) found that medication errors were amongst the most frequent unintended events that endanger critically ill patients. This snapshot survey of more than 200 ICUs found 10.5 medication errors per 100 patient days, split about equally between prescription error and administration error (Valentin et al., 2006). In another study of medical errors based on a voluntary reporting system, 17.7% of medical errors in a US medical ICU were found to be medication errors (Osmon et al., 2004). This study also highlighted the consequences of medication error on the ICU: 9.8% of errors necessitated life sustaining treatments.

The importance of drug administration error on the ICU is supported by several observational studies: the reported frequency of drug administration ranges from 3.3 – 44% of drug administration episodes depending on the study design, ICU studied and data collection technique (Tissot et al., 1999; Calabrese et al., 2001; van den Bemt et al., 2002; Kopp et al., 2006). The finding that drug administration errors tend to have serious consequences is independent of data collection technique, however. A prospective study conducted over one year in a medical ICU and coronary care unit in the United States found that 61% of serious medical errors occurred during the ordering or execution of treatments, especially medications (Rothschild et al., 2005b).

None of these studies differentiated between drugs given as an infusion or bolus. The path from the prescription of a drug infusion to its administration involves many steps (figure 38) and may be performed by more than one individual,

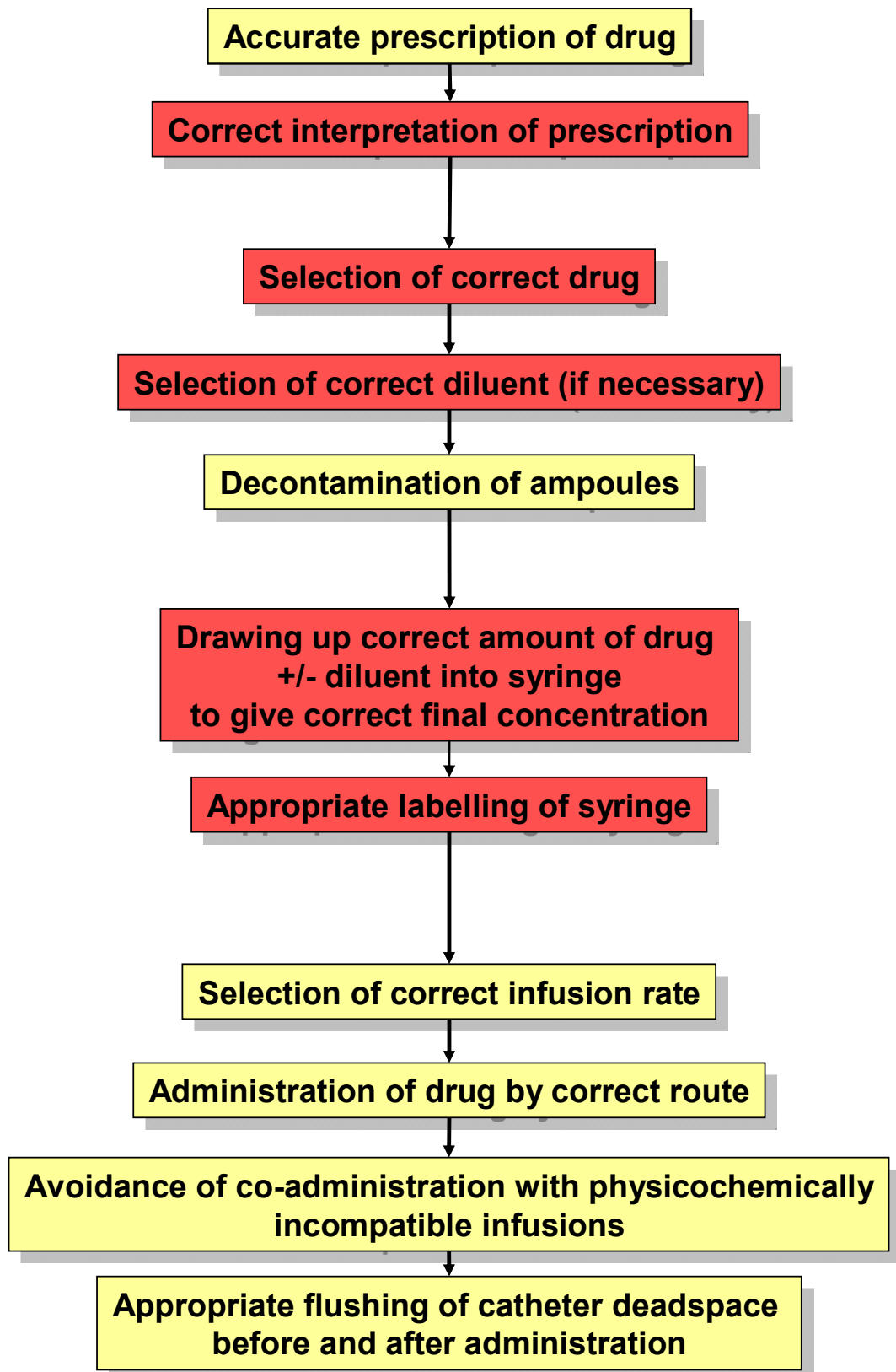


Figure 38: The multiple steps involved in preparing an intravenous drug infusion. This study concentrates on the steps indicated by the red boxes.

making the procedure particularly prone to error. This view is supported by a study of drug infusions on a surgical ICU in the US, which found an error rate of 10.6 per 100 patient days (Herout and Erstad, 2004), marginally greater than that found for all medication errors in the SEE study. In the perioperative setting drug infusions seem to account for about 20% of drug administration errors (Webster et al., 2001a). Significant differences between the prescribed and delivered concentrations of positive inotropes (Allen et al., 1995), opioids (Parshuram et al., 2003) and acetylcysteine (Ferner et al., 2001) have previously been described.

The majority of drug infusions in my hospital are prepared on the ward or at the bedside, with stock solutions of drugs drawn up into syringes and then diluted if necessary. I sought to examine whether there were differences between the prescribed and delivered concentrations of drug infusions delivered in the 22-bed neurocritical care unit in my institution, and the influence of the quality of syringe labelling on the delivered concentration. The concentrations of sedative, hormone, inotrope and electrolyte infusions were audited.

Methods

Syringes used for drug infusions in the neurocritical care unit of Addenbrooke's Hospital were collected over three weeks in May 2006. Staff were asked to not to discard syringes, but to place them in designated, secure containers that were emptied every 24 h. Syringes containing propofol, atracurium or opioids were not collected. The remnants of the drug solution in the syringe were removed and stored in sterile containers at -20 °C until analysis. All specimens were assayed in triplicate against standard curves of known dilution and positive and negative controls when appropriate, and resolved against 4-parameter curve fit models. Controls were included to ensure that the initial storage at room temperature did not result in appreciable changes in drug concentration. The assay protocols are described below. The study was registered as an audit with the hospital authorities.

Insulin

Specimens were diluted 10 000-fold in tris(hydroxymethyl)aminomethane hydrochloride (pH 7.8) so that their expected concentrations lay within the assay range of 0 – 1080 pmol.L⁻¹, then assayed on a 1235 AutoDELFIA automatic immunoassay system (PerkinElmer, Turku, Finland). The assay is a solid phase, two-site fluoroimmunoassay based upon the direct sandwich technique in which two monoclonal antibodies derived in mice are directed against separate antigenic determinants on the insulin molecule (Andersen et al., 1993). The coefficient of intra-assay variation at the concentrations seen in this study was 3.7%, with an analytical sensitivity of 3 pmol.L⁻¹. The mass of insulin was converted to International Units according to the formula 6 pmol = 1 µU (Volund, 1993).

Potassium

Specimens were diluted 1 000-fold in purified deionised water and measured on QuikLYTE Integrated Multisensor Analyzer (Dade Behring, Milton Keynes, UK). The analyser contains a potassium ion selective electrode that generates an electrical potential proportional to the concentration of K⁺ in the specimen when compared to a reference electrode and a standard solution (Frant and Ross, 1970), the final concentration being calculated using the Nernst equation (Nernst, 1888). The coefficient of intra-assay variation at the concentrations seen in this study was 0.07%.

Magnesium

Specimens were diluted 1 000-fold in purified deionised water and analysed using the methylthymol blue (MTB) complexometric method, which forms a blue complex in the presence of magnesium (Connerty et al., 1971). The amount of magnesium-MTB complex is proportional to the magnesium concentration and was measured using a bichromatic endpoint technique with light at 600 nm and 510 nm (Dade Behring, Milton Keynes, UK). The coefficient of intra-assay variation at the concentrations seen in this study was 2.0%.

Dopamine and noradrenaline

Dopamine samples were diluted 3 000-fold and noradrenaline by a factor of 500 in plasma. These specimens were analysed using high pressure liquid chromatography (HPLC) with amperometric detection (Hartwick and Brown, 1980) according to the manufacturer's instructions (Chromsystems, München, Germany). The coefficient of intra-assay variation at the concentrations seen in this study was 3.3%.

Midazolam

Samples were diluted a million times with plasma before the assay, then analysed using a similar HPLC method to that described by Lehmann and Boulieu (Lehmann and Boulieu, 1995), with a minor modification in that methyl *t*-butyl ether was used in a liquid-liquid procedure to extract the drug from plasma. Calibration (range 5 - 150 $\mu\text{g.L}^{-1}$) was undertaken by carrying plasma standards that had been complemented with midazolam through the procedure with each batch of samples. Each assay run was subject to tri-level quality control with appropriate internal standards. The assay has a lower limit of quantification of 3 $\mu\text{g.L}^{-1}$ and a coefficient of variance of 6 to 9% within and between batches at 20 $\mu\text{g.L}^{-1}$.

Inspection of syringe labels

All syringes were inspected independently by two investigators to ensure that they had been adequately labelled, using the criteria in table 13. One point was awarded for each label attribute that had been completed correctly. If an attribute was left blank or the information was incorrect or illegible, no points were awarded. In this way, an ordinal scale was created in which a syringe labelled entirely correctly scored 11 points with a minimum possible score of zero. Patient details were not recorded and syringes were incinerated after the labels had been assessed.

Statistical analysis

Data were entered into a spreadsheet and statistical analysis performed with Statview. The measured concentration of each sample was divided by the expected concentration and the ratio expressed as a percentage, so that when the measured concentration equalled the expected concentration the ratio was 100%. Data are plotted in box and whisker plots, showing the median, interquartile range and 10th – 90th centiles of the concentrations of the drug solutions analysed, with the standard deviation (expressed as a percentage) and coefficient of variance stated in tables and text (Appendix 4). The adequacy of syringe labelling was subject to further statistical analysis using the χ^2 test. To examine the relationship between the adequacy of syringe labelling and syringe contents, drug concentration data were normalised by subtracting 100 from the percentage, and transformed by the root mean square resulting in a value termed ‘concentration error’ that was then analysed by Spearman rank correlation (Appendix 4).

Results

In three weeks 126 syringes were collected. Thirty-eight contained noradrenaline, 35 human insulin, 26 potassium chloride, 12 dopamine, eight midazolam and five magnesium sulphate. One syringe each of heparin and sodium phosphate were collected but not analysed. All syringes contained the drug with which they had been labelled. The storage and collection protocol was found not to influence the measured drug concentrations.

Drug concentrations

The most striking result was that all five magnesium syringes contained much higher concentrations of Mg^{2+} than expected (median 409.4%, SD 50.9%, coefficient of variance 0.118), where 100% would represent equal measured and expected concentrations (figure 39). For the other drugs measured there was much less variability, with median concentrations gathered around 100% (figure 40, table 14). The measured potassium tended to be stronger than expected

(median 120.0%) and dopamine weaker than expected (median 87.9%). Noradrenaline had the greatest coefficient of variance (0.271).

Syringe labelling

Fifty-one out of 124 syringes (41.1%) were labelled entirely correctly according to all the criteria listed in table 13. A further 17 (13.7%) had one label attribute left blank or incorrect, and 40 more (32.3%) were incorrectly labelled in two respects. Giving no indication of the drug concentration (63 out of 124, 50.8%) or omitting the diluent (59 out of 124, 47.6%) were the most common errors. There was a significant difference in the quality of labelling depending on

Label attribute	Number satisfactorily labelled (%)	Number unsatisfactorily labelled (%)
<i>Drug related</i>		
Drug name	123/124 (99.2%)	1/124 (0.8%)
Amount of drug	119/124 (96%)	5/124 (4.0%)
Indication of concentration	61/124 (49.2%)	63/124 (50.8%)
Identity of diluent	65/124 (52.4%)	59/124 (47.6%)
<i>Patient related</i>		
Name	121/124 (97.5%)	3/123 (2.5%)
Location	122/124 (98.4%)	2/124 (1.6%)
<i>Preparation related</i>		
Preparer's initials	124/124 (100%)	0 (0%)
Countersigned	116/124 (93.5%)	8/124 (6.5%)
Date	123/124 (99.2%)	1/124 (0.8%)
Time	119/124 (96%)	5/124 (4.0%)
Legible?	118/124 (95.2%)	Borderline 6/124 (4.8%) No 0 (0%)

Table 13: The criteria used to assess the adequacy of drug infusion syringe labels, together with the numbers and proportions of syringes meeting each standard.

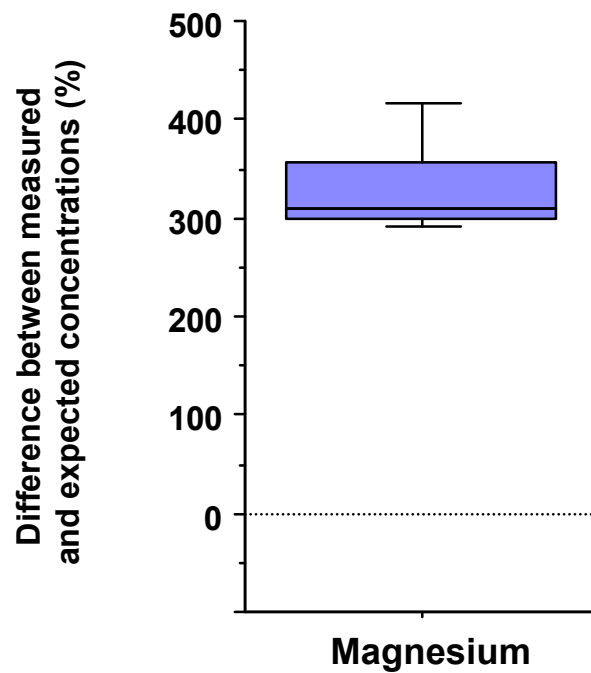


Figure 39: Box and whisker plot showing the median, interquartile range and 10th – 90th centiles of the concentrations of the magnesium solution analysed (n = 5).

syringe contents (table 14): magnesium syringes were least likely to be labelled entirely correctly (1 out of 5, 20%) and insulin syringes the most likely (22 out of 35, 62.9%, χ^2 p = 0.012). Only two of the five magnesium syringes (40%) were labelled with a final volume. The worst labelled syringe stated only that the contents were 4 mg noradrenaline and was initialled and countersigned by the preparers. There were no other details on the label; importantly the patient's details and the final volume or concentration was absent. No syringes were illegible, but 6 (4.8%) were considered borderline.

Relationship between syringe labelling and concentration

Syringes with more complete labels were more likely to contain the drug at its expected concentration. Spearman rank correlation of the normalised, transformed drug concentration data showed a highly statistically significant relationship (p = 0.002, corrected for ties). These data are plotted in figure 41: the increasing proximity of data points to zero on the y axis with higher labelling scores shows how better drug preparation correlates with better syringe labelling.

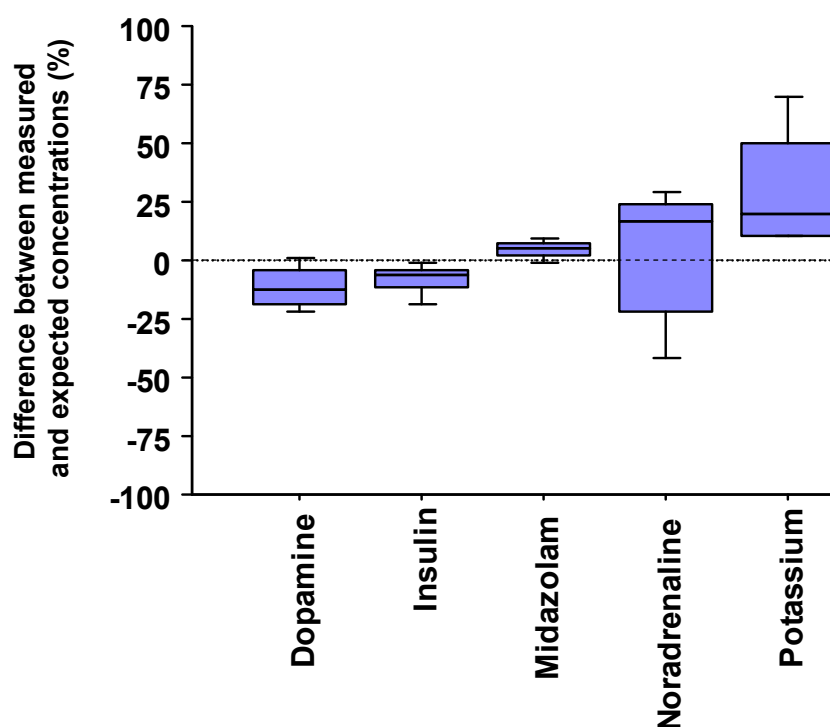


Figure 40: Box and whisker plots showing the median, interquartile range and 10th – 90th centiles of the concentrations of the remainder of the drug solutions analysed (n = 119). Data are presented as a separate figure to magnesium due to the large difference in scale of the y-axes.

Drug	Mean measured concentration (expected)	Median (%)	Mean (%)	SD (%)	Min (%)	Max (%)	IQR (%)	Coefficient of variance
Dopamine	3.55 (4.0) mg.mL ⁻¹	-12.1	-11.3	8.5	-22.9	1.1	13.9	0.096
Insulin	0.91 (1.0) IU.mL ⁻¹	-6.7	-8.7	6.9	-24.5	4.3	6.5	0.075
Magnesium	1.33 (0.32) mmol.mL ⁻¹	309.4	331.2	50.9	290.6	417.5	56.0	0.118
Midazolam	1.05 (1.0) mg.mL ⁻¹	5.5	4.8	3.9	-1.0	10.0	5.0	0.037
Noradrenaline	0.082 (0.08) mg.mL ⁻¹	16.8	3.2	27.9	-56.4	33.8	45.8	0.271
Potassium	1.31 (1.0) mmol.mL ⁻¹	20.0	30.8	23.0	10.0	80.0	40.0	0.176

Table 14: The variability of concentrations of infused drugs expressed as percentages, where 100% indicates that the measured concentration equals the expected concentration.

Magnesium data were excluded from this plot to allow the relationship to be visualised more clearly, as the y axis would have had to extend to 500 to include these data points.

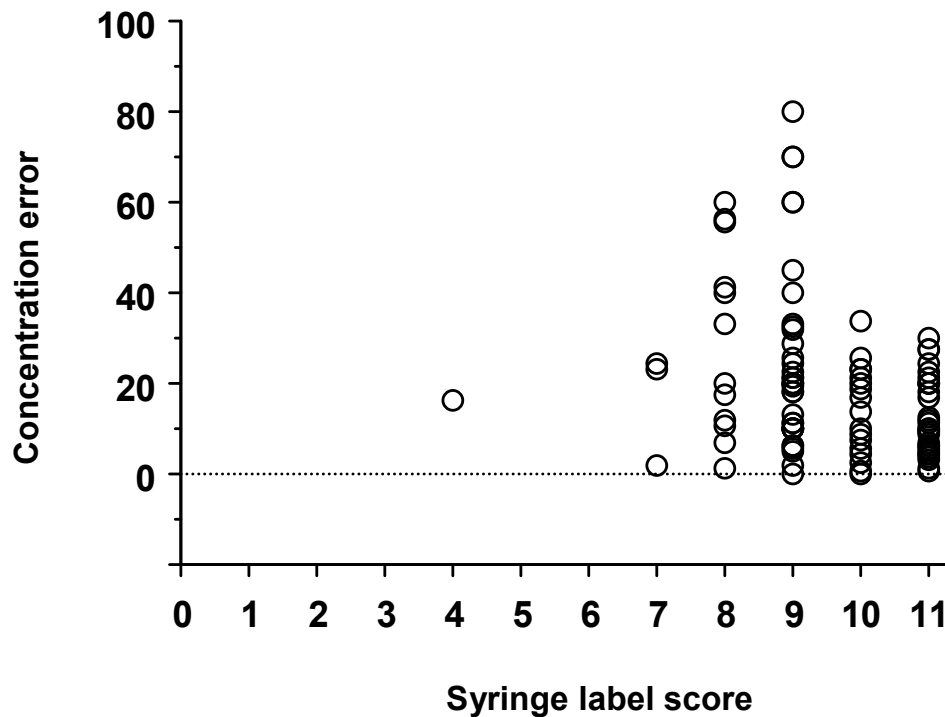


Figure 41: Plot showing the relationship between the ordinal syringe labelling score and the normalised, transformed syringe concentration data. In this plot, a y axis value of zero indicates that the measured concentration of that syringe equalled the expected concentration. Magnesium data excluded from plot.

Discussion

This study was designed to quantify the variability of drug infusion preparation on a typical ICU, but the finding that all five magnesium syringes contained approximately 4 – 5 times too much Mg^{2+} implied a repeated drug administration error was occurring, and warranted further investigation. Label analysis showed that the five syringes were prepared on different days spread evenly throughout the study period by four different nurses; furthermore all were countersigned as checked. The ICU drug preparation protocol states that for the treatment of acute

hypomagnesaemia, 8 – 16 mmol of magnesium sulphate should be diluted to a final volume of 50 mL in 0.9% NaCl and infused via a central venous catheter over at least 20 min. Sometimes 20 mmol is administered over 30 min, after dilution to 60 mL with 0.9% NaCl. On the ICU in my institution magnesium sulphate is presented as a 50% w/v solution for injection, with packaging also indicating that the concentration is 5 g magnesium sulphate heptahydrate in 10 mL and that this approximates to 2 mmol per millilitre (figure 42). It is notable that the expression of the concentration in mmol.mL⁻¹ is in much smaller print. I believe that the drug administration errors must have occurred because the preparers mistook 5 g for 5 mmol, for example drawing up 20 g rather than 20 mmol into 60 mL, hence explaining the 4 – 5-fold dilution error.

As three of the syringes had no final volume or concentration indicated on the label, it could be that these infusions were deliberately made more concentrated. Under these circumstances intention to treat analysis results in a median concentration of 0.32 mmol.L⁻¹, but the mean magnesium concentration falls from 1.33 to 0.76 mmol.L⁻¹ and the coefficient of variance becomes 0.831. The nature of this study meant that the nurses who prepared the syringes were not



Figure 42: The ampoule of magnesium sulphate and its box.

identified nor were the patients followed up. Retrospective analysis of samples means that the concentration of the original ampoules could not be checked but the manufacturers (Auden McKenzie, Middlesex, UK) are not aware of any quality control issues (personal communication). It is notable that the cause of these drug infusion errors was not preparation technique but was much more likely to be a result of misinterpreting different means of expressing the concentration of drugs in solution, a problem that has been highlighted throughout this thesis and by others.

Reaudit of magnesium infusions

The specific problem with magnesium was addressed by improvements to protocols and drug labels to avoid future errors. A new magnesium prescription form was introduced that included clear instructions about syringe preparation (figure 43). To complete the audit cycle, 25 further magnesium samples were collected and their concentrations measured after the introduction of the new form. These specimens were found to be significantly closer to the expected concentration, the observed mean concentration being $0.50 \text{ mmol.mL}^{-1}$, 48.2% more than expected ($p = 0.0005$, figure 44). There was still wide variation in the concentrations measured, the standard deviation for these specimens being 47.3% compared to 50.9% for those collected before the intervention. The coefficient of variance was higher at 0.319 compared to 0.118 beforehand. In this respect, the concentrations in the syringes prepared using the more detailed protocol did not differ significantly from the contents of the potassium syringes ($p = 0.151$), suggesting that this degree of variation may be the inevitable and unavoidable result of preparing drug infusions from stock solutions at the bedside.

Wide variations in the concentrations of the other infused drugs were also found. These may occur due to imprecision during the process of drawing up drugs from ampoules, and using the correct volume of diluent. A drug solution would be too dilute if a small amount of concentrated drug is left in an ampoule after drawing up, especially if the preparer does not inject and withdraw the dilute solution from the ampoule several times, and / or too much diluent is used. A solution is likely

Draw up 60mmol of Potassium Chloride = 30ml of 15% KCl Dilute in (circle as appropriate): Sodium Chloride 0.9 % or 0.45% to total volume of 60 ml Infuse at 20ml/ h (over 3 hours)				P o t a s s i u m	Start when $K^+ \leq$ _____ mmol/L Stop when $K^+ \geq$ _____ mmol/L Dr Signature: Valid for 24 hours from : 10:00 – 10:00 Last dosing should not start after 7am without consulting medical staff.																	
<table border="1"> <thead> <tr> <th>Doses / 24 hours</th> <th>K^+ level</th> <th>Nurse Signatures</th> <th>Time</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">1</td> <td></td> <td></td> <td></td> </tr> <tr> <td style="text-align: center;">2</td> <td></td> <td></td> <td></td> </tr> <tr> <td style="text-align: center;">3</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>					Doses / 24 hours	K^+ level	Nurse Signatures	Time	1				2				3				Inform NCCU Doctor if: $K^+ < 3.5$ mmol/L Or $K^+ > 5.0$ mmol/L	
Doses / 24 hours	K^+ level	Nurse Signatures	Time																			
1																						
2																						
3																						
Draw up 20mmol of Magnesium Sulphate = 10ml of 50% $MgSO_4$ Dilute in (circle as appropriate): Sodium Chloride 0.9% or 0.45% to a total volume of 50ml Infuse at 25ml/hr (over 2 hours)				M a g n e s i u m	Mg^{2+} 0.6 - 0.7 mmol/L Give 20mmol Magnesium $Mg^{2+} < 0.6$ mmol/L Give 20mmol Magnesium and repeat U+E at the end of the infusion Dr Signature: Valid for 24 hours from : 10:00 – 10:00 Last dosing should not start after 8am without consulting medical staff.																	
<table border="1"> <thead> <tr> <th>Doses / 24 hours</th> <th>Mg^{2+} level</th> <th>Nurse Signatures</th> <th>Time</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">1</td> <td></td> <td></td> <td></td> </tr> <tr> <td style="text-align: center;">2</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>					Doses / 24 hours	Mg^{2+} level	Nurse Signatures	Time	1				2				Inform NCCU Doctor if: $Mg^{2+} < 0.5$ mmol/L or $Mg^{2+} > 1.2$ mmol/L					
Doses / 24 hours	Mg^{2+} level	Nurse Signatures	Time																			
1																						
2																						
Draw up 10mmol of (Potassium) Phosphate = 10ml of 17.4% K_2HPO_4 Dilute in (circle as appropriate): Sodium Chloride 0.9% or 0.45% to a total volume of 50ml Infuse over at least 12 hrs (4ml / hour) (If hyperkalaemic ($K^+ > 5$ mmol/L) use Na Phosphate)				P h o s p h a t e	$PO_4^{2-} < 0.8$ mmol/L Give 10mmol Potassium Phosphate Dr Signature: Valid for 24 hours from : 10:00 – 10:00 Last dosing should not start after 10pm without consulting medical staff.																	
<table border="1"> <thead> <tr> <th>PO_4 level</th> <th>Nurse Signatures</th> <th>Time</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> </tr> </tbody> </table>					PO_4 level	Nurse Signatures	Time				Inform NCCU Doctor if: $PO_4^{2-} < 0.6$ mmol/L or $PO_4^{2-} > 1.4$ mmol/L											
PO_4 level	Nurse Signatures	Time																				

Figure 43: The more detailed electrolyte prescription chart introduced as an intervention after the problem with magnesium infusions was identified. NCCU = Neurocritical care unit.

to be too concentrated if insufficient diluent is used. The volume of diluent is generally measured using the graduations on the barrel of the 50 mL syringe, and their close proximity makes precise measurement difficult. The positive

correlation between the quality of syringe labelling and drug preparation is also worthy of comment. Some preparers may be less experienced, may have been inadequately taught, may simply take less care over drug preparation, or may have been hurrying or distracted at the time.

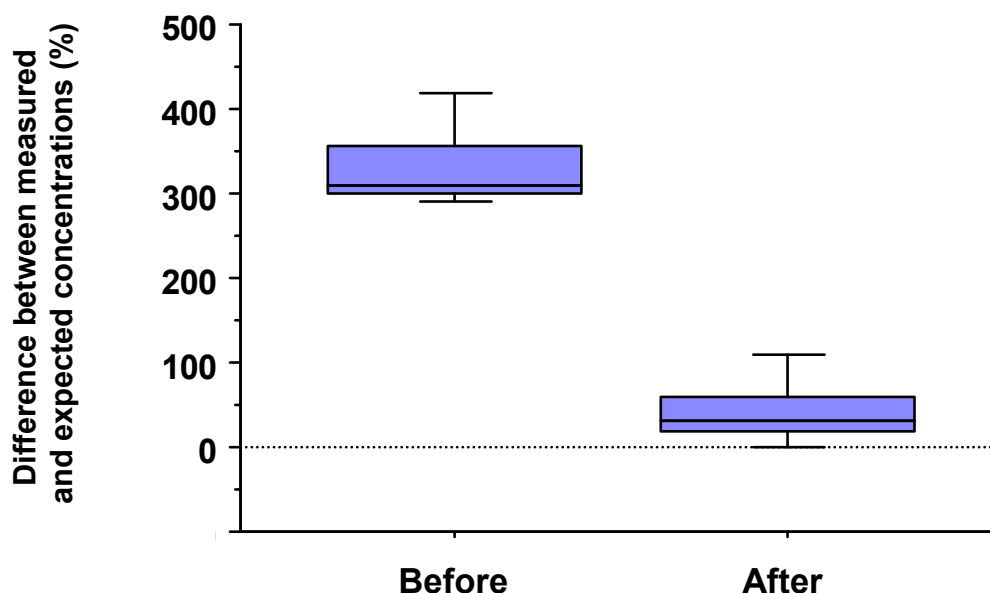


Figure 44: Box and whisker plot showing the median, interquartile range and 10th – 90th centiles of the concentrations of the magnesium solution analysed before (n = 5) and after (n = 25) the introduction of the new prescription form.

The United States Pharmacopoeia and Canadian pharmaceutical industry standard requirements for pharmaceutical preparations state that it is unacceptable for the concentration of preparations to vary by more than 10% of the stated concentration (US Pharmacopeial Convention, 1999), but figures 39, 40 and 44 show that many infusions do not fulfill these criteria. Are the wide variations in the concentrations documented here clinically significant? This study cannot say: any study designed to do so would need to detect haemodynamic or metabolic compromise and examine patient outcomes, then show that these primarily resulted from variation in infused drug concentration and not any other of the myriad factors that influence outcome on ICU. Given the relative rarity of life threatening adverse drug events and the frequency of haemodynamic and metabolic fluctuations, this would mean that such a study would have to be large and expensive.

Not all drug infusions administered during the study period were collected or analysed for a variety of reasons. On the ICU studied, several drugs are administered undiluted, such as propofol, atracurium and fentanyl. The means to assay pharmaceutical preparations of propofol were not available; however there have been occasions when the lack of labelling of 1% and 2% preparations of propofol have caused confusion when transferring patients between units in the hospital. As it was only practical to collect syringes once daily, atracurium was not assayed due to its rapid Hoffman degradation at room temperature, and anyway it is generally administered undiluted on the ICU studied. The collection, storage and analysis of opioids also presented practical and legal difficulties due to their controlled drug status in the United Kingdom. Therefore this study may have missed some 'wrong patient', 'wrong drug' or, with propofol, 'wrong preparation' errors, and could not have detected diversion of controlled drugs. Moreover, denominator data were not collected so the study does not reveal the frequency of errors.

This study relied upon the co-operation of the nursing staff to place used infusions in the designated containers. The nurses were fully informed about the nature of the study and the data being collected; but it was felt that a disguised study would do little to foster a team approach in the workplace. When nurses chose to deposit a syringe in the containers it implied consent to participate, but it is not certain that all the syringes of interest were deposited there. First, some patients receiving drug infusions were transferred out of the ICU to other clinical areas, and the nature of the once-daily collection procedure meant that samples could not be taken from these syringes. Second, some syringes may have been discarded by the normal route because the nurses were busy, had forgotten about the study, or possibly because a nurse might be concerned that the infusion had not been drawn up correctly. This syringe collection protocol could be criticised, but resources were not sufficient to allow an investigator to be stationed on the ICU 24 hours a day for 3 weeks. An alternative data collection technique would have been to sample all patients' infusions on a daily basis. This approach was not used as interrupting infusions may have resulted in haemodynamic compromise for some patients, and would have compromised drug sterility.

The large number of steps involved in preparing a drug for infusion is highlighted in figure 38. This may involve several different people: a prescriber, a preparer and an administrator of the infusion, although there are times when these roles may be combined. This study demonstrates that the preparation stage of drug infusions is a potential source of drug administration error, due to the potential to select the wrong quantity of drug, and practical difficulties drawing up the correct volume of diluent.

Does it matter if the concentrations of infused drugs vary when infusion rates can be titrated against response on the ICU? For example, when alterations are made to the infusion rate of positive inotropes, the blood pressure response can be seen immediately, especially if arterial pressure is monitored invasively. However, not all physiological endpoints can be measured so frequently or precisely. Blood glucose or electrolyte concentrations can be measured easily, but practicalities dictate that this is rarely more frequently than once per hour. Some clinical endpoints, for example sedation, are much less easy to measure (Tonner et al., 2003). Under these circumstances, it is vital to ensure that the correct doses of drugs are administered by infusion – after all, bolus doses of drugs are expected to be given correctly so why should infusions be any different? This argument is strengthened when other potential confounding factors are considered. Factors inherent in the mechanisms of infusion pumps can cause haemodynamic fluctuations, especially at low infusion rates (Klem et al., 1993), as may the orientation of the pump, the size of the syringe chosen and the compliance of the infusion line (Weiss et al., 2000). It would therefore seem prudent to remove one potential variable by choosing to use pre-prepared standardised syringes.

As James Reason stated, one should always be wary of causing a new error by trying to prevent one (Reason, 2000), and there are several arguments against stocking an ICU pharmacy with drugs prepared by the manufacturers at their final delivered concentration. Paediatric units that use protocols in which the concentration of the drug varies with the child's weight would have to move to an alternate system, which might cause confusion and potentially increase drug error. Another potential source of error would be if babies needed more dilute solutions of certain drugs than larger children, although this could be mitigated by syringe

recognition and ‘smart infusion’ technology (Rothschild et al., 2005a). Adequate drug storage space might also be an issue: boxed pre-prepared syringes may appear bulky but whilst the requirement for storage of empty syringes, needles and diluents would generally be reduced, storing pre-prepared refrigerated and controlled drugs could be problematic. Pre-prepared drugs also tend to be more expensive, even when the cost of syringes, diluents and drawing-up needles are taken into account (Webster et al., 2001b). There may, however, be savings such as decreased workload for the ICU nurses, improved sterility reducing the incidence of cannula and intravenous line infections, potentially shorter ICU stay and reduced litigation.

To conclude, the use of pre-prepared syringes for drug infusions would have a positive impact on patient safety. Also, these results add further weight to the case for standardising the labelling of drug solutions to reduce the confusion caused by expressing concentrations in different ways. That this study was not a randomised, controlled trial should not detract from these recommendations. Any randomised trial seeking to examine the impact of such interventions on patient outcome or healthcare expenditure would need to be so highly powered that it would be difficult, if not impossible, to perform.

CHAPTER 10

DISCUSSION AND FINAL CONCLUSIONS

The research presented in this thesis shows that medical students, doctors and nurses have difficulty when calculating drug doses, and preparing and administering drugs in solution. The extent of the problem was investigated using online questionnaires and an audit on a neurocritical care unit. Expressing drug concentrations as ratios and percentages caused particular difficulty, as did conversions between different mass units such as milligrams, millimols and micrograms. Interventions aimed at reducing the likelihood included better drug administration teaching, removing ratios and percentages from ampoule labels, and the design of clearer protocols for the preparation of drug infusions at the bedside. Extensive use of online tests and high fidelity simulation was made to examine the efficacy of the interventions, as well as reaudit of drug preparation. All the interventions were found to be effective to a certain extent, and consideration of all the results together suggests that these approaches when combined could substantially reduce dose errors made with drugs in solution.

The extent of the problem

Medical students' understanding of ratios and percentages

The original online pilot questionnaire showed that medical students at the University of Cambridge had a poor understanding of expressions of drug concentration (Wheeler et al., 2004b). Just under two thirds could convert a solution of 1:1 000 adrenaline to milligrams per millilitre, just over one third knew that a 1% solution equates to 10 mg.mL^{-1} . The questionnaire format comprised five stems so that students would be expected to be correct 20% of the time by guessing alone. The results suggested that the students were not guessing, and showed an improvement with seniority. The implication was that drug

administration was poorly taught, and that students were acquiring knowledge on an *ad hoc* basis as they engaged in the clinical course.

Doctors' understanding of ratios and percentages

The pilot project led to a more elaborate questionnaire that was used to assess doctors' understanding of drug concentrations and added a clinical context. Almost 3 000 doctors participated and a substantial minority also struggled with the concept. They were more familiar with ratios – 85.2% correctly identified the mass of adrenaline in the ampoule – but approximately one in ten would have given the wrong dose in the ensuing clinical scenario (Wheeler et al., 2004a). Percentages caused greater difficulty. Only 65.8% correctly identified the mass of lidocaine in the ampoule, but 81.0% knew the correct volume. Just over one third made an error converting a dose of atropine from micrograms to milligrams. Further analysis showed clear associations between doctors' experience, specialty and grade and their performance in the survey (Wheeler et al., 2007).

The validity of the online questionnaire format

Surveys are widely used in health services research for data collection and are traditionally administered by postal questionnaire, face-to-face or telephone interview. Surveys have the advantage of being cost-effective and easy to administer to large scale populations. The recent emergence of the Internet has expanded the scope of surveys tremendously. Electronic surveys offer the further benefits of relative ease of implementation, the potential to conduct very large surveys whilst eliminating the costs of stationery, postage and administration (Wyatt, 2000). Simple questionnaires do not require extensive programming skills or time, and the cost of sending multiple e-mail invitations and reminders is negligible. Electronic surveys allow tight control of the order in which respondents see specific questions, thus preventing respondents from changing their answers retrospectively. More sophisticated programming allows validation checks as data are collected or randomisation of respondents to different versions of the questionnaire. Although automated systems of electronic entry of data into

a database exist for paper-based surveys, these are relatively expensive. Internet based surveys allow straightforward automatic transfer of data into a database, thus eliminating the need for manual inputting and avoiding potential errors of data entry.

These advantages are reflected in the recent increase in the popularity of the Internet for administering surveys. The technique was not mentioned in an editorial reviewing best practice in the design and use of questionnaires of health service staff and patients published in 2001 (McColl et al., 2001), yet entering “internet survey” as a search term into PubMed in 2007 returns 147 papers on subjects as diverse as fibromyalgia (Bennett et al., 2007), the impact of methamphetamine use (Looby and Earleywine, 2007) and improving hospital doctors’ working lives (Dornhorst et al., 2005). The latter survey was widely advertised in medical journals and on medical Royal College websites, attracting 1,843 respondents. Many Internet-based surveys do not report a response rate, presumably because the investigators are not aware of (or choose to ignore) the number of visitors to their web page that constitutes the denominator data.

At almost 3 000 respondents, the survey used to collect the data presented in this thesis had the most participants of any published health services research undertaken before or since (Wheeler et al., 2004a; Wheeler et al., 2007). A link to the survey was included on the home page of all Doctors.net users, along with several others. The Doctors.net software was capable of recording the number of users logging on to the site and thus viewing their home page. This was used as a denominator to calculate the response rate of 24.6%. When manuscripts were submitted to the *Lancet* and the *British Medical Journal* they were automatically rejected as the response rate was considered too low. Surveys with low response rates tend to be automatically rejected by many journals. An editorial in *Anaesthesia* has stated that surveys with response rates of around 50% are generally published but ideally the proportion of responders should be 70–80% for meaningful inferences to be made (Bruce and Chambers, 2002).

Relatively low response rates in Internet surveys have been reported in studies that have directly compared them with traditional paper methods (Hollowell et al.,

2000; Kim et al., 2000; Kim et al., 2001; Raziano et al., 2001). This may be because the ease of access to doctors by email or the Internet means that they receive increasing numbers of questionnaires from academics, industry and other health service providers leading to electronic overload that might be of far greater magnitude than in postal surveys (McAvoy and Kaner, 1996). An 'acceptable' response rate for Internet-based surveys has not yet been defined and that quoted by Bruce and Chambers above may not be appropriate. Response rates of published Internet surveys vary from 9% (Kim et al., 2000) to 94% (Potts and Wyatt, 2002).

One survey of general practitioners in the United Kingdom used a similar technique to recruit participants, namely a link from a web page of an online community exclusively for doctors (Braithwaite et al., 2003). This yielded a response from 30% of subscribers, which rose to more than 50% with an e-mailed reminder. The privacy policy of Doctors.net did not allow members to be contacted directly, but the initial response rate reported by Braithwaite and colleagues compares favourably with the survey presented herein.

The sample is a proportion of a larger defined population and usually the only means by which inferences can be made about the full population, given time, logistic and financial constraints. Ideally participants should be selected randomly, but frequently this is not possible. The sample responding to the survey herein is made up of those subjects available for study ('convenience sampling'). This may introduce selection bias that makes the findings difficult to generalise to the wider population. Bias may exist because subscribers to Doctors.net and / or those choosing to participate are not representative of doctors generally. It is not possible make any inferences about the characteristics of responders *versus* non-responders, but the survey was successful in attracting a very large sample that accurately reflected the demographic characteristics of doctors in the United Kingdom (Sang, 2003). Nonetheless, high impact journals rejected the manuscript, although interestingly the *Lancet* published an editorial discussing the findings in the context of physicians' difficulties interpreting numbers shortly after publication of the first paper (Ghosh and Ghosh, 2004). No changes to ampoule labelling policy have yet been made as a result of these or

other previously reported findings of the smaller paper-based surveys (Kelly and Henderson, 1983; Scrimshire, 1989; Rolfe and Harper, 1995; Oldridge et al., 2004).

In 2004, the National Patient Safety Agency (NPSA) commissioned a project on the graphic design of medication packaging, to establish good practice design principles that ensured maximum differentiation between packs and improved the conveyance of key information to the patient. This resulted in a publication 'Information design for patient safety – A guide to the graphic design of medication packaging' (NPSA, 2006), which built upon the packaging guidelines of the Medicines and Healthcare products Regulatory Agency (MHRA, 2003).

These recommendations are in the process of being updated. An NPSA committee is working on new recommendations (NPSA, 2007) that give guidance about the presentation of drug packaging, ampoules, pre-filled syringes, powdered drugs for reconstitution and fluids for infusion. The document, which currently exists as a draft, recognises that drug errors can occur because of the appearance of drug packaging and confusion about their labels. It cites one of the published papers that reports the findings of this thesis in the section concerning expression of drug concentration (figure 46) (Wheeler et al., 2007). Perhaps disappointingly it does not recommend that ratios and percentages are removed from ampoule labels. However, the committee allowed a period of consultation and I submitted evidence from this thesis supporting such a move. At the time of writing, it is not clear whether this will be included in the final recommendations, but it is encouraging that the problem is finally being recognised.

Why are problems with ratios and percentages not reported more frequently?

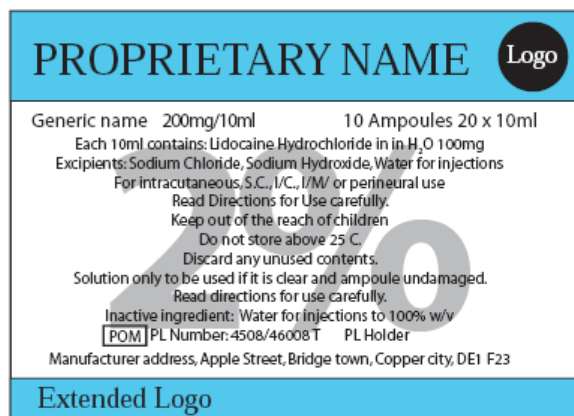
Establishing a reliable, reproducible and precise method of detecting medication errors in hospitals has proved to be a long-standing problem (Barker and McConnell, 1962). Local or national critical incident reporting systems are very

1.5 Concentration

Issue

Differing representations of concentration create confusion and complicated dose calculations.¹

Information should not be superimposed on other information.



¹ Wheeler DW et al. Factors influencing doctors' ability to calculate drug doses correctly, Int J Clin Pract, February 2007, 61, 2, 189–194

Figure 45: Page 22 of the NPSA document concerning improving drug labelling that cites work from this thesis (NPSA, 2007).

poor at detecting errors, identifying only a tiny fraction of errors compared to observational techniques (Flynn et al., 2002). The NPSA has established the National Reporting and Learning System and Patient safety Observatory to collect information about errors from local, national and international sources, quantify and characterise them, learn from them and then disseminate guidance to all NHS organisations and healthcare settings in England and Wales. The National Reporting and Learning System publishes quarterly overviews of all patient safety incidents. It relies on incident reporting by hospitals, trusts and individuals, so suffers from the drawbacks of any reporting system. Its reports are very general, providing summaries of the types of error, their location and consequences in the broadest terms. Medication errors typically comprise 8 – 10% of total errors in

their reports, but further detail is lacking. A personal enquiry to the NPSA yielded no additional information.

Novel reporting systems such as patient reporting (Weingart et al., 2005) or reporting by poisons centres (Volans et al., 2007) are being introduced but have not yet made an impact. The scientific literature contains sporadic reports of problems with ampoule labels, some of which pertain to problems with expression of concentration (Keohane and Luney, 2001; Adekanye and Vasoya, 2006), but it would appear not to be a useful means of reporting or detecting drug errors. Many observational studies of intravenous drug administration have been conducted and are discussed on page 23. A recurrent theme is that dose errors are amongst the most common medication errors and causes of ADEs, but no study has explicitly mentioned expression of drug concentration amongst the causes.

Of course many errors may go unnoticed. Drug infusions are often titrated against response, or against blunt endpoints, so variability in their preparation can easily be undetected. Catecholamines tend to be the only drugs labelled as a ratio. They are mainly used in emergencies so it is easy to imagine how errors could be overlooked. Administration of too low a dose could be attributed to a lack of a physiological response by the patient, too high a dose may result in arrhythmias that could be attributed to the natural history of the illness. As a senior house officer in general medicine in 1997 I treated a patient with acute anaphylaxis in ventricular fibrillation. This had probably resulted from a tenfold overdose of intravenous adrenaline given by an Accident & Emergency doctor, but was not reported as a critical incident as it was considered impossible to rule out whether the arrhythmia had simply been part of the disease process. In retrospect I believe that this was used as an excuse to avoid blame and exposure to liability, which is also a major cause of incident underreporting. It could be argued that the absence of reporting of problems with ratios and percentages is because there *are* no problems, but I believe that the evidence in this thesis abundantly demonstrates that there are.

Interventions

This work describes better drug administration education, less confusing ampoule labels and improved electrolyte prescription charts as potential interventions to reduce drug error during intravenous administration, and presents data in support.

Better drug administration education

The realisation that clinical medical students were acquiring drug administration knowledge by 'osmosis' without any formal teaching led to the introduction of an online educational module. The module's influence on students' factual knowledge and clinical skills was assessed by means of written tests and simulated scenarios.

Use of the online module improved short term factual knowledge when performance in regular assessments was measured and analysed using logistic regression and statistical modelling (Wheeler et al., 2006). Initially, 130 students were invited to undertake the online teaching. Those participating were identified and the number of web pages viewed recorded. The students' knowledge retention was tested by means of drug administration questions incorporated into routine assessments and examinations over the next 6 months, whilst other indices of all students' performance were recorded to correct for potential confounding factors. The amount of interest shown in the teaching module correlated positively with students' performances in questions about drug administration that waned over time. Surprisingly, correcting for students' general ability and keenness revealed that the less able students were most likely to undertake the teaching module.

In a randomised study, the module was also found to have a positive influence on students' performances in simulated critical incident scenarios (Degnan et al., 2006). It was instructive that 48 students were invited to participate, and whilst 44 (92%) attended only nine of the 20 students (45%) directed to the extra teaching viewed it. Nevertheless, the teaching module significantly improved the students' ability to calculate the correct volume of lidocaine ($p = 0.005$) and

adrenaline ($p = 0.0002$), and benefited each student's overall performance ($p = 0.0007$). Very few interventions to reduce drug administration error are known to be effective, so it was encouraging to be able to show that focusing on better teaching at medical school may benefit patient safety. The online module is cheap to run and administer, but its value is limited by students' enthusiasm and generally only half viewed it. At best the module can only complement traditional teaching methods, but the findings also serve to remind medical teachers that basic skills like drug administration should not be overlooked in the curriculum.

An additional and unexpected finding was that the students found the simulated scenarios engaging and stimulating, to such an extent that it had an intrinsic educational value of its own that was retained for the longer term. Participation in the simulated scenario only significantly improved scores in a practical examination when supplemented by online teaching, but study power was limited by the size of the year group. Performance in the simulator also proved to be a good predictor of performance in the later examination. Students found simulation much more engaging than online teaching, so it would appear to be a very useful educational tool but one that is costly to run from financial and staffing perspectives.

Less confusing ampoule labels

In the randomised study presented in Chapter 8, 28 physicians undertook a simulated paediatric acute anaphylaxis scenario in which they were required to administer 0.12 mg adrenaline intramuscularly, having been randomised to receive ampoules labelled either with a ratio (1:1 000) or mass concentration (1 mg in 1 mL). Only two of those using ratios (14.3%) gave within 10% of the correct dose, compared to 11 of those using mass concentration (78.6%, $p = 0.009$). The ratio group took more than three times as long to administer the adrenaline than the mass concentration group (mean times 140 s and 46 s respectively, $p < 0.0001$). These findings demonstrate the extent to which doctors can make mistakes under pressure, as converting ratios to mass concentration requires only basic arithmetical skills. I believe that they contribute powerful

evidence to the argument that a drug's concentration should be expressed in one standard way on ampoules and in protocols and formularies.

Improved electrolyte prescription chart

The audit presented in Chapter 9 quantified the variability in the concentration of drug infusions prepared on an intensive care unit, and established a relationship between the quality of syringe labeling and drug preparation. Discarded syringes containing midazolam, insulin, noradrenaline, dopamine, potassium or magnesium were collected daily, the residual solutions in the syringes were sampled and the concentrations measured. Syringe labels were inspected and awarded a score for labeling adequacy. The measured concentration of all five syringes containing magnesium sulphate were found to exceed the expected concentration by a factor of 4 – 5, presumably because of confusion about converting millimols to grams. The anonymous study design meant that the nurses who had prepared the syringes could not be identified. The majority of the other infusions differed from the expected concentration by more than 10%. Magnesium infusions were least likely to be properly labelled ($p = 0.012$) and there was a positive correlation between quality of syringe labelling and drug preparation ($p = 0.002$).

As a result of the audit new electrolyte prescription charts were introduced and the audit cycle was completed by analysing 25 more syringes containing magnesium. These specimens were found to be significantly closer to the expected concentration (median 148.2%, $p = 0.0005$) but there was still wide variation in the concentrations measured, and the coefficient of variance was found to be higher. It would appear that this degree of variation may be the inevitable and unavoidable result of preparing drug infusions from stock solutions at the bedside. These findings present a strong argument for the use of pre-prepared syringes of drugs at their final concentration in the critical care environment, and highlight once again the difficulties healthcare professionals encounter when dealing with different ways of expressing drug concentrations, on this occasion a conversion from grams to millimols.

Placing the findings in the context of other published evidence

In 2004, Jensen and colleagues performed a wide-ranging systematic literature review to identify evidence-based interventions with the same aim (Jensen et al., 2004). On the basis of evidence published at the time, they made 12 recommendations. The strongest recommendations were that ampoule labels should be carefully read, label legibility and contents should be optimised to an agreed standard, syringes should almost always be labelled, and that the workspace should be tidy and well organised. Other recommendations that were less well supported by published evidence included checking all drugs with a second person, avoiding similar packaging and drug presentations, and the use of pre-filled syringes. In addition, the same investigators have designed clearer labels for syringes used for drug infusions used in the operating theatre, and have shown a significant reduction in drug errors in approximately 29 000 anaesthetics (Merry et al., 2007). It is encouraging that many of the patient safety themes that became evident in this thesis are recognised as being important by other researchers and that my findings may contribute to evidence-based recommendations in the future.

Is simulation a valid research tool?

The contribution of ampoule labelling towards drug dosing errors is almost impossible to study in real life, due to the unpredictable nature of medical emergencies and the need for observation of physicians in practice. Using high fidelity patient simulation as a research tool to examine drug safety issues in a randomised, controlled trial is a novel approach and avoids these pitfalls. It is also the only practicable means of assessing medical students' clinical competence as they are forbidden from treating patients independently. Merry and colleagues have used high fidelity simulation to pilot a safety device aimed at reducing medication errors in the operating theatre before testing it in clinical practice (Merry et al., 2002; Webster et al., 2004). The results of the two studies were remarkably similar, lending weight to the argument that high fidelity simulation is a valid and appropriate technique to have chosen.

Simulation is gaining credence as an assessment tool for doctors. In Ottawa it is being used to evaluate the crisis resource management skills of trainee doctors, and Likert scales have been developed for performance in five categories that are distilled into an overall score (Kim et al., 2006). The paradigm appears robust, with low levels of inter-rater scoring variability and overall scores that correlate with participants' seniority. A multi-centre study of anaesthetic trainees' performance in simulated scenarios has also been conducted that are used as formal assessments of competence (Schwid et al., 2002). Evidence is also emerging that high fidelity simulator-based training improves clinical competence in endovascular surgery (Dawson et al., 2007), paediatric airway management (Overly et al., 2007), colonoscopy (Sedlack et al., 2007) and the management of shoulder dystocia (Crofts et al., 2006) amongst others. Proving that simulated scenarios accurately reflect real life or improve patient outcome are two further steps that have not yet (and may never be) made. It is noteworthy that the concept of simulation is accepted as highly beneficial in other safety critical arenas such as the airline and nuclear power industries.

Causing a new problem by solving an old one

Consensus will probably never be reached about the best way to label ampoules. Many safety researchers recommend that ampoule labels should use colour, text and font to allow drugs to be differentiated from each other, whilst others argue that if all ampoules were identical then at least doctors would be forced to read them (Wildsmith, 2002). A frequent concern is that by making any changes to improve safety, there are unforeseen consequences that can cause harm. Reason describes this as 'Dangerous Defence' and an example from the airline industry is given on page 40. When syringe labels were changed from a variety of different systems used in the United Kingdom to the International Colour Coding system, there were reports of increased likelihood of wrong drug administration errors, interestingly using a simulated scenario as a research tool (Haslam et al., 2006). Although only one drug was given in active error, latent errors occurred in 15% of drug administrations. The only factor conferring protection against error was

prior experience of the new labelling system. The authors concluded that the period of transition represented a time of increased risk of drug administration error.

In correspondence generated by the paper, Webster and Merry (2007) pointed out that ‘a short term increase in the risk of drug error during the introduction of a consistent colour-coding scheme seems likely to lead to less iatrogenic harm in the long term than the continued use of up to three inconsistent colour-coding schemes in the same country and, indeed, sometimes simultaneously within the same hospitals’. In essence, they are arguing that a short term increase in error is worth the long term benefits, which is controversial when drug errors and their consequences are so difficult to quantify. This argument is equally applicable to removing ratios and percentages from ampoule labels, meaning that in essence such a move would be a ‘leap in the dark’. Perhaps this is why no regulatory authority has ruled to remove ratios from ampoules. In 1995, a senior executive of the NHS Executive in the North Thames Region involved in medicines sourcing stated that potential dangers of making such changes had been highlighted when such a move was considered (Nunn, 1995). In the mean time the new local anaesthetic levobupivacaine (ChirocaineTM, Abbott Laboratories, IL, USA) has become available. It is presented in ampoules labeled with mass concentration only and there have been no reports in the literature of dose errors since its introduction, although this does not mean that there have *been* no problems!

Will an outcome measure randomised study be required before changes are made?

These issues beg the question: what would be the catalyst that persuaded regulatory authorities to rule that drug concentrations should be expressed exclusively as mass concentration? I would argue that the findings presented in Chapter 8 make a powerful case, however at the time of writing high impact journals are once again rejecting the manuscript. Feedback suggests that the use

of high fidelity patient simulation as a research tool may be a factor, as it is perceived as being weaker evidence than that of a clinical trial.

A clinical trial designed to answer these research questions could be designed but would be impractical, unwieldy, expensive and potentially unethical. A hospital or hospitals would need to stock resuscitation areas and trolleys with adrenaline ampoules labelled either as a ratio or mass concentration. Ideally an observer would attend all emergencies and record events, including time taken to calculate the dose, the amount administered, and the outcome for the patient. The unpredictable timing and relative rarity of such events would mean a substantial staff of observers would be required. There are two major ethical difficulties with such a study. First, participants would be unlikely to be able to consent to participate in the study due to unconsciousness or lack of time in an emergency, which poses some difficulties under the Mental Capacity Bill and European Union clinical trials directive 2001/20/EC (Liddell et al., 2006). Second, it could be argued that the data presented in this thesis is sufficient to show that patients randomised to be treated with the ampoules labelled as a ratio would be at such a great risk of harm that the study should not be conducted. Comparing dual labelled ampoules with those solely labelled with mass concentration might be an option, under which circumstances it would be reasonable to expect smaller differences between the groups and increasing the size of the study population. Conducting a pilot in the simulator would guide the necessary power studies but there is a danger of creating a circular argument. A study to validate high fidelity patient simulation against clinical performance or even patient outcome would be another approach but such studies would be even more difficult to design.

Will one nationally reported case be the catalyst?

It is possible that a scientific study will not drive change, but a case or cases reported in the media. Two errors occur with depressing regularity: the accidental and almost invariably fatal administration of intrathecal vincristine in a 'syringe swap' error for methotrexate or cytosine, and the inadvertent administration of enteral feed into the lungs through an incorrectly positioned naso- or orogastric

tube. Publicity about a case of the former that resulted in the death of Wayne Jowett at the Queen's Medical Centre, Nottingham, in January 2001 was critical to the formation of the NPSA and the government committed to eliminating the error by the end of the same year (Donaldson, 2002). A great deal of endeavour has gone into addressing wrong route errors, yet the June 2007 issue of *Anaesthesia* contained reports of the inadvertent epidural administration of insulin (Kal et al., 2007), fatal neuroglycopenia after the accidental use of 5% glucose solution to flush an arterial catheter (Sinha et al., 2007) and the administration of enteral drugs intravenously (Nicholson Roberts and Swart, 2007) with an accompanying editorial expressing the view that such errors bring shame upon the medical profession (Bell, 2007). The monotony of these reports suggests that exhortations to 'try harder', suspending the doctors, outrage in the headlines, or even guilt will not make a difference – the remedy lies in better design (Nolan, 2000; Reason, 2000; Wu, 2000). In wrong route error, efforts are concentrated on designing incompatible Luer lock connectors that prevent universal connection (Lanigan, 2002). In drug administration error, information technology and bar-code readers may offer a solution.

Information technology as an intervention in intravenous drug administration error

Computers are now a well established adjunct to drug prescribing, computerised physician order entry (CPOE) in combination with clinical decision support systems were discussed in detail on page 38. Their use has been shown to reduce ADEs (Bates et al., 1998; Bates et al., 1999a), length of hospital stay and expenditure on drugs (Evans et al., 1998), but not by all investigators (King et al., 2003; Potts et al., 2004; Han et al., 2005). The use of these systems is confined to the prescription of drugs, not their administration.

Bar-code technology

Bar-codes are now well established to aid dispensing, inventory keeping and billing in pharmacies worldwide. Computerised systems using bar-codes have

been shown to reduce dispensing errors and hence potential ADEs (Poon et al., 2005; Poon et al., 2006). The US Food and Drug Administration has now ruled that all drug and biological products sold to hospitals incorporate bar-codes on their labels with effect from this year (2004). This prepares the way for widespread adoption of bar-code enabled point of care systems, which allow bar-codes on a patient's identification wristband to be checked against the medication packaging. Such systems will only become truly effective if medications are widely available in unit dose packaging, but only about a third of all medications are currently available in this form. Although this situation is likely to improve, hospitals wanting to take advantage of this technology soon may need to repackage some drugs themselves or have it done by a third party. In the US, these systems have been in routine use by nurses on drug rounds since 2004 in some acute and long term care settings. When used in conjunction with electronic drug charts, direct observation revealed substantial and significant increases in administration accuracy and a halving of drug administration errors (Paoletti et al., 2007).

Bar-code technology in the operating theatre

A group based at the University of Auckland in New Zealand has been developing an integrated electronic drug administration and automated anaesthesia record system that aims to improve patient safety in the operating theatre and beyond (Merry et al., 2001b). The system consists of a set of rules and devices for organising the anaesthetic workspace and a computer with a bar-code reader to provide a crosscheck for drug administrations and to generate an anaesthetic record automatically. All drugs, whether administered by bolus or infusion, are identified by preprinted labels, which are organised in trays and colour- and bar-coded. When a drug is needed (or an infusion started or its rate changed) the anaesthetist is expected to read the label and then scan it with the bar-code reader before administering its contents. A computer interprets the bar-code, announces the name of the drug (with a pre-recorded voice), and redisplay the name on a screen in large font along in its corresponding colour code. The computer identifies and displays a default dose, which may be accepted or altered by the anaesthetist. The name, time, and dose of the drug are recorded and may be

displayed and edited at will. Infusion rates are distinguished from intravenous boluses and infusion purges, and it is assumed that these rates remain constant until the next entry related to the same infusion. The voice file contains the drug name but does not indicate concentration, so that the enunciated information will be correct even if the user elects to dilute the contents of the syringe. Pre-filled syringes and ampoules have their expiry date included in their bar code, enabling the computer to warn of attempts to administer outdated drugs. The system can also compile a running tabulation of drug cost for inventory and billing purposes.

The system has been evaluated in a high fidelity patient simulator and in a clinical trial. In the pilot evaluation in the simulator, 10 anaesthetists were observed while providing anaesthesia for two simulated surgical procedures, using conventional methods and the drug administration system (Merry et al., 2000; Merry et al., 2002). Users rated aspects of each method on 10 cm visual analogue scales and comments were invited. They perceived the bar-code system as being safer, better organised, well laid out and acceptable for clinical use. The use of pre-filled syringes saved time in the preparation of drugs both before and during anaesthesia. Although only 40 anaesthetics were observed, three drug administration errors were seen during conventional anaesthesia and one (which was intercepted by the bar-code reader) using the bar-code system. Anaesthetists clearly took some time to get used to the system, on occasions failing to use the syringe tray correctly or forgetting to swipe a syringe past the bar-code reader.

The clinical evaluation of the bar-code system was undertaken with the co-operation of 15 anaesthetists who used it in 15 cardiac cases and compared it with 15 conventional cardiac anaesthetics (Webster et al., 2004). The findings were remarkably similar to the simulated evaluation, with documented improvements in perception of safety, organisation and usability. The bar-code system had been refined to rely more upon pre-filled syringes, which was found to add approximately €23 to the anaesthetic costs.

The bar-code and anaesthesia record system appears to be an important step forward in reducing medication errors in the operating theatre. It is now marketed as SaferSleep™, and has been installed in several hospitals in the US. No

improvements in patient outcome or overall reduction in costs (when increased drug costs and the cost of the hardware are balanced against potentially reduced litigation) have yet been documented.

The system as it stands would not address the problem of drug administration error due to difficulties with dose calculations, whether mass concentration, ratio or percentage. The system identifies the drug in the ampoule or syringe but not the concentration, to allow the user flexibility to dilute the drug to their preferred concentration – a feature that is very important in many situations, for example paediatric anaesthesia. The system suggests a default dose, but does not specify the volume to be administered. It has only been evaluated in elective cases in the operating theatre, and it is not known whether it would be equally effective in the hands of non-anaesthetists, in other clinical areas, or in emergencies. It remains to be seen whether it could be modified for use under these circumstances.

Final conclusions

The findings presented in this thesis repeatedly show that ampoule labels in their current format cause confusion amongst doctors and medical students that is highly likely to lead to clinical error and thus potentially patient harm. The influences of two interventions are examined. Improving drug administration education for medical students improves their skills and knowledge, especially when the high fidelity simulator is used. Such intensive teaching is time consuming and expensive; online modules were also found to be useful but at best only seem to be viewed by approximately half the students. Removing confusing expressions of drug concentration from ampoule labels would also appear to be an effective intervention, but doctors and nurses still struggle with units of mass like micrograms and mols. Smart infusion pumps and bar-code technology coupled with the wide availability of pre-filled syringes may offer a solution, but the technology is relatively new, not fully proven and only time will tell whether it solves or adds unforeseen levels of complexity to the problem.

APPENDIX 1

ONLINE CONTINUING MEDICAL EDUCATION MODULE

Improving doctors' understanding of drug administration

As a result of the findings of the online questionnaire hosted by Doctors.net, an online continuing medical education module was written targeted at trainee doctors and medical students in their foundation years. The module was first published online in 2005, has been completed by 431 doctors since. Those who complete the module successfully by scoring 70% in the final assessment are awarded continuing professional development points. The module is currently in its third revision.

Format of drug administration module

The module consists of an introduction followed by 12 multiple choice questions. These are completed before the main part of the module and repeated afterwards to see if the candidate has achieved the goals of the module and passed. There are three interactive cases to illustrate the main teaching points of the module, which are to introduce the concept of bioavailability, the different routes of administration of drugs and the means of reducing ADEs, and also to teach how to calculate the correct drug doses in solution.

The module can be undertaken either on Doctors.net or on the University of Cambridge ERWeb. To participate, Doctors.net subscribers should log in, then follow the link to the Education section. The menu contains a link to the Clinical Foundation programme, where the Drug Dosage and Administration module can be found in the Good Clinical Care section. The module is recognized as being worth two hours of continuing professional development by the UK Conference of Educational Advisors (UKCEA), which accredits all educational resources for general practitioners. Alternatively the module can be viewed at (<http://erweb.medschl.cam.ac.uk/drug-dosage/?s=G>).

For completeness, the text is reproduced below.

Basics of drugs dosages and administering drugs.

Dan Wheeler – University Department of Anaesthesia, University of Cambridge

Prescribing and administering drugs is a fundamental part of being a doctor but sometimes teaching the skills involved is overlooked in favour of mechanisms of drug action. Every year tens of thousands of people die or are disabled by medication errors: about 1% of prescriptions contain a serious error, 19% of drug administration episodes involve a mistake and 1-2% of inpatients are harmed by medication errors.

The number of reported deaths in England and Wales from medication errors and the adverse effects of medicines showed an upward trend from 1999-2000 (Audit Commission report, 2001). They account for about one-fifth of deaths due to all types of adverse events in hospital and are also an increasingly common stimulus to litigation (Ferner RE, Whittington RM, 1994).

The DH's report, *An Organisation with a Memory*, found that 10 000 hospital patients each year have serious adverse reactions to medicines, and one-fifth of clinical negligence litigation stems from hospital medication errors. This report suggested that adverse drug reactions and medication errors cost the NHS about £0.5 billion per annum and that

'about 70 per cent of prescribing decisions are made by house officers and senior house officers even though they have little experience of medicines. Studies have also shown that they are prone to increasing error rates when they are stressed, tired, distracted, or are working in unfamiliar surroundings... Only a small proportion of new doctors believe that their induction dealt adequately with medicines management issues.'

The Chief Medical Officer (*Building a Safer NHS for Patients, 2001*) has set trusts a target to reduce serious medication errors by 40% by 2005.

Given the above it is important for all new doctors to understand the basics of drug dosages and administration. This module will address drug administration, the process by which a drug gets from its container to the systemic circulation. It will discuss the relative merits of different routes of administration, and how to calculate drug doses correctly.

Learning objectives

1. be aware of the concept of bioavailability and the different routes of administration of drugs
2. be able to calculate the correct drug doses in solution for a patient
3. understand that Adverse Drug Events (ADEs) are very common and associated with substantial mortality, morbidity, costs and litigation

Format:

All correct answers are in bold.

Questions (12)

Text:

- The concepts of pharmacokinetics
- Routes of drug administration (pros and cons)
- Factors affecting bioavailability related to route of drug administration
- Calculation of drug doses
- Adverse Drug Events including an introduction to drug interactions

Cases (3)

Questions (12) – Repeated

Questions

1. In acute severe asthma, salbutamol should be administered by the intravenous route immediately.

True

False

2. Adverse Drug Events in the community are thought to be responsible for 4% of acute medical admissions to the hospital.

True

False

3. Adrenaline (epinephrine) can be effectively administered by the following routes:

Oral (PO)

Rectal (PR)

Intramuscular (IM)

Intravenous (IV)

Endotracheal (ET)

4. Diclofenac given rectally is less likely to cause gastric ulcers than when given orally.

True

False

5. Anticoagulation with warfarin can be adversely affected by:

Co-proxamol

NSAIDs

Ciprofloxacin

Phenytoin

Metronidazole

6. Considering morphine, place the routes of administration in the order of decreasing bioavailability.

Intravenous (IV), Oral (PO), Intramuscular (IM)

Oral (PO), Intramuscular (IM), Intravenous (IV)

Intramuscular (IM), Oral (PO), Intravenous (IV)

Intravenous (IV), Intramuscular (IM), Oral (PO)

Oral (PO), Intravenous (IV), Intramuscular (IM)

7. In bowel obstruction, drugs can be effectively delivered by the following routes:

Oral (PO)

Rectal (PR)
Intramuscular (IM)
Intravenous (IV)
Nasogastric (NG)

8. Water soluble drugs are better delivered by the topical route than lipid soluble drugs.

True
False

9. The following can cause hyperkalaemia when administered together:

Losartan - bendrofluazide
Perindopril - sando K
Enalapril - furosemide
Ramipril - spironolactone
Lisinopril - co-amilofruse (Frumil™)

10. How much adrenaline is there in 15 mL of 1:1 000 solution of adrenaline (epinephrine)?

150 mcg (micrograms)
1 500 mcg
150 mg
15 mg
15 000 mg

11. How much lidocaine is there in 12 mL of 1% w/v lidocaine?

120 mcg
12 g
12 mg
120 mg
1 200 mg

12. Some Mini-Jets™ of atropine contain 3 mg of drug in 30 mL. What is the concentration of the solution?

1 mg/mL
10 mcg/mL
0.1 mg/mL
1 mcg/mL
0.1 mcg/mL

Pharmacokinetics

Pharmacokinetics describes how the body affects the processes of drug:

Distribution
Absorption
Metabolism
Elimination

As this module is concerned with drug *administration*, it will only address absorption.

Drugs can be absorbed by the following routes:

- oral (PO)
- intramuscular (IM)
- subcutaneous (SC)
- intravenous (IV)
- rectal (PR)
- sublingual (SL)
- inhaled or nebulised
- topically

Most drugs are absorbed by simple diffusion down a concentration gradient. The rate of absorption depends on the water or fat solubility of the drug and its ionic charge, which are related to the pH of the surroundings. The permeability, surface area and blood supply of the tissue across which absorption occurs are also important.

Most drugs are administered orally. However, the gut is an inhospitable environment for many drugs. Drugs can be destroyed by the acidic environment and by peptic enzymes. Their absorption can also be diminished in bowel obstruction, bowel disease, vomiting, overgrowth of intestinal bacteria, during decreased intestinal blood flow and by interacting with foods.

Once a drug has crossed the gut wall it is transported to the liver by the portal vein. One of the liver's many functions is to clear toxins from the blood and metabolise them. Many drugs are therefore cleared from the portal blood and metabolised without entering the systemic circulation. This is called 'first pass metabolism'. Some drugs are particularly prone to first pass metabolism, for example morphine, GTN and propranolol.

Bioavailability

Bioavailability describes the proportion of a drug dose (expressed as a percentage) that reaches the systemic circulation compared to the amount that would be present in the systemic circulation had the same dose been administered IV. An IV injection has 100% bioavailability. If a drug has a low oral bioavailability,

another route should be chosen. The table below summarises the pros and cons of different routes of drug administration.

Route	Advantages	Disadvantages
Oral	Easy. Preferred by patients. 'Slow-release' preparations may be available to extend duration of action. Drugs can be formulated in such a way as to protect them from digestive enzymes, acid, etc.	Unsuitable in patients who are uncooperative, strictly "nil by mouth", are vomiting profusely or have ileus. Most orally administered drugs are absorbed slowly. Unpredictable absorption due to degradation by stomach acid and enzymes.
Rectal	Good absorption - the haemorrhoidal veins drain directly into the inferior vena cava, avoiding hepatic first pass metabolism.	May not be suitable after rectal or anal surgery. Some patients dislike suppositories.
Subcutaneous or intramuscular	Good absorption, especially for drugs with a low oral bioavailability. Onset is more rapid than the above routes. Depending on formulation can have very long duration of action, e.g. depot antipsychotics and contraceptives.	Absorption may still be unpredictable if peripheries are poorly perfused. Injections hurt, cause bruises and frighten children and needle phobics.
Intravenous	Dependable and reproducible effects. Entire administered dose reaches the systemic circulation immediately - the dose can be accurately titrated against response.	Requires a functioning cannula. More expensive and labour intensive than other routes. Cannulation is distressing to some patients, especially children. Cannulae are prone to infection. IV injection of drugs may cause local reactions.
Topical	Easy. Non-invasive. High levels of patient satisfaction.	Most drugs have a high molecular weight and are poorly lipid soluble, so are not absorbed via skin or mucous membranes. Very slow absorption.
Inhaled	Very rapid absorption due to the huge surface area of the respiratory endothelium. Bronchodilators and inhaled steroids can be targeted to lungs with low levels of systemic absorption.	Bioavailability depends on patients' inhaler technique and the size of drug particles generated by the delivery technique.

Adverse Drug Events

Adverse Drug Events (ADEs) can be due to:

- **a medication error** in the process of prescribing, dispensing, or administering a drug, whether there are adverse consequences or not
- **a drug administration error**, leading to:
 - administration of the wrong drug *and/or*
 - administration of the wrong dose *and/or*
 - administration of the wrong formulation *and/or*
 - administration by the wrong route *and/or*
 - administration to the wrong patient
- **a dose error** when the wrong dose of a drug is administered
- **an Adverse Drug Reaction (ADR)** when a noxious and unintended response has occurred to a drug in doses normally used in man

Knowing about ADEs is important because:

- They are common.
- They are related to substantial morbidity and mortality.
- They can result in considerable direct or indirect costs.

Knowing about ADRs is important because:

- They can cause substantial morbidity and even mortality.
- Anaphylactic and anaphylactoid reactions do not always present with “textbook” features of urticarial rash and wheeze.
- Many anaphylactic reactions occur when a patient *who is known have an allergy to a certain drug* is given that drug or a similar drug by accident.

Drug interactions

Drug interactions are a common cause of adverse drug events. There are too many to list, but the principles behind drug interactions and some examples follow:

Pharmacokinetic

- Drugs can interact outside the body before administration. For example, when morphine and cyclizine solutions are mixed in patient-controlled analgesia infusion devices, cyclizine can precipitate as crystals.
- The absorption of drugs in the intestine is altered by drugs that influence gastric emptying, for example opioids that slow emptying or metoclopramide that promote it.
- Distribution of drugs can be altered if they are displaced from protein binding sites by other compounds. Warfarin is liberated from serum albumin by aspirin.
- Metabolism of drugs by the liver can be altered by drugs that induce or inhibit hepatic cytochrome P₄₅₀ enzymes. For example, phenytoin increases the metabolism of digoxin, thyroxine and tricyclic antidepressants.
- Elimination of some drugs from the kidneys can be altered by others, for example probenecid decreases excretion of penicillin.

Pharmacodynamic

Different classes of drugs may act by different mechanisms but have the same physiological effect. For example, beta-blockers, ACE inhibitors and nitrates can all reduce systemic blood pressure. The additive effect of each drug can be summative (net effect equals the sum of the individual drug effects), or there may be synergy (net effect exceeds sum of individual drug effects) or potentiation (one drug increases the effect of another). Alternatively, drugs may antagonise each other. Interactions may also be indirect, for example the hypokalaemia induced by diuretics increasing the risk of digoxin toxicity.

Calculation of doses

Drugs can be administered safely up to certain doses, beyond which they become toxic. Doses are calculated usually based on the patient's age and are expressed as mass of drug per lean mass of the patient. Doses can be found in the British National Formulary (also online at <http://www.bnf.org/>) or the drug information sheet in the drug packaging.

An error can be made when administering a drug in any formulation, although calculating the correct volume of a drug in solution is most open to large errors.

Errors commonly occur when doctors or nurses become confused about how many micrograms there are in a milligram.

It is important to remember that:

$$\begin{array}{rcl} 1000 \text{ mcg} & = & 1 \text{ mg} \\ 1000 \text{ mg} & = & 1 \text{ g} \\ 1000 \text{ g} & = & 1 \text{ kg} \end{array}$$

and that:

$$\begin{array}{rcl} \text{kilogram (kg)} & = & 10^3 \text{ g} \\ \text{milligram (mg)} & = & 10^{-3} \text{ g} \\ \text{microgram (}\mu\text{g or mcg)} & = & 10^{-6} \text{ g} \\ \text{nanogram (ng)} & = & 10^{-9} \text{ g} \end{array}$$

It is also important to write prescriptions clearly. It is easy to mistake the Greek symbol mu (μ) meaning micro (10^{-6}) for an 'm' meaning milli (10^{-3}) if it is not written clearly. If such a prescription is not read correctly, the patient could receive 1 000 times too much or too little drug. It is wise to write out micrograms in full, or if pressed for space to abbreviate to 'mcg'.

The concentration of drugs in solution can also be expressed in a number of different, confusing ways, for example as mass per unit volume (e.g. milligrams or millimols per millilitre), ratios (e.g. 1 in 1 000), or percentages.

To calculate the mass of drug in a solution:

- If the solution is expressed as *mass per unit volume*, then multiply by the volume of the solution. This is probably the most straightforward calculation but is still open to error, especially when milligram to microgram conversions are needed.

E.g. 10 mL of 3 mg/mL solution = 30 mg of drug

- If the solution is expressed in a *ratio*:

A 1:1 000 solution means there is 1 g in **1 000 mL**.

Another way of expressing this is to divide by 1 000, so that 0.001 g = 1 mg is in 1 mL.

Therefore 1 mL of 1:1 000 solution = 1 mg of drug

A 1:10 000 solution means there is 1 g in 10 000 mL.

Another way of expressing this is to divide by 10 000, so that 0.0001 g = 0.1 mg = 100 mcg is in 1 mL.

Therefore 10 mL of 1:10 000 solution = 1 mg of drug

You can see that any error made here is likely to be by a factor of 10 or even more!

- If the solution is expressed as *a percentage*:

A 1% solution means that there is 1 g in **100 mL**.

If there is 1 g in 100 mL, there is $\frac{1}{100}$ g in 1 mL.

$\frac{1}{100}$ g is 0.01 g = 10 mg.

Therefore the concentration is 10 mg/mL.

Again you can see that confusing percentages with ratios can lead to errors of 10 times or more!

E.g. 10 mL of 0.5% w/v (weight/volume) = 10 mL of 5 mg/mL = 50 mg of drug

Case 1

An 82 year old woman is admitted to the hospital with a torrential GI bleed. She has fresh haematemesis, is passing malaena and has a two-day history of epigastric pain. She was recently started on a course of enteric coated diclofenac for osteoarthritis of the hip.

Q: If she has a gastric ulcer, it could not have been caused by diclofenac as it was the enteric coated preparation.

True

False

NSAIDs inhibit prostaglandin synthesis systemically, therefore the route of administration does not affect the incidence of gastric side effects.

You see in the patient's records that she has been on warfarin for atrial fibrillation.

Q: Is there a known drug interaction between NSAIDs and warfarin?

Yes

No

Drug interactions are very common. It has been found that in the U.S.A, 1-4% of acute medical admissions are directly precipitated by an adverse drug event. Warfarin seems to be involved in ADEs most frequently, with the commonest combinations being:

1. Warfarin - NSAIDs
2. Warfarin - Sulfa drugs
3. Warfarin - Macrolides
4. Warfarin - Quinolones
5. Warfarin - Phenytoin
6. ACE inhibitors - Potassium supplements
7. ACE inhibitors - Spironolactone
8. Digoxin - Amiodarone
9. Digoxin - Verapamil
10. Theophylline - Quinolones

Her clotting screen comes back and she has an INR of 13. The medical registrar advises you to give 5mg Vitamin K (10mg/mL).

Q: The intramuscular route would be most suitable to administer Vitamin K

True

False

Intravenous administration of a drug results in greater bioavailability compared to the intramuscular route. In addition, when administering a drug intramuscularly in a patient with a raised INR, the risk of intramuscular bleeding is dramatically increased and should therefore be avoided. Vitamin K should be given intravenously. Nevertheless, you ought to be aware of the fact that the commonest preparation of Vitamin K is known to cause anaphylactic reactions in a considerable number of patients, and use of intravenous Vitamin K should be balanced against the risks of bleeding.

Case 2

A 15 year old boy is brought to A&E increasingly wheezy and short of breath. He has a history of asthma, which is normally controlled by inhalers. However, on this occasion the inhalers have not provided any significant relief of the symptoms. As the doctor on call you decide to give him oxygen and nebulised β_2 -agonists.



Q: Nebulisers are better than inhalers at delivering bronchodilators because they can be given more quickly.

True

False

Nebulisers are better than inhalers as the particle size of bronchodilators delivered is smaller. The proportion of inhaled drugs delivered to the lungs depends on particle size. Particles with a diameter $>10\mu\text{m}$ tend to be deposited in the mouth, nose, pharynx and larynx. Droplets of $\sim 5\mu\text{m}$ diameter, the size generated by inhalers, are deposited in the trachea and larger bronchi. Droplets of $1\mu\text{m}$ are delivered to the small bronchioles and alveoli, but in large numbers may impair gas exchange. Therefore the ideal particle diameter is $1\text{--}5\mu\text{m}$, which is achieved by a nebuliser.

Your hospital protocol suggests that steroids should be given in an acute asthma attack.

Q: Administering steroids intravenously would be more effective than orally.

True

False

Steroids can be given either orally or intravenously. It is important to remember that there does not seem to be a significant difference which route is chosen as steroids act in the long term so may not have much of an effect for at least 30 minutes. If the patient can tolerate oral medication, then 40mg oral prednisolone is perfectly acceptable, whereas if the patient is unable to swallow, 200mg hydrocortisone intravenously can be given instead.

The patient does not seem to be improving and you decide to give aminophylline. It is mentioned in the patient's records that he has been taking 200 mg aminophylline orally, three times per day.

Q: The best management would be to start a slow IV infusion of aminophylline without giving a loading dose.

True

False

Theophylline is the active ingredient of aminophylline. In normal concentrations its metabolism by liver enzymes is based on first order kinetics. However, once all the enzymes are saturated, the remaining active drug accumulates (zero order kinetics). Metabolism can also vary in patients with hepatic impairment or heart failure, smokers, or if certain other drugs are taken concurrently.

Patients who have never had aminophylline before need to be loaded first with an IV bolus followed by a slow infusion. However, if a patient has been on oral aminophylline, the loading dose should be omitted as a steady state concentration has already been achieved.

It is important to know the plasma levels of theophylline as theophylline has a narrow therapeutic index. That means the toxic dose is not considerably greater than the therapeutic one. It is recommended that when managing patients taking oral theophylline or aminophylline, intravenous aminophylline should not be given unless plasma theophylline concentration is available to guide dosage. If the patient is severely unwell, and there is uncertainty about the plasma theophylline levels, an IV salbutamol infusion could be started instead.

Therefore, in the example above the patient should not be given aminophylline before the plasma theophylline levels are known.

Case 3

You are called to see a 67 year old gentleman whose ECG shows a ventricular tachycardia. You can feel the radial pulse and the blood pressure is 120/60. Following the hospital's protocol, you decide to give a bolus of 50 mg lidocaine over 30 seconds. Lidocaine 1% w/v is available in 10 mL vials.

Q: You need to administer 0.5 mL of the solution.

True
False



The concentration of 1% w/v means that there is a gram (1 g = 1000 mg) of solute (lidocaine) in 100 mL of solution (ratios are based on thousands, so there is the possibility of making an order of magnitude error here). This divides down to 10 mg/mL. Therefore, this gentleman needs 5 mL of 1% lidocaine, not 0.5 mL. If you have trouble remembering this, simply move the decimal point one place to the right to get the correct concentration in mg/mL. So, using another local anaesthetic as an example:

$$\text{Bupivacaine 0.5\%} = \underline{0.5} = \underline{5.} = 5 \text{ mg/mL}$$

The above dose is immediately followed by a slow intravenous infusion of lidocaine at 4 mg/minute for 30 minutes, 2 mg/minute for 2 hours, then 1 mg/minute.

Q: The total amount of lidocaine that will have been administered 3 hours later is 390mg.

True
False

The patient has been given 50 mg as a loading bolus. Over the first 30 min he will also be administered $30 \times 4 = 120$ mg. The following two hours (120 min), $120 \times 2 = 240$ mg will be infused. That will be followed by $30 \times 1 = 30$ mg given for the last half hour. Total time: 3 hours. Therefore the total dose would be $50 + 120 + 240 + 30 = 440$ mg.

Despite all your efforts the patient is not improving. He is now becoming more bradycardic and hypotensive. You have been advised to give atropine at 20 mcg/kg. The patient weighs 70 kg. You are given a Mini-Jet™ of atropine with 3 mg in 30 mL.

Q: You need to give 140 mcg atropine.

True
False

The total amount of atropine that needs to be given is $20 \times 70 = 1400$ mcg, which is 1.4 mg (1000 mcg = 1 mg).

Q: The concentration of the Mini-Jet™ is 0.1% w/v.

True
False

Since there is 3 mg in 30 mL of solution, there would be 10 mg in 100 mL solution = 0.01 g in 100 mL; therefore the solution is 0.01% w/v.

Unfortunately the patient does not respond to the atropine and goes into asystolic arrest. You begin Advanced Life Support. ALS guidelines state that 1 mg adrenaline (epinephrine) is to be administered every three minutes.

Q: If adrenaline (epinephrine) is available in 1:10 000 vials, you need to administer 1 mL every three minutes.

True
False

A ratio of 1:10 000 means that there is one gram of solute (adrenaline, epinephrine) in 10 000 mL of solution. This means that there is 0.1 mg adrenaline (epinephrine) in 1 mL. Therefore, for 1 mg adrenaline (epinephrine), 10 mL of 1:10 000 solution should be given.

Questions

1. In an acute severe asthma attack, salbutamol should be intravenously immediately.

True

False

2. Adverse Drug Events in the community are responsible for 4% of acute medical admissions to the hospital.

True

False

3. Adrenaline (epinephrine) can be administered by the following routes:

Oral (PO)

Rectal (PR)

Intramuscular (IM)

Intravenous (IV)

Endotracheal (ET)

4. Diclofenac given rectally is less likely to cause gastric ulcers than when given orally.

True

False

5. Anticoagulation with warfarin can be adversely affected by:

Co-proxamol

NSAIDs

Ciprofloxacin

Phenytoin

Metronidazole

6. Considering morphine, place the routes of administration in the order of decreasing bioavailability.

Intravenous (IV), Oral (PO), Intramuscular (IM)

Oral (PO), Intramuscular (IM), Intravenous (IV)

Intramuscular (IM), Oral (PO), Intravenous (IV)

Intravenous (IV), Intramuscular (IM), Oral (PO)

Oral (PO), Intravenous (IV), Intramuscular (IM)

7. In bowel obstruction, drugs can be effectively delivered by the following routes:

Oral (PO)

Rectal (PR)

Intramuscular (IM)

Intravenous (IV)

Nasogastric (NG)

8. Water soluble drugs are better delivered by the topical route than lipid soluble drugs.

True

False

9. The following can cause hyperkalaemia when administered together:

Losartan - Bendrofluazide

Perindopril - Sando K

Enalapril - Furosemide

Ramipril - Spironolactone

Lisinopril - Co-amilofruse

10. How much adrenaline is there in 15 mL of 1:1 000 adrenaline (epinephrine)?

150 mcg (micrograms)

1 500 mcg

150 mg

15 mg

15 000 mg

11. How much lidocaine is there in 12 mL of 1% w/v lidocaine?

120 mcg

12 g

12 mg

120 mg

1 200 mg

12. Mini-Jets™ of atropine contain 3 mg of drug in 30 mL. What is the concentration of the solution?

1 mg/mL

10 mcg/mL

0.1 mg/mL

1 mcg/mL

0.1 mcg/mL

APPENDIX 2

PROTOCOL USED FOR SIMULATED ANAPHYLAXIS SCENARIO



ASSOCIATION OF ANAESTHETISITS OF GREAT BRITAIN AND
IRELAND

MANAGEMENT OF A PATIENT WITH SUSPECTED ANAPHYLAXIS

Initial therapy

1. Stop administration of drug(s) likely to have caused the anaphylaxis
2. Call for help
3. Maintain airway: give 100% oxygen
4. Lay patient flat with feet elevated
5. Give **ADRENALINE (epinephrine)**. This may be given intramuscularly in a dose of 0.5 mg and may be repeated every 10 minutes according to the blood pressure and pulse until improvement occurs.

Alternatively, 50 to 100 µg intravenously over 1 minute has been recommended for hypotension, with titration of further doses as required.

In a patient with cardiovascular collapse, 0.5 to 1 mg may be required intravenously, in divided doses by titration. This should be given at a rate of 0.1 mg/minute, stopping when a response has been obtained.

6. Start intravascular volume expansion with suitable crystalloid or colloid.

TURN OVER

Secondary therapy

1. Antihistamines
(chlorphenamine) infusion
CHLORPHENIRAMINE
10-20 mg by slow intravenous infusion
Consider H₂ antagonists
2. Corticosteroids
HYDROCORTISONE - 100-300 mg intravenously
3. Catecholamine infusions - Starting doses:
ADRENALINE (epinephrine) 0.05-0.1 µg/kg/min; (approx. 4-8 µg/min)
5 mg adrenaline in 500 mL saline = 10 µg/mL
NORADRENALINE (norepinephrine) 0.05-0.1 µg/kg/min; (approx. 4-8 µg/min)
4 mg noradrenaline in 500 mL saline = 8 µg/mL
4. Perform arterial blood gas analysis
Consider **BICARBONATE** (0.5-1.0 mmol/kg iv) for acidosis.
0.5 – 1.0 mmol is equivalent to 0.5 – 1.0 mL of an 8.4% solution of sodium bicarbonate
5. Airway evaluation (before extubation).
6. Bronchodilators may be required for persistent bronchospasm.

Investigations

1. Do not attempt any investigation until the immediate treatment of the emergency had not been completed.
2. Diagnosis is made on clinical grounds. It is important to make a detailed written record of events, including timing of administration of all drugs in relation to onset of reaction.
3. Approximately 1 hour after the beginning of the reaction, take 10 mL venous blood into a plain glass tube. Separate serum and store at –20C until the sample can be sent to a reference laboratory for estimation of serum tryptase concentration.
4. The patient and his/her general practitioner should be made aware of the reaction and its implication.

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APPENDIX 3

PEER REVIEWED PAPERS PUBLISHED REPORTING THIS WORK

The following papers have been published as a result of the research reported in this thesis. List presented in reverse chronological order, correct as of 17th July 2008.

Wheeler DW, Degnan BA, Sehmi JS, Burnstein RM, Menon DK, Gupta AK. Variability in the concentrations of intravenous drug infusions prepared in a critical care unit. *Intensive Care Medicine*, advance online publication Apr 22.

Wheeler DW, Degnan BA, Murray LJ, Dunling CP, Whittlestone KD, Wood DF, Smith HL, Gupta AK. Retention of drug administration skills after intensive teaching. *Anaesthesia*, 2008 Apr;63(4):379-84.

Wheeler DW, Carter JJ, Murray LJ, Degnan BA, Dunling CP, Salvador R, Menon DK, Gupta AK. The effect of drug concentration expression on epinephrine dosing errors: a randomized trial. *Annals of Internal Medicine* 2008 Jan;148(1):11-4.

Wheeler DW, Wheeler SJ, Ringrose TR. Factors influencing doctors' ability to calculate drug doses correctly. *International Journal of Clinical Practice* 2007 Feb;61 (2):189-94.

Degnan BA, Murray LJ, Dunling CP, Whittlestone KD, Standley TDA, Gupta AK, Wheeler DW. Additional teaching improves medical students' drug administration skills in a simulated emergency scenario. *Anaesthesia* 2006 Dec;61 (12):1155-60.

Wheeler DW, Whittlestone KD, Salvador R, Wood DF, Johnston AJ, Smith HL, Menon DK. Influence of improved teaching on medical students' acquisition and retention of drug administration skills. *British Journal of Anaesthesia* 2006 Jan;96 (1):48-52.

Wheeler SJ, Wheeler DW. Medication errors in anaesthesia and critical care. *Anaesthesia* 2005 Mar;60 (3):257-73.

Wheeler SJ, Wheeler DW. Dose calculation and medication error – why are we still weakened by strengths? *European Journal of Anaesthesiology* 2004 Dec;21 (12):929-31.

Wheeler DW, Remoundos DD, Whittlestone KD, House TP, Menon DK. Calculation of doses of drugs in solution: are medical students confused by different means of expressing drug concentrations? *Drug Safety* 2004 Oct;27 (10):729-34.

Wheeler DW, Remoundos DD, Whittlestone KD, Palmer MI, Wheeler SJ, Ringrose TR, Menon DK. Doctors' confusion over ratios and percentages in drug solutions: the case for standard labelling. *Journal of the Royal Society of Medicine* 2004 Aug;97 (8):380-3.

APPENDIX 4

DESCRIPTIONS OF STATISTICAL TESTS USED

This appendix briefly summarises the statistical tests used to analyse the data presented.

Parametric tests

These statistical tests are used on data that are close to being normally distributed (Kirkwood and Sterne, 2003). In this thesis, the Kolmogorov Smirnov test was used to ascertain normality. If data were not normally distributed, they were subject to analysis with non-parametric tests (see below).

Kolmogorov Smirnov test for normality

Statview (SAS Institute, 1998) tests for deviations from normal distribution using the Kolmogorov Smirnov test, which is often referred to as a normality test. The Kolmogorov Smirnov statistic quantifies the discrepancy between the distribution of a dataset and an ideal normal distribution – larger values denoting larger discrepancies. The statistic is not informative by itself, but is used to compute a p value.

The original method of Kolmogorov and Smirnov cannot be used to calculate a p value because their method assumes that the mean and standard deviation (SD) of the overall population are known (perhaps from prior work). When analysing data, only the mean and SD of the sample are generally known, not those of the overall population. To compute the p value, therefore, Statview uses the Dallal and Wilkinson approximation to Lilliefors' method (Dallal and Wilkinson, 1986).

The p value from the normality test answers this question: If one was to randomly sample from a normal population, what is the probability of obtaining a sample that deviates from a normal distribution as much (or more so) as this sample does?

Or more precisely: If the population is really normal, what is the chance that a randomly selected sample of this size would have a Kolmogorov Smirnov value as large as, or larger than, observed? Therefore if the p value is <0.05 , the data failed the normality test and the population is unlikely to be normal.

By looking at the distribution of a small sample of data, it is hard to tell whether or not the values came from a normal distribution. Running a formal test does not make it easier. The Kolmogorov Smirnov test has insufficient power to discriminate between normal and non-normal populations with sample sizes smaller than about two dozen values.

t tests

These tests are used to compare the means of two groups. A paired test is used when the two populations are matched, for example when a variable is measured in a single subject before then after an intervention, or matched controls are used. The test calculates the difference between each set of pairs and Statview analyses the list of differences based on the assumption that the differences in the entire population follow a normal distribution. The t statistic and p value are calculated from tables.

Analysis of variance

If the means of three or more groups need to be compared, the one way analysis of variance test is used. The Bonferroni / Dunn test was used to compare selected pairs of groups as part of *post hoc* testing.

Contingency tables

Contingency tables are used to record and analyse the relationship between two or more variables, most usually categorical nominal variables. In a 2 x 2 table, the categories for one variable define the rows, and the categories for the other variable define the columns. Individuals are assigned to the appropriate cell of the contingency table according to their values for the two variables. A contingency table can also be used for discrete quantitative variables or for continuous quantitative variables that have been grouped.

A χ^2 test is then used to test whether there is an association between the row variable and the column variable or, in other words, whether the distribution of the individual data points among the categories for one variable is independent of their distribution among the categories of the other. In a 2 x 2 table, this is equivalent to the comparison of proportions.

Fisher's exact test should be used instead when the overall total of the table is less than 20, or the overall total is between 20 and 40 and the smallest of the four numbers is less than five. This test is based on calculating the exact probabilities of the contingency table, as the test statistic calculated by the χ^2 test is less accurate under these circumstances.

Cramer's V is a statistic measuring the strength of association or dependency between two nominal categorical variables in a contingency table, and is calculated from the χ^2 statistic. The closer V is to 0, the smaller the association between the categorical variables, V being close to 1 is an indication of a strong association.

Coefficient of variance

The coefficient of variance is the degree to which a set of data points varies. It is often called the relative standard deviation, since it takes into account the mean. It is calculated by dividing the standard deviation by the mean.

The coefficient of variance is a dimensionless number, and is useful when discussing distributions of data in populations when the standard deviation is much less than the mean.

Non-parametric tests

Non-parametric methods are an alternative set of statistical techniques for analysing numerical data that make no assumptions about their underlying distribution, for example whether they are normally distributed or not.

Mann-Whitney U test

The Mann-Whitney test, also called the rank sum test, is a non-parametric test that compares two unpaired groups. The two samples must be independent, i.e. the response of the n^{th} person in the second sample is not a function of the response of the n^{th} person in the first sample. The observations must be ordinal or continuous measurements, so that one can at least say, of any two observations, which is the greater.

To perform the Mann-Whitney test, all the values are ranked from low to high, paying no attention to which group each value belongs. If two values are the same, they are both given the average of the two ranks for which they tie. The smallest number is given a rank of 1. The largest number gets a rank of n , where n is the total number of values in the two groups. Statview then sums the ranks in each group, and reports the two sums. If the sums of the ranks are very different, the p value will be small.

In small samples with no ties, the exact p value can be calculated. In large samples, or if there are ties, the p value is approximated from a Gaussian approximation. In the Mann-Whitney test, the p value answers this question: if the populations really have the same median, what is the chance that random sampling would result in medians as far apart (or more so) as observed in this study? If the p value is small, the idea that the difference is a coincidence can be

rejected, instead the populations must have different medians. If the p value is large, it cannot be concluded that the overall medians differ, but this is not the same as saying that they are the same. The Mann-Whitney test has little power in small samples, and will always give a p value ≥ 0.05 no matter how much the groups differ if there are seven or fewer values.

For larger samples, such as those greater than eight, a normal approximation can be used to approximate the significance level for the test. Called the z value, this value is a standard normal deviate whose significance can be checked in tables of the normal distribution. Statview routinely corrects this value for the presence of tied ranks. If the observed z value does not equal or exceed the critical z value of 1.96 ($p \leq 0.05$ critical z value for a two-tailed test), then the null hypothesis is correct and there is no difference between groups. If the z value, however, exceeds 1.96 then this is sufficient evidence to reject the null hypothesis.

The Mann-Whitney U test is preferred to the independent samples Student's t test when the data are ordinal but not interval scaled, so that the spacing between adjacent values cannot be assumed to be constant. It is considered much less likely than the t test to give a spuriously significant result because of one or two outliers, and when the data are not normally distributed.

Kruskal-Wallis one-way analysis of variance

The Kruskal-Wallis one-way analysis of variance by ranks is a non-parametric method for testing equality of population medians among three or more unpaired groups. It is identical to a one-way analysis of variance except that it does not assume that the population is normally distributed, and the data are replaced by their ranks. It is an extension of the Mann-Whitney U test to three or more groups.

In the test, all the values are ranked from low to high, disregarding which group each value belongs. If two values are the same, they are given the average of the two ranks for which they tie. The smallest number gets a rank of 1. The largest

number gets a rank of n , where n is the total number of values in all the groups. Statview then sums the ranks in each group, and reports the sums. If the sums of the ranks are very different, the p value will be small.

The p value provided by the Kruskal-Wallis test gives an indication of the chance that the median values of each group are the same. If $p \leq 0.05$ the null hypothesis can be rejected and it can be concluded that the differences are not observed by chance alone. This does not mean that every group differs from every other group, only that at least one group differs from one of the others.

If the overall Kruskal-Wallis p value is large, this is not evidence that the overall medians differ, but this is not the same as saying that the medians are the same. If samples are small, the Kruskal-Wallis test has little power, and if the total sample size is seven or less, the Kruskal-Wallis test will always give a p value greater than 0.05 no matter how the groups differ.

The discrepancies among the rank sums are combined to create a single value called the H statistic. A larger H statistic corresponds to a larger discrepancy among rank sums.

Spearman's rank correlation

This is a non-parametric measure of the degree of association between two numerical or ordinal variables. The values of each variable are independently ranked and the measure is based on the differences between the pairs of ranks of the two variables.

Regression analysis

The term "regression" is used in statistics quite differently than it is used in other contexts. The method was first used to examine the relationship between the heights of fathers and sons. The two are related, but the slope is less than 1.0. A

tall father tended to have sons shorter than him, whilst a short father tended to have sons taller than him. The height of sons regressed to the mean. The term “regression” is now used for many sorts of curve fitting. Dr Raymond Salvador of the Wolfson Brain Imaging Centre at the University of Cambridge performed the regression analyses reported in this thesis.

Linear regression

Linear regression is the process of fitting a model to data and finding a best fit line or curve to describe the relationship between two sets of data. The goal of linear regression is to adjust the values of slope and intercept on a graph to find the line that best predicts y from x . More precisely, the goal of regression is to minimise the sum of the squares of the vertical distances of the points from the line, as if the scatter is normal (or nearly so), the line determined by minimising the sum-of-squares is most likely to be correct.

Linear regression assumes that for any value of x , y is normally distributed. The second is that the magnitude of the scatter of the points about the fitted curve is the same throughout the length of the line.

Generalised linear models

The generalised linear model applies likelihood-based approaches to regression analysis for a variety of outcome measures (Stiratelli et al., 1984; Zeger et al., 1988).

Linear models typically include systematic and random (error) components, with the errors usually assumed to have normal distributions. Least-squares theory is used to analyse the data, which in its classical form assumes just one error component; extensions for multiple errors have been developed primarily for analysis of designed experiments and survey data. Techniques developed for non-normal data include probit analysis and contingency tables in which the systematic part of the model has a linear basis.

Generalised linear mixed models include random terms in the linear predictor and are useful for accommodating the overdispersion that may be seen among outcomes that have binomial or normal distributions and for modeling the dependence among outcome variables inherent in longitudinal or repeated measures study designs.

LOESS

LOESS is also known as locally weighted polynomial regression. It combines much of the simplicity of linear regression with the flexibility of nonlinear regression. It does this by fitting simple models to localised subsets of the data to build up a function that describes the deterministic part of the variation in the data, point by point.

Correlation

Correlation quantifies the degree to which two variables are related. This is different to linear regression, which finds the line that best predicts y from x . The correlation coefficient (r) indicates how much one variable tends to change when the other one does. It gives no indication of cause and effect.

Statview calculates the correlation coefficient, r . When $r = 0$, the two variables do not vary together at all. When $r = 1$, there is a perfect positive correlation, when $r = -1$ there is a perfect negative correlation. The coefficient of determination, r^2 , ranges from 0 to 1, and represents the fraction of variance that is shared between the two variables. For example, if $r^2 = 0.59$, then 59% of the variance in x can be explained by variance in y and *vice versa*. Statview also calculates a p value, which indicates the probability that the degree of correlation apparently seen might be due to chance alone and the null hypothesis holds.

Correlation is almost always used when both variables are measured. It rarely is appropriate when one variable is manipulated in an experiment, when linear regression is more appropriate.

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