Worldwide withdrawal of medicinal products because of adverse drug reactions: a systematic review and analysis

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ABSTRACT

We have systematically identified medicinal products withdrawn worldwide because of adverse drug reactions, assessed the level of evidence used for making the withdrawal decisions, and explored the patterns of withdrawals over time. We searched PubMed, the WHO database of withdrawn products, and selected texts. We included products that were withdrawn after launch from 1950 onwards, excluding non-human and over-the-counter medicines. We assessed the levels of evidence on which withdrawals were based using the Oxford Centre for Evidence Based Medicine Levels of Evidence. Of 353 medicinal products withdrawn from any country, only 40 were withdrawn worldwide. Anecdotal reports were cited as evidence for withdrawal in 30 (75%) and deaths occurred in 27 (68%). Hepatic, cardiac, and nervous system toxicity accounted for over 60% of withdrawals. In 28 cases, the first withdrawal was initiated by the manufacturer. The median interval between the first report of an adverse drug reaction that led to withdrawal and the first withdrawal was 1 year (range 0–43 years). Worldwide withdrawals occurred within 1 year after the first withdrawal in any country. In conclusion, the time it takes for drugs to be withdrawn worldwide after reports of adverse drug reactions has shortened over time. However, there are inconsistencies in current withdrawal procedures when adverse drug reactions are suspected. A uniform method for establishing worldwide withdrawal of approved medicinal products when adverse drug reactions are suspected should be developed, to facilitate global withdrawals. Rapid synthesis of the evidence on harms should be a priority when serious adverse reactions are suspected.

Keywords: Adverse reaction; side effect; worldwide recall; interval; systematic review

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INTRODUCTION

Before a new medicinal product is approved, its safety and efficacy are assessed through preclinical testing in animals, and phase I, II and III studies in humans (FDA, 2014a). If a drug regulatory authority determines that the new drug is efficacious and that there are no major concerns about adverse reactions, marketing licences are usually granted within the geographical jurisdiction of that regulatory authority.

Although adverse events associated with a newly approved medicinal product are observed in the period before and around the time of regulatory approval, the frequency and intensity of such events is generally not quantifiable during the pre-approval phase. In addition, rare but potentially important adverse drug reactions may not be apparent. Consequently, the benefit-to-harm balance of a newly approved medicinal product may change over time (Guo et al., 2010). In cases where the harms outweigh the benefits, one of several courses of action may be taken by the regulatory authority or the manufacturer, including addition to the label of an adverse reaction or a warning or a contraindication, and/or revision of the risk minimization plan (European Commission, 2009). In the most extreme cases, the product may be withdrawn from the market (FDA, 2013; EMA, 2012).

Post-marketing withdrawal of medicinal products occurs when evidence is obtained from case reports, non-randomized studies, randomized trials, or systematic reviews. Post-marketing withdrawal of medicinal products can be controversial, especially when the drug-event observation has not been shown to be causative. It could also result in the removal of effective compounds, loss of confidence in pharmaceutical products, and negative incentives for drug companies.

In previous reports (Onakpoya et al., 2015a; Onakpoya et al., 2015b), we have shown that there are inconsistencies in the patterns of withdrawals when deaths or adverse drug reactions are attributed to the use of medicinal products. For example, drugs are not always withdrawn in every country in which they have been marketed, even though they would be expected to be withdrawn worldwide. However, there has been no specific research on the pattern of worldwide withdrawals when medicinal products are suspected to have caused adverse drug reactions. In addition, the evidence on which withdrawal decisions were based has not been systematically assessed. Therefore, we have systematically identified medicinal products that were withdrawn worldwide because of adverse drug reactions, assessed the level of evidence used for making the withdrawal decisions, and explored the patterns of withdrawals over time.

METHODS

Search strategy

We searched for medicinal products withdrawn worldwide after regulatory approval because of adverse drug reactions from the following sources:

- the World Health Organization's (WHO's) database of Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted, or not approved by governments (Issues 6, 8, 12 and 14);
- the WHO's Drug Information (Volumes 1–28);
- the WHO's Pharmaceuticals Newsletter (1997–2014);
- *Meyler's Side Effects of Drugs: The International Encyclopaedia of Adverse Drug Reactions and Interactions,* volumes 1–8 and editions 9–16, and the *Side Effects of Drugs Annuals* 1–36;

- *Stephens' Detection of New Adverse Drug Reactions*, 5th edition (2004);
- *the Pharmaceutical Manufacturing Encyclopedia*, 3rd edition (2007);
- *The Merck Index*, 15th Edition (2013);
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the website of the US Food and Drug Administration (FDA);
- the database of withdrawn drugs of the European Medicines Agency (EMA).

For each medicinal product withdrawn, we then searched the following databases for the first reported adverse drug reaction:

- Pubmed;
- Medline;
- Google Scholar;
- the database of withdrawn drugs of the European Medicines Agency (EMA);
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the website of the US Food and Drug Administration (FDA);

Search terms used included "drug withdrawal", "fatal*", "death(s)", "side effect", "adverse effect", "adverse reaction", "adverse event", "poison", "toxicity", "voluntary recall", "suspension", "prohibition", "banned", "remov*", "revoke*", "discontinued", "worldwide", "global". [A Medline search strategy is included as a web appendix]. Wherever we refer to the "first report" of an adverse reaction we mean the first publication in which the adverse reaction that was primarily responsible for the product's subsequent withdrawal was mentioned. If we could not find information for a medicinal product using its chemical name for searches, we used the trade name or code name. We also searched the bibliographies of retrieved full texts for any earlier dates of reports of suspected adverse reactions. If an article had evidence of an earlier reported date, that date was chosen as the first adverse reaction

date. If a drug was withdrawn because of two or more adverse reactions, we used the first reported date of any such reactions.

Inclusion/exclusion criteria

To be included in the review, a product must have been withdrawn worldwide from the market because of reports of a suspected adverse reaction or reactions, or problems related to hazards or harms. Such products must also have been introduced into the market from 1950 onwards. By worldwide withdrawal we mean the withdrawal of a product in all the countries in which it had been marketed, even if it was not marketed globally; furthermore, it must have been specifically stated, either by the manufacturer or a regulatory authority, that the drug was being withdrawn worldwide.

We included medicinal products that had previously been withdrawn because of adverse reactions but had been re-introduced or made available in other, safer, formulations. We excluded medicines for which there was documented regulatory evidence that they had been voluntarily withdrawn by marketing authorization holders solely for commercial reasons. We also excluded herbal products, non-human medicines, and non-prescription medicines.

Assessing the types of evidence

We documented the highest level of available evidence before the year of first withdrawal of products, based on the Oxford Centre for Evidence-based Medicine (OCEBM) criteria (2011), rating the levels of evidence of harms as follows: Level 1 (highest)—systematic reviews, n-of-1 trials, or dramatic observational studies; Level 2—randomized clinical trials or exceptional observational studies; Level 3—non-randomized, cohort or follow-up studies; Level 4—case-series or case-control studies; Level 5—mechanism-based reasoning. One

reviewer (IJO) documented the levels of evidence, which were independently verified by a second reviewer (JKA). Discrepancies were resolved through consensus.

Classification of adverse drug reactions

The possible clinical mechanisms whereby the reported adverse reactions occurred were described using the DoTS system (Aronson and Ferner, 2010), which examines three domains, namely: Dose-relatedness (Do), which determines toxic, collateral, or hypersusceptibility reactions; Time-course (T), varying from immediate to delayed; and Susceptibility factors (S).

Data extraction

For each withdrawn product, we extracted data on: the date of marketing authorization, the launch date, or the date of first recorded use; the drug class, and therapeutic indication (WHO, 2008); the year in which an adverse drug reaction related to the reason for withdrawal was first reported; the year of first withdrawal and the party that initiated the withdrawal; the year of worldwide withdrawal; and the reported organ or system that was affected by the drug. One reviewer (IJO) extracted the data and a second reviewer (JKA) verified them independently. When there were discrepancies in the attributed dates, the reviewers re-checked the dates together and arrived at a consensus by discussion.

Statistical analyses

We used summary tables to document the intervals between launch year and the year of first reports of adverse drug reactions, the interval between launch year and the year of first withdrawal, and the interval between the first report of an adverse drug reaction and the year of first withdrawal. Because these intervals were skewed, we used medians and interquartile

ranges (IQR) as measures of central dispersion. We used scatter plots to explore the relationships between launch dates and times to first reports of adverse drug reactions and withdrawals. Box and whisker plots were used to examine the trends in intervals over decades.

RESULTS

We identified 353 medicinal products withdrawn after regulatory approval between 1950 and June 2015, of which 40 were withdrawn worldwide (Figure 1). The worldwide withdrawals occurred between 1969 and 2011. Analgesics (mainly COX-1 and COX-2 inhibitors) accounted for 10 (25%) of the withdrawals (see Table 1).

In seven cases (17.5%), the first withdrawals were initiated by drug regulatory authorities; manufacturer-initiated withdrawals accounted for 27 cases (67.5%). In five cases, the drug manufacturer and drug regulatory authorities simultaneously withdrew the products from the market. The worldwide withdrawal of one product (fenclofenac) by the manufacturer was as a result of a refusal by the UK regulatory authorities to renew the product licence.

The adverse reactions that occasioned withdrawals were due to off-target effects in all but two cases, paralytic ileus due to loperamide, a μ opioid receptor agonist, and cardiovascular adverse reactions to prenylamine, a calcium channel blocker.

Evidence for withdrawal

Case reports were used as evidence for withdrawal in 30 cases (75%), while systematic reviews were used in only two cases (5%) (Table 1). Evidence from animal research was used as the basis for withdrawal in one case. In 27 cases (68%), deaths were attributed to the

withdrawn products. The most common mechanisms through which the adverse drug reactions occurred were hepatotoxicity (25%), cardiotoxicity (20%), and nervous system toxicity (12.5%).

In 24 cases (60%), the adverse reactions resulted from collateral reactions, i.e. reactions that occurred at therapeutic doses (Table 2), while hypersusceptibility reactions (reactions at doses below the usual therapeutic range) accounted for 13 cases (33%). Toxic reactions were responsible for adverse reactions in five cases (13%). The dose relationship for one product (nebacumab) was unknown.

Interval between launch year and first adverse drug reaction reports

The longest interval between launch and the first ADR report was 26 years (L-tryptophan and eosinophilia–myalgia syndrome). The median interval between launch year and first ADR report was 4 years (IQR = 2–8 years). The more recent the launch year, the quicker the ADR reports appeared in the literature (Figure 2; and e-appendix Figure 1). In 14 cases (35%), such reports appeared within 2 years of the product launch; in 30% of cases, the first reports of ADRs occurred at 2–5 years after the launch of the product. When deaths were reported, the median delay before the reports of the deaths appeared in the literature was 1 year (IQR = 0 to 4 years); in 75% of cases (18/24) the adverse reaction reports occurred within 2 years of launch. The more recent the launch year, the quicker reports of deaths appeared in the literature (Figure 2 inset; and e-appendix Figure 1 inset).

Interval between launch year and worldwide withdrawal

The longest interval between launch year and worldwide withdrawal was 48 years (aprotinin and anaphylaxis). The median interval between first launch and worldwide withdrawal was 4

years (IQR = 1–12.5 years). Worldwide withdrawals occurred within two years of product launch in nine cases (23%). The more recent the launch year, the sooner a product was withdrawn from the market worldwide following ADR reports (Figure 3; and web-appendix Figure 2). When deaths were attributed to the use of a product, the median interval between launch and worldwide withdrawal was 7 years (IQR = 4 to 24 years). There was a decadal stepwise shortening in the intervals between launch year and worldwide withdrawals when deaths were attributed to a medicinal product (Figure 3 inset; and e-appendix Figure 2 inset).

Interval between first reports of adverse drug reactions and worldwide withdrawal

The longest interval between the first adverse drug reaction reports and worldwide withdrawal was 43 years (aprotinin and anaphylaxis). The median interval was 1 year (IQR = 0–5.8 years). The more recent the launch year, the sooner a product was withdrawn worldwide after adverse drug reaction reports; however, the interval to first withdrawal over time did not change consistently (Figure 4; and web-appendix Figure 3). In 26 cases (65%), worldwide withdrawals occurred within 2 years of adverse drug reaction reports; and worldwide withdrawals occurred within the first year of initial withdrawal in any country in 39 cases (see web appendix Table 1). In 18 cases (75%), withdrawals because of deaths occurred within 2 years of the first adverse drug reaction reports. There was also a shortening in the intervals to worldwide withdrawals when death was attributed to a product (Figure 4 inset; and e-appendix Figure 3 inset).

Comparison of worldwide withdrawals with all withdrawals

There was a marked distinction between products withdrawn before and after 1980. Between 1950 and 1979 only one product was withdrawn worldwide out of a total of 71 products (1.4%)that were withdrawn anywhere; from 1980 onwards, the number of worldwide

withdrawals was on average 14% of all withdrawals (40 out of 283), without much variation from decade to decade.

DISCUSSION

We identified 40 medicinal products withdrawn worldwide because of adverse drug reactions. Hepatotoxicity, cardiotoxicity and neurotoxicity accounted for over half of the withdrawals, and most of the adverse reactions showed collateral dose-responsiveness. The proportion of worldwide withdrawals compared with all withdrawals increased considerably from 1980 onwards.

The evidence used for withdrawal in 75% of cases was anecdotal reports, and deaths were attributed to the use of withdrawn products in over a third of cases (68%). In almost all cases (97.5%), the product was withdrawn worldwide within the first year after withdrawal in any country. The interval between the first adverse drug reaction reports and worldwide withdrawals shortened inconsistently over time. These results confirm our previous observations (Onakpoya et al., 2015a; Onakpoya et al., 2015b) which showed that case reports are most often cited as evidence for the need to withdraw medicinal products after marketing. These results also confirm that the interval between launch and the first adverse drug reaction reports and first withdrawals has shortened over time.

Evidence for withdrawals

Most of the worldwide withdrawals were based on evidence obtained from case reports. This is consistent with evidence that formal studies are not often conducted when adverse reactions are suspected (Loke et al., 2006). However, worldwide withdrawals may have been justified because of the precautionary principle (Wingspread Conference, 1998), especially

when deaths were reported. However, one would expect confirmatory studies to be conducted if a medicinal product is withdrawn from the market because of suspected non-fatal adverse reactions. In addition, it has been argued that the precautionary principle may not be applicable in health care, because it is based on the avoidance of risk, and not on assessment of the benefit-harm balance (ter Meulen, 2005), although this has been disputed (Ashford, 2004). Some authors have suggested further modification of this principle to make it more relevant to decision-making processes in health care (Tubiana, 2000; Ricci et al., 2004). However, where adverse drug reactions are concerned the crux is the balance of benefit to harm. When this is clearly favourable drugs will not be withdrawn. When it is clearly unfavourable, withdrawal will be likely. However, when the balance is in doubt the precautionary principle may tip the decision towards withdrawal.

One product, anagestone acetate, was withdrawn worldwide because of the risk of tumors, based on evidence from animal studies. Subsequent confirmatory studies after worldwide withdrawal confirmed an increased risk of mammary gland tumors in animals (Kwapien et al., 1980; Giles et al., 1978). The extrapolation of animal results to human research is controversial and generates strong debate (Akhtar, 2015; Bracken 2009). Some authors have suggested that systematically combining the evidence on harms from several animal studies could improve translation of the data into clinical practice (van Luijk et al., 2014), but this has been vehemently contradicted by others (Knight, 2008; Barnard and Kaufman, 1997). Furthermore, systematic reviews of animal studies show that they are often methodologically poor (Mueller et al., 2014; Hirst et al., 2014). A meeting of experts to seek a consensus on "the way forward" has been suggested (Gruber, 2004).

Most of the withdrawals were initiated by drug manufacturers, suggesting that they are likely to withdraw their products from the market when there is evidence that the harms outweigh the benefits. However, the processes for the withdrawals in the face of accumulating evidence for harms do not appear to be consistent. For example, worldwide withdrawal of fenclofenac was initiated because renewal of its licence was refused in the UK (Anonymous, 1984) after data from the UK's erstwhile Committee on Safety of Medicines showed records of seven deaths and almost 895 suspected adverse drug reactions within a year of approval (Aronson, 2015).

Strengths and limitations

We used a robust method to search for medicinal products that have been withdrawn worldwide, and we systematically documented data on their launch dates and withdrawal dates. In addition, we went to great lengths to identify the first reports of adverse drug reactions, and we accounted for the quality of the evidence for which worldwide withdrawal decisions were based, and also examined the clinical pathways through which the adverse reactions occurred. However, we recognize some limitations. We have defined worldwide withdrawal as the withdrawal of a product in all the countries in which it was marketed, even if it was not marketed globally. However, we cannot be sure that we have identified all medicinal products that have been withdrawn worldwide. This difficulty implies that all countries in which drugs have been marketed should be registered (e.g. with the WHO), so that the progress of the drugs can be monitored as widely as possible, and so that even countries in which local information about adverse reactions is not readily available may benefit from access to information gathered in other countries.

We did not have access to information to enable computation of the intervals between actual occurrences of the first adverse reactions, as opposed to their being reported, and subsequent worldwide withdrawals. Nevertheless, we do not think that such information would have significantly affected the trends that we have observed.

Implications for future monitoring and reporting of harms

Although we do not know whether or to what extent withdrawals of the specific drugs that we have studied have influenced subsequent drug development, we do know that compounds that have caused serious adverse drug reactions (e.g. thalidomide, benoxaprofen, TGN1412) have markedly affected subsequent pharmacovigilance, stressing the importance of studying such withdrawals.

The inconsistency in the delays between reports of adverse reactions and worldwide withdrawals suggest difficulty in making withdrawal decisions when reports of such reactions accumulate. Therefore, the need for greater co-ordination across regulatory authorities cannot be overemphasized. Low-to-middle income economies with limited pharmacovigilance capabilities could be assisted in setting up standardized operating procedures for drug recalls. When there has been accelerated approval of products for marketing (FDA, 2014b), there should be correspondingly accelerated withdrawal or at least suspension of licences when serious treatment-emergent adverse events are detected.

Evidence syntheses on harms should be expedited when adverse drug reactions are suspected. This could prevent unnecessary exposure of patients to harmful products before withdrawal from the market. As an example, researchers queried why drug regulatory authorities and the drug manufacturer failed to monitor and summarize accumulating data on harms for

rofecoxib after regulatory approval (Jüni et al., 2004). Therefore, rapid systematic reviews could be conducted swiftly when adverse reactions are suspected, to help strengthen the evidence used for withdrawal decisions (Khangura et al., 2012). Drug manufacturers should also be encouraged to investigate whether a withdrawn medicinal product may have a possible favorable benefit-to-harm balance in other indications, especially when the product had a good population benefit; e.g. thalidomide caused birth defects when it was first introduced as a hypnotic in pregnancy, but it has since been used beneficially in multiple myeloma (Kim and Scialli, 2011).

CONCLUSIONS

The time it takes for drugs to be withdrawn worldwide after reports of adverse drug reactions has shortened over time. However, the speed with which worldwide withdrawals occurred after initial withdrawal suggests possible selective reporting of potentially serious harms in the pre-approval phase, improving with time. There are inconsistencies in current withdrawal procedures when adverse drug reactions are suspected. A uniform method for establishing worldwide withdrawal of approved medicinal products when adverse drug reactions are suspected should be developed, to help facilitate global withdrawals. Rapid synthesis of the evidence on harms data in the pre- to post-approval phases should be a priority when adverse reactions are suspected.

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JKA has edited textbooks on adverse drug reactions; he is President Emeritus and an Honorary Fellow of the British Pharmacological Society, a member of a NICE technology appraisal committee, a member of the advisory board of the British National Formulary, an Honorary Fellow of the Faculty of Pharmaceutical Medicine, and chair of the British Pharmacopoeia Commission's Expert Advisory Group on Nomenclature; however; the opinions expressed in this article are not necessarily shared by those organizations or their other members.

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FIGURE LEGENDS

Figure 1: Flow chart showing the process for the inclusion of medicinal products withdrawn worldwide.

Figure 2: Intervals between launch and first ADR reports for medicinal products withdrawn worldwide. Inset shows the intervals between launch and first reports of deaths.

Figure 3: Intervals between launch and worldwide withdrawal of medicinal products because of adverse drug reactions. Inset shows the intervals to withdrawals where deaths were reported.

Figure 4: Intervals* between 1st ADR reports and worldwide withdrawals. Inset shows delays to worldwide withdrawals occasioned by reports of deaths.