Glass micro-particulate contamination of intravenous drugs – should we be using filter needles?

Lewis Fry
Fourth Year Medicine (Undergraduate)
Monash University

After crossing the Tasman from New Zealand, Lewis has developed a range of interests including student wellbeing, rural health and opthalmology. This article stemmed from ampoule-opening difficulties and discussions with anaesthetists.

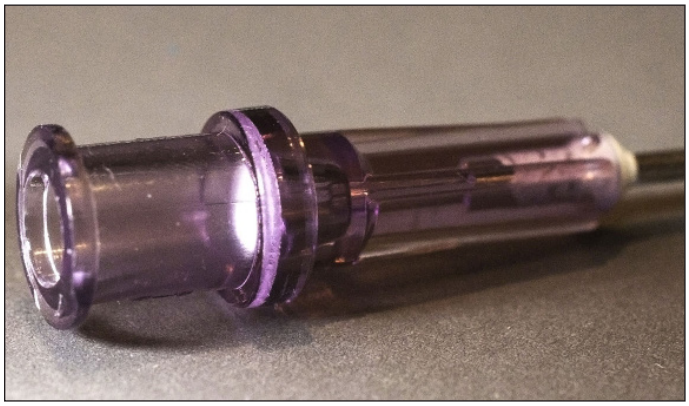
The universal use of filter needles in the aspiration of all medications from glass ampoules for intravenous administration has been recommended due to safety concerns surrounding possible inadvertent injection of glass micro-particulate created from snapping open ampoules. Implementing this would involve significant costs. This article aims to review the relevant literature to evaluate whether sufficient evidence for patient harm due to glass micro-particulate contamination exists to justify the universal introduction of filter needles for the aspiration of medications from glass ampoules for intravenous administration. **Methods**: A search of OVID Medline, TRIP, Embase and Google Scholar databases was conducted with a wide variety of terms with no limitation on publication date. Papers addressing the research question were included in the review. **Result**s: Contamination of drugs by glass micro-particulates does occur with aspiration from glass ampoules. Pathological changes such as granuloma formation, embolic or thrombotic events may occur if these are injected intravenously. There is, however, a lack of evidence of consequent clinical harm in humans. **Conclusion**: A recommendation for the universal introduction of filter needles for aspiration of drugs from glass ampoules for intravenous administration cannot be justified on the basis of the paucity of available evidence showing harm and in light of the significant cost of this recommendation. Concerns regarding the lack of studies demonstrating that particle contamination poses no threat remain valid from a perspective of total patient safety.

Introduction

Glass ampoules are common containers for many drugs. The ampoules are usually broken open by hand and the drugs are then drawn up for administration. In the last 60 years, many questions have been raised over the potential patient safety issues related to glass micro-particulate contamination of drugs from glass ampoules, particularly for intravenous administration. [1-6] There have been few conclusive answers, however there are suggestions it may lead to complications including pulmonary thrombi, micro-emboli, and end-organ granuloma formation. [6]

It has been recommended that filter needles should be used in the aspiration of all medications from glass ampoules. [7] This is not yet standard practice, but follows recommendations made for over forty years that practice should err on the side of caution until further studies can demonstrate that any type of particle contamination poses no threat. [5,6,8,9] This must also be balanced however, against the significant cost the universal use of filter needles would incur. The cost of a 5 µm 18 g filter needle ($0.315) is approximately ten times that of a standard 18 g drawing up needle ($0.029). [10]

For the universal implementation of filter needles to be justified in the light of this expense, three important questions should be satisfied. Firstly, does micro-particulate contamination occur when drugs are aspirated from glass ampoules? Secondly, if so, is this particulate contamination of clinical significance and a threat to patient safety? Thirdly, are filter needles effective in preventing contamination of medications by glass particles? This article reviews the relevant literature and through answering these questions attempts to evaluate whether sufficient evidence exists to warrant the universal introduction of filter needles for the aspiration of medications from glass ampoules for intravenous administration.



Methods

A search of OVID Medline, TRIP database, Embase and Google Scholar databases was conducted. In order to capture all possible evidence and relevant background history on this topic in this review, there was no restriction on date of publication and a wide range of search terms were used. Terms used included (but were not limited to): 'glass', 'ampoule', 'drug contamination', 'intravenous', 'filter needles', 'filter straws', 'filtration' and 'needles'. This search was supplemented with additional papers sourced from reference lists to ensure completeness. Both human and animal studies were included. Papers addressing the research question were included in the review as decided by the author, including papers addressing other micro-particulate contamination. Explicitly defined criteria were not used in the selection of the papers.

Definitions

A filter needle or filter straw is a needle attached to a syringe in place of a drawing up needle, designed to filter out particulates from a contaminated fluid. Generally they contain a 5 micron filter.

Glass ampoules are widely used in the production of parenteral medications. Glass is an attractive material to industry as it can be vacuum-sealed, sterilized, is easy to clean, it is chemically inert, it is difficult to tamper with and is possibly recyclable. [2,4] To access the drug, the top of the ampoule is snapped off by applying manual force at a pre-weakened point. [2]

Results

Does particulate contamination occur?

There is clear evidence that the action of snapping off the top of an ampoule can lead to contamination of ampoule contents, primarily with glass micro-particles. [11-15] Glass micro-particles are primarily composed of inorganic compounds (SiO_2, Na_2CO_2, $CaCO_2$) and metallic oxides. [2] They have a sharp microscopic appearance. [16] Particulate size ranges from 8-172 microns. [15] The amount of particulate matter varies slightly amongst different manufacturers and more particles are found in transparent metal etched ampoules compared with coloured chemically etched ampoules. [17]

Is glass particulate contamination of clinical significance?

Brewer and Dunning (1947) demonstrated that massive micro-

particulate infusions in rabbits can cause foreign body reactions which result in pulmonary granulomas, pulmonary silicosis, and cause nodular fibrosis of the liver, spleen and lymph nodes. [1] These were reported as chronic rather than acute changes. Notably, a dose equivalent to a total human dose of 14g of glass over a month given in daily doses was required to produce these effects. Animals receiving small doses, equivalent to those that a human might receive in normal clinical practice, however, exhibited no pathological changes and no glass was found in the lungs. No animals died within the full investigation period of up to a year until euthanised for pathological examination. The authors concluded that "occasional particle contamination of ampoule preparations produces no significant pathology in animals". [1]

Garvan and Gunner (1964) conducted a similar small experiment infusing saline from glass ampoules into an ear vein of three rabbits. [3] After killing the animals, autopsy showed the formation of capillary and arterial granulomas, all containing cellulose fibres. They estimated that every half-litre of IV fluid injected into a rabbit caused the formation of 5000 granulomas scattered through the lungs. They also found similar lesions in the lungs of patients who had died and had received large volumes of IV fluid before death. In this study there was no specific reference to glass as the causative particle of the granulomas, nor was it associated with any morbidity or mortality apart from the histological changes.

Two case reports have been published recently regarding glass contamination. In the first a patient was found on arthroscopy to have glass particles within the right knee joint possibly due to recent steroid or local anaesthetic injection into the joint. [18] In the second report a single glass particle lodged within a cannula caused leakage out of the injection port of the cannula during an infusion. [19]

Contamination with other micro-particulates

Contamination of IV fluids by other materials such as rubber or cellulose has also been shown to occur and these particulates may have similar effects to glass. A review of relevant work concluded however, that although pathological changes had been associated with these various contaminants in both human and animal studies, it was not possible to correlate particular clinical manifestations with a specific contaminant, and nor was there any association with mortality. [20]

Similarly, in an autopsy study Puntis *et al.* (1992) found pulmonary granulomata in two of 41 parentally fed infants who had died of unstated causes following stays in a neonatal intensive care unit with a median duration of 14 days of parenteral feeding. These were compared to 32 control infants who died of Sudden Infant Death Syndrome (SIDS) within the same time period and who had not received any IV treatment. [21] No granulomata or foreign bodies were found in the controls. Of the two cases, some pulmonary granulomas contained cotton fragments or glass, but the majority exhibited no obvious foreign body. The authors point out that the parental nutrition solutions themselves contain many micro-particles that may also have pathological effects. Further to this a recent study found silicon particles (common contaminants in solutions stored in glass ampoules) caused suppression of macrophage and endothelial cell cytokine secretion in vitro, suggesting that micro particle infusion could have immune-modulating effects in vivo. [22]

A recent Cochrane Review of the use of in-line filters for preventing morbidity and mortality in neonates attributable to particulate matter and bacterial contamination, concluded that there is insufficient evidence to recommend the use of these devices. [23] Falchuck *et al.* found that in-line filtration significantly reduced the incidence of infusion-related phlebitis, however a recent meta-analysis of trials investigating the benefit of in-line filters was inconclusive. [24,25]

There is further inconclusive evidence that epithelioid granulomas, containing macrophages and giant cells, can occur at the entry points of silicone coated needles used for acupuncture (a polymer containing the element silicon) but these granulomas can also occur following venipuncture or at skin biopsy sites. [26]

Are filter needles effective in preventing contamination of medications by glass particles?

Sabon *et al.* (1989) found that control ampoules contained an average of 100.6 (SE ± 16.3) particles with size ranging from 10 to 1000 µm. [17] Aspiration through an 18 g needle reduced particulate contamination to a mean of 65.6 (SE ± 18.7) particles with a maximum size of 400 µm, whereas aspiration through a 19 g 5 µm filter needle reduced the number of particles to 1.3 (SE ± 0.3), with a decrease in the average particle size. More recently Zabir *et al.* (2008) found that of 120 ampoules aspirated using a 5 µm filter, 0% of the aspirated fluid samples were contaminated with glass, in comparison to when 120 ampoules were aspirated using an unfiltered 18 g needle, 9.2% of the aspirated fluid samples were contaminated. [27] The use of smaller gauge non-filter needles has also been found to reduce contamination when compared to large bore needles. [5, 27]

In contrast to this Carbone-Traber *et al.* (1986) found no difference between unfiltered and filtered needles or between different needle bore sizes. Using a 3 mm tubing as a control, the contents of ten ampoules were aspirated for each group. The control group was contaminated with a mean of 12 (SD ± 5) glass particles, compared to 13 (SD ± 6) and 13 (SD ± 7) glass particles in the aspirate contents of unfiltered 18 g and 5µm filter needle respectively. [28] The authors suggest that the force of aspiration may cause glass particles to penetrate the filter.

Discussion

The clinical significance of the effects of glass particulates on the human body remains unclear. A number of historical investigations and case reports have been published, however there are no recent systematic reviews or prospective studies relating directly to glass particulates. Perhaps not surprisingly, there are no relevant controlled human studies and much of the data that forms the basis for the evidence of harm comes from animal studies. It is worth noting that while the findings of Brewer and Dunning and often cited as evidence for the harm of caused by glass, their clinical conclusions that glass causes no significant pathology in animals are often ignored. [1]

The lack of studies investigating the effects of glass particulate contamination is due to many factors including the ethical difficulties associated with infusing contaminated fluids into human subjects, cost, and the lack of interest by pathologists. [29] The lack of evidence available from high quality and recent investigations is the significant limiting factor of this review.

In this light, a number of recommendations have been made for over forty years that practice should err on the side of caution until further studies can demonstrate that any type of particle contamination poses no threat. [5,6,8,9] This is a valid perspective with a view to ensuring total patient safety.

In evaluating the introduction of any intervention however, both the costs and consequences must be considered. With the current evidence, evaluation of the efficacy or the effectiveness of the global introduction of filter needles cannot be undertaken, nor can cost-benefit be appraised. It is clear however, that the large-scale introduction of filter needle use for all drugs aspirated from glass ampoules destined for intravascular injection would incur a significant cost.

Filter needle use in current practice

Injection of contaminants may occur via various pathways including the intravenous, intramuscular, subcutaneous, intrathecal, epidural, and intraocular routes. There are no data describing the prevalence of filter needle use, and perhaps the most accurate appraisal is that they are at least widely available. Anecdotally their use seems favoured when drawing up drugs from glass ampoules prior to intrathecal, epidural and intraocular administration, likely due to fear of significant

consequences of microbiological contamination of these sites. [30]

Alternatives to filter needles

Several alternative solutions have been considered to reduce glass contamination. The use of a machine that cuts the ampoules and aspirates the contents using a vacuum produced less glass particulate contamination of ampoules compared to opening by hand, however this is impractical for everyday use. [16] The use of prefilled syringes showed far less contamination than aspirating glass ampoule contents into syringes however this a very expensive option. [31,32] A commercial ampoule opener showed no difference in particulate contamination compared to hand-opened. [29] While there have been no recommendations made, the use of smaller gauge needles may reduce contamination as discussed above.

Conclusion

In conclusion, studies have shown evidence of glass particle contamination in injectable drugs drawn from glass ampoules, and have generally demonstrated that use of filter needles would reduce patient exposure to these particulates. There is, however, a lack of definitive evidence for significant harm from the injection of these glass particle contaminants. There is a potential that drugs administered intravenously containing glass fragments may cause granuloma formation, embolic, thrombotic and other vascular events, however this is not supported by any recent literature or conclusive studies. The paucity of evidence further limits economic evaluation into efficacy, effectiveness and cost-benefit analysis, into an intervention that would incur substantial cost. Arguments that practice should err on the side of caution until studies can prove that contamination does not cause harm are valid, however it is unlikely these studies will be able to be conducted. Considering the limited evidence for harm of glass particulate injection found in well over fifty years of observation, it would appear that the cost of filter needles outweighs the questionable benefits gained from their universal introduction for aspiration of intravenously administered drugs from glass ampoules.

Acknowledgements

I gratefully acknowledge the help of Associate Professor Simon Mitchell, Head of Department, Department of Anaesthesiology, University of Auckland, and Professor Ben Canny, Deputy Dean (MBBS), Faculty of Medicine, Nursing and Health Sciences, Monash University for their critical assessment and review of the manuscript.

Conflicts of Interest

None declared.

Correspondence

L Fry: lefry3@student.monash.edu

References

[1] Brewer JH, Dunning JH. An in vitro and in vivo study of glass particles in ampules. J Am Pharm Assoc. 1947 Oct;36(10):289-93.
[2] Carraretto AR, Curi EF, de Almeida CE, Abatti RE. Glass ampoules: risks and benefits. Rev Bras Anestesiol. 2011 Jul-Aug;61(4):513-21.
[3] Garvan JM, Gunner BW. The harmful effects of particles in intravenous fluids. Med J Aust. 1964 Jul 4;2:1-6.
[4] Lye ST, Hwang NC. Glass particle contamination: is it here to stay? Anaesthesia. [Letter]. 2003 Jan;58(1):93-4.
[5] Preston ST, Hegadoren K. Glass contamination in parenterally administered medication. J Adv Nurs. 2004 Nov;48(3):266-70.
[6] Stein HG. Glass ampules and filter needles: an example of implementing the sixth 'r' in medication administration. Medsurg Nurs. 2006 Oct;15(5):290-4.
[7] Provisional Infusion Standards of Practice. Intravenous Nursing New Zealand Incorporated Society; 2012.
[8] Heiss-Harris GM, Verklan MT. Maximizing patient safety: filter needle use with glass ampules. J Perinat Neonatal Nurs. 2005 Jan-Mar;19(1):74-81.
[9] Davis NM, Turco S. A study of particulate matter in I.V. infusion fluids--phase 2. Am J Hosp Pharm. 1971 Aug;28(8):620-3.
[10] Personal communication with hospital procurement department (Monash Medical Centre). 2013.
[11] Turco S, Davis NM. Glass particles in intravenous injections. N Engl J Med. 1972 Dec 7;287(23):1204-5.
[12] Bohrer D, do Nascimento PC, Binotto R, Pomblum SC. Influence of the glass packing on the contamination of pharmaceutical products by aluminium. Part I: salts, glucose, heparin and albumin. J Trace Elem Med Biol. [Research Support, Non-U.S. Gov't]. 2001;15(2-3):95-101.
[13] Glube ML, Littleford J. Paint chips and glass ampoules. Can J Anaesth. [Letter]. 2000 Jun;47(6):601-2.
[14] Kawasaki Y. Study on insoluble microparticulate contamination at ampoule opening. Yakugaku Zasshi. 2009 Sep;129(9):1041-7.
[15] Unahalekhaka A, Nuthong P, Geater A. Glass particles contamination in single dose ampoules: patient safety concern. Am J Infect Control. 2009;37(5):E109-E10.
[16] Lee KR, Chae YJ, Cho SE, Chung SJ. A strategy for reducing particulate contamination on opening glass ampoules and development of evaluation methods for its application. Drug Dev Ind Pharm. 2011 Dec;37(12):1394-401.
[17] Sabon RL, Jr., Cheng EY, Stommel KA, Hennen CR. Glass particle contamination: influence of aspiration methods and ampule types. Anesthesiology. 1989 May;70(5):859-62.
[18] Hafez MA, Al-Dars AM. Glass foreign bodies inside the knee joint following intra-articular injection. Am J Case Rep. 2012;13:238-40.
[19] Mathioudakis D. One drip too much: contamination in intravenous injectate [BJA Out Of The Blue]. BJA. 2012 Mar 19.
[20] Thomas WH, Lee YK. Particles in intravenous solutions: a review. N Z Med J. 1974 Aug 28;80(522):170-8.
[21] Puntis JW, Wilkins KM, Ball PA, Rushton DI, Booth IW. Hazards of parenteral treatment: do particles count? Arch Dis Child. 1992 Dec;67(12):1475-7.
[22] Jack T, Brent BE, Boehne M, Muller M, Sewald K, Braun A, *et al.* Analysis of particulate contaminations of infusion solutions in a pediatric intensive care unit. Intensive Care Med. [Research Support, Non-U.S. Gov't]. 2010 Apr;36(4):707-11.
[23] Foster J, Richards R, Showell M. Intravenous in-line filters for preventing morbidity and mortality in neonates. Cochrane Database Syst Rev. 2006(2):CD005248.
[24] Falchuk KH, Peterson L, McNeil BJ. Microparticulate-induced phlebitis. Its prevention by in-line filtration. N Engl J Med. 1985 Jan 10;312(2):78-82.
[25] Niel-Weise BS, Stijnen T, van den Broek PJ. Should in-line filters be used in peripheral intravenous catheters to prevent infusion-related phlebitis? A systematic review of randomized controlled trials. Anesth Analg. 2010 Jun 1;110(6):1624-9.
[26] Yanagihara M, Fujii T, Wakamatu N, Ishizaki H, Takehara T, Nawate K. Silicone granuloma on the entry points of acupuncture, venepuncture and surgical needles. J Cutan Pathol. [Case Reports]. 2000 Jul;27(6):301-5.
[27] Zabir AF, Choy YC. Glass particle contamination of parenteral preparations of intravenous drugs in anaesthetic practice. Southern African Journal of Anaesthesia and Analgesia 2008;14(3):17-9.
[28] Carbone-Traber KB, Shanks CA. Glass particle contamination in single-dose ampules. Anesth Analg. 1986 Dec;65(12):1361-3.
[29] Giambrone AJ. Two methods of single-dose ampule opening and their influence upon glass particulate contamination. AANA J. 1991 Jun;59(3):225-8.
[30] Pinnock CA. Particulate contamination of solutions for intrathecal use. Ann R Coll Surg Engl. 1984 Nov;66(6):423.
[31] Eriksen S. Particulate contamination in spinal analgesia. Acta Anaesthesiol Scand. 1988 Oct;32(7):545-8.
[32] Yorioka K, Oie S, Oomaki M, Imamura A, Kamiya A. Particulate and microbial contamination in in-use admixed intravenous infusions. Biol Pharm Bull. 2006 Nov;29(11):2321-3.