

such a massive disaster. Most deaths were due to drowning, followed by tsunami related injury and crush. Only four cases were assumed to be non-tsunami related—three due to cardiovascular events and one to injury unrelated to the tsunami.

Discussion

Mortality related to the Indian Ocean tsunami in 2004 was concentrated in the first few days of the disaster and no death was reported from one week after the tsunami up to two and a half months of the study period. At least six deaths could have been expected among the 3076 survivors and the recall period of 80 days in our study, on the basis of an assumed crude mortality of 0.25 per 10 000 person days, a benchmark for displaced populations in South Asia.¹ The massive additional mortality due to infectious diseases, as warned by the World Health Organization,² was not substantiated.

Our finding can be partly explained by the phenomenon of the “harvesting” effect—that is, decreased mortality after a large number of deaths as a result of an adverse health event among a vulnerable population. This effect has been documented in other disaster settings, such as the earthquake in Taiwan³ and the heat waves in the Czech Republic.⁴

The low mortality may also indicate successful aid activities. Prompt international responses were started with sufficient funds. Moreover, the Sri Lankan government functioned sufficiently to coordinate the influx of aid by using its well structured administrative and public health systems.

If this low level of mortality was primarily due to the nature of the disaster, however, then the use of the vast available funds may be questioned. How effective these activities and funds were in relieving the crisis is important in view of, for example, the massive humanitarian crisis that continued at a 10-fold or higher crude mortality among the displaced population in Darfur, Sudan.⁵

The argument may be circular because the mortality could have been minimised by the extensive relief

What is already known on this topic

Massive additional mortality among survivors of the 2004 tsunami was a concern, especially due to infectious diseases

What this study adds

Mortality due to the 2004 tsunami was concentrated in the first few days of the disaster

Increased mortality among displaced persons was not observed

effort of the international community. Nevertheless it can be speculated that the fund raised for the tsunami was disproportionate to need, especially in the context of other ongoing humanitarian crises and global health issues that are continuously costing millions of lives.

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2 World Health Organization. WHO appeals for US\$ 66 million to prevent disease outbreaks in tsunami-affected Southeast Asia; 150 000 people at ‘extreme risk’ of dying of preventable disease. www.who.int/mediacentre/news/releases/2005/pr01/en/index.html (accessed 20 May 2005).

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Case reports of suspected adverse drug reactions—systematic literature survey of follow-up

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Abstract

Objective To determine whether anecdotal reports of suspected adverse drug reactions are valuable early warning signals.

Design Systematic literature survey.

Data sources We evaluated all case reports of adverse drug reactions published in 1997 in five medical journals. Reports were excluded if the adverse reaction had previously been described in earlier publications and was already listed in the product information of the drug reference source (the *British*

National Formulary (BNF) or the Medicines Compendium). We used the Web of Knowledge Citation Index and Medline for 2003 to identify follow-up studies.



References to the 63 included case reports (w1-w63) and nine validation studies (w64-w72) are on *bmj.com*.



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Main outcome measures Primary: the number of suspected adverse reactions subjected to formal validation studies and the findings of these studies. Secondary: the number of instances in which the warning from the case report was incorporated into the product information.

Results We evaluated 63 suspected adverse reactions and found that most (52/63, 83%) had not yet been subjected to further detailed evaluation. Data from controlled studies that supported the postulated link between the drug and the adverse event were available in only three cases. Of the 48 agents listed in the drug reference sources, details of the suspected reaction were subsequently added to the *Medicines Compendium* in 15 instances, and to the *BNF* in seven instances. In each case, only one reaction had been confirmed.

Conclusions Published case reports of suspected adverse reactions are of limited value as suspicions are seldom subjected to confirmatory investigation. Furthermore, these alerts are not incorporated into drug reference sources in a systematic manner.

Introduction

Case reports of suspected adverse drug reactions are common in the medical literature—for example, more than a thousand anecdotes were cited in the *Side Effects of Drugs Annual* (2000) in one year alone.¹ While information on drug safety is of unquestionable importance, the profusion of case reports and the marked variation in their quality^{2,3} create a challenging conundrum. Should physicians and patients alter their treatment plans in response to every fresh report of a suspected adverse reaction?

Opinion is divided. Hoffman argues that case reports are of extremely limited value and that it would be foolhardy to translate the information into clinical practice without stronger evidence.⁴ On the other hand, research carried out by Venning in the 1980s⁵ is sometimes cited as an example of the “amazingly good” predictive accuracy of case reports,⁶ in that “more than half of suspected adverse drug reactions were confirmed by subsequent, more detailed research.”⁷ Venning’s findings, however, have not been replicated (see bmj.com).

How then can we be reassured that case reports of adverse drug reactions are genuinely valuable information resources? We need to be certain that the suspicions raised in such anecdotes are consistently validated by further research. Moreover, an early warning alert is of limited value if the information comes to the attention of only the restricted readership of learned medical journals. Are the safety concerns from such reports communicated to clinicians and patients via the commonly used drug information sources?

Methods

We retrieved case reports of suspected adverse drug reactions published in 1997 and established whether each case report had been followed by more definitive studies. We also determined whether the warning signal from the report had been incorporated into subsequent versions of published drug information.

Case reports of adverse drug reactions in general medicine, neurology, and psychiatry are often cited in the *Side Effects of Drugs Annual*.¹ We therefore chose four high impact journals: two general medical journals (*British Medical Journal* and *Lancet*) and two specialist journals (*Neurology* and *American Journal of Psychiatry*). We also included a haematology journal (*American Journal of Hematology*) to broaden our coverage as there are fewer anecdotal reports of adverse reactions in haematology.¹

Identification and selection of case reports

We searched Medline using the following search string: (“journal title” in SO) and (case-report in TG) and (py = 1997). We evaluated the titles and abstracts (when available) of the retrieved articles and excluded those that were clearly not case reports of adverse drug reactions. We then checked the full texts of the remaining articles for relevance based on previously published criteria.⁸ We excluded those cases for which previous reports of the adverse reaction were found in Medline and the adverse reaction was already listed in the product datasheet of the 1996-7 *Medicines Compendium*⁹ or the September 1996 issue of the *British National Formulary* (*BNF*)¹⁰ (see bmj.com for details).

Outcome measures

We used two methods to establish whether validation studies had been carried out after publication of the early warning signals. Firstly, we carried out a “cited reference” search of the Web of Knowledge Citation Index (April 2003). We believed that a follow-up study to investigate newly reported adverse drug reactions would usually cite the original reports in its reference list. We examined the citing articles to determine which ones were studies conducted for the specific purpose of validating the suspected adverse reaction (see bmj.com).

The second method allowed for the possibility that there might be studies in which the suspected adverse reaction had been evaluated without the original case report being cited. We checked Medline 1998-2003 using the adverse drug reaction term and drug name to identify any additional validation studies.

We also determined whether the suspected adverse effect had been added to the product information after the publication of the anecdotal report. The drug reference sources were issues of the *Medicines Compendium* published from 1996 to 2002 and its electronic version from 2003⁹ and issues of the *BNF* No 32 (September 1996) to No 45 (September 2003)¹⁰ (see bmj.com for details).

Results

We identified 696 case reports from the Medline search, of which 63 met the inclusion criteria as reports of suspected new adverse drug reactions.^{w1-w63}

Studies validating adverse drug reaction reports

From the citation index, we found that 56 of the 63 case reports had been cited at least once. However, only nine of these reports were validation studies. The table gives details of these nine reports. Follow-up studies provided controlled data that supported the hypothesised link between three drugs and the adverse

Case reports of suspected adverse reactions that had been subjected to further evaluation: case reports that had been cited by validation studies (identified through the Web of Knowledge Citation Index)

Drug	Adverse events	Times cited	Follow-up validation studies	Nature of validation studies (and date of first study)
Tacrolimus ^{w1}	Aplastic anaemia, marrow aplasia	1	1	Records of 106 patients reviewed; 11 haematological abnormalities thought to be due to tacrolimus (2001) ^{w64}
Omeprazole ^{w2}	Lethargy	3	1	Prescription event monitoring study showed that rate of malaise/lethargy was 0.07 per 1000 days' exposure (2000) ^{w65}
Trimethoprim ^{w3}	Uveitis, aseptic meningitis	7	1	Laboratory study found increased IL6 production in response to trimethoprim in mononuclear cells of trimethoprim-sensitive women compared with controls (1999) ^{w66}
Omeprazole ^{w4}	Optic neuropathy	9	1	CYP2C19 genotyping of patients with ocular adverse effects; only 2/279 were poor metabolisers, probably not related to ocular effects (2002) ^{w67}
Clarithromycin-disopyramide interaction ^{w5}	QT interval prolongation, cardiac arrest, ventricular arrhythmias	9	1	Controlled laboratory study found that troleandomycin was a potent inhibitor of disopyramide metabolism in liver microsomes (2000) ^{w68}
Indinavir ^{w6}	Severe acute hepatitis	77	10	10 uncontrolled cohort studies showed varied rates of hepatotoxicity, but confounded by hepatitis B and C coinfection and the use of multiple antiviral drug combinations (1999)
Indinavir ^{w7}	Lipomatosis	79	15	Four controlled cohort studies showed metabolic changes and abnormal fat distribution; nine uncontrolled cohort studies; one data mining study; and one laboratory investigation of adipocytes exposed to indinavir (1998)
Vigabatrin ^{w8}	Visual field constriction/defect	153	34	10 controlled cohort studies showed that rate of visual constriction was much higher in patients who took vigabatrin; 20 uncontrolled cohort studies; one trial; one genetic study; one animal study; one prescription event monitoring study (1999)
Acarbose ^{w9}	Hepatotoxicity	23	2	Data from clinical trials and surveillance study showed no rise in liver enzymes (1999) ^{w69-70}

event: clarithromycin-disopyramide interaction; indinavir and lipomatosis; and vigabatrin and visual field defects. In contrast, detailed studies on acarbose repeatedly failed to confirm its hepatotoxicity.

In Medline, we identified two validation studies that evaluated the postulated link between drug and adverse event. The 1997 case reports, however, were not cited by these validation studies, and it is possible that the later investigations may have been instigated by other factors.

Changes in published product information

We evaluated 48 datasheets and monographs to see whether they had been updated with the information from the case report. By October 2003, 15 product datasheets in the *Medicines Compendium* had been amended to include details of the suspected adverse reaction. However, only two of these had been subjected to follow-up evaluation. By September 2003 (No 45) seven monographs in the *BNF* had been revised, three with follow-up studies.

There were five products for which the information on adverse effects had been revised in both the *Medicines Compendium* and the *BNF*. Of these, only two had follow-up studies. Both reference sources have added hepatotoxicity to the list of adverse effects for acarbose, even though the published evidence suggests otherwise.

Discussion

Case reports of suspected adverse reactions are common in medical journals, but the value of such anecdotes remains far from certain. Though anecdotal reports should serve to initiate further research,⁶ we found that 83% of reports of suspected new adverse drug reactions from 1997 had not been subjected to any further validation. This finding contrasts sharply with the findings of Venning, who thought that only 26% of new adverse reactions had been left unverified.⁵

Venning looked at 47 case reports of adverse drug reactions in four general medical journals using various criteria based on site of reaction, time course, pharmacological plausibility, and effects of repeated administration. He concluded that 28 of the 47 anecdotes were "convincing" and needed no further study.⁵ Meyboom and colleagues challenged the reliability of such an approach.¹¹ Studies have shown that assessors of adverse events were often unable to reach complete agreement with each other when judging the strength of a causal link and determining the culprit drug.¹²⁻¹³ To avoid these pitfalls, we stipulated that the suspected reaction needed to have been evaluated by a more formal study.

Venning's initial evaluation left 19 reports of adverse reactions unconfirmed, and he proceeded to search the subsequent literature and reference sources (published papers, regulatory authority databases, and textbooks of adverse drug reactions) for additional information about any of these anecdotes. From this, he judged that seven of the 19 had subsequently been "satisfactorily verified" and were "generally accepted."⁵ Venning provided no details about whether his decisions were based on further case reports, expert opinion in textbooks, or formal evaluation of safety. In contrast, we defined "validation" studies explicitly (see bmj.com for details).

Adverse reaction reports are transmitted into product information in a haphazard way, leaving clinicians and patients poorly informed. Less than half of anecdotal reports led to updates, possibly because of the lack of data confirming the link between the drug and the adverse event. Manufacturers might justifiably argue that in the absence of a more definitive study, they are right not to include the adverse drug reaction in the datasheet. On the other hand, in some instances (such as acarbose) both the compendium and *BNF* entries were altered, despite the lack of evidence in subsequent studies.

What is already known on this topic

Anecdotal reports of suspected adverse drug reactions are common in the medical literature and are thought to have a valuable role in providing early warning alerts

Some evidence shows that these case reports have good predictive accuracy and that the suspicions are often confirmed to be valid on further evaluation

What this study adds

Anecdotal reports are of limited value as the suspected reactions are seldom subjected to confirmatory investigation

The warning signals from these case reports are not systematically incorporated into commonly used drug information sources

More than twice as many product listings were altered in the *Medicines Compendium* as in the *BNF*. The editorial content of the *BNF* is the responsibility of a joint formulary committee, whereas pharmaceutical companies work together with regulatory authorities to draw up product information for the compendium. How can prescribers and patients negotiate a path between benefit and harm when the updating of product information does not conform to any clear pattern of accumulation of evidence?

Limitations of our study

We studied only one year and the journals were not randomly selected. Most of the case reports, however, came from journals with high impact factors, giving them a higher profile and thus the greatest chance of being followed up. Suspected adverse reactions that have a major impact on decisions about treatment¹⁴ should be investigated, irrespective of the journal or year of publication.

Compared with Venning's analysis, which encompassed 18 years, our follow-up period of five years was short. However, Venning included only 19 reports of adverse drug reactions in this long term search, and he had already classified 28 reactions without any further checking. We consider that five years is sufficient time for further studies to be carried out and the results published, especially if the adverse reactions had been considered important enough to be reported in a high impact medical journal. Indeed the single case report on vigabatrin that we identified stimulated 34 detailed studies, while the report on hepatitis induced by indinavir stimulated 15 published studies, all within five years.

We may not have identified all relevant validation studies, even though such studies may have been carried out. Studies performed by pharmaceutical companies or regulatory authorities but not published form one category of possible omissions. Alternatively, if a validation study did not cite the original case report, we would not have found it through the citation index search. We took steps to address this by conducting a parallel Medline search, but we are aware that computerised searches for adverse effects do not pick up all relevant articles.¹⁵

Conclusions

Although published reports of suspected adverse drug reactions have their uses,³ they are of limited value because suspicions are seldom investigated further and alerts are not consistently incorporated into drug reference sources. The nature of the information available to physicians and patients is therefore not readily interpretable.

Who is responsible for verifying these reactions? Is it regulatory authorities, drug companies, or independent research teams? Firm leadership from regulatory authorities is needed because drug companies seldom have any economic incentives to investigate such problems.¹⁶ Given the expense of hypothesis testing studies and the relative paucity of funding, we propose that regulatory authorities and pharmaceutical companies should jointly fund independent academic research into suspected adverse drug reactions. Awards of compensation claims against manufacturers who fail to investigate anecdotal reports of adverse reactions to their drugs might act as an additional incentive.

We also recommend the development of a consistent and transparent policy on how information from case reports might (or might not) be incorporated into published drug information and how information should be identified as being anecdotal or formally verified.

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