# clinical pharmacology

## Adverse drug reactions – an update

Over the last few years, a series of recalls of high-profile prescription medicines has aroused serious concerns regarding the safety of medicines. Clinical trials and regulatory oversight, as practised currently, often fail to uncover important adverse effects for widely marketed products. Journals have published numerous articles and editorials relating to drug safety and regulation, with recommendations to overhaul drug safety monitoring, improve vigilance, ensure greater protection of the public and restore trust.[1]

**Although most ADRs can be anticipated, others are unpredictable and often rare idiosyncratic reactions.**

Adverse drug reactions (ADRs) are an important cause of iatrogenic disease. They can involve any organ system, can present clinically in many different ways, and are important disease mimics. Although estimates of the incidence of ADRs vary, they are an important cause of morbidity and mortality.

Although most ADRs can be anticipated, others are unpredictable and often rare idiosyncratic reactions. ADRs have been separated into type A and B reactions. Type A reactions are expected exaggerations of a drug's known pharmacological effects. Therefore they are usually dose dependent, predictable, and preventable. Type B reactions are idiosyncratic and tend to be unrelated to the known pharmacological action of the drug. They are usually not related to dose, unpredictable, uncommon, and potentially more serious than type A reactions. They may be due to hypersensitivity reactions or immunological reactions. Type B reactions represent a major focus of pharmaco-epidemiological studies of ADRs.

### Epidemiology

In a large meta-analysis of 39 studies from 1966 to 1996 from hospitals in the USA, the annual incidence of severe ADRs was 6.7%.[2-4] An ADR prevalence of 1.5% was found in another study involving 4.3 million patients with adverse drug events who visited doctors' offices, hospital outpatient clinics and emergency facilities.[5-8] A review of 14 Australian studies found that ADRs occurred in 2.4 - 3.6% of hospital admissions.[9-11] Despite programmes to promote rational and safer use of medicines in Western Australia, a study that was limited to ADRs of sufficient severity to warrant or extend hospitalisation found the rate of ADR-related hospital stays increased from 2.5 per 1 000 person years in 1981 to 12.9 per 1 000 patient years in 2002.[12] The largest increases occurred in those aged over 80 years.

In the UK 6.5% of hospital admissions were found to be medication related.[12] The median age of patients admitted with ADRs was 76 years, which was significantly older than that of patients without ADRs (median age 66 years).

A recent South African study in a secondary hospital found that 6.3% of medical admissions were due to an ADR, which is similar to proportions found in developed countries.[13] This study reported that antiretrovirals (ARVs) were the commonest drugs implicated in ADR-related admissions, and among HIV-infected patients those on ARVs were 10 times more likely to have a ADR-related admission. ARVs are more toxic than most other medications used by primary care doctors. Given our enormous HIV burden, it is not surprising that ARVs are currently the commonest drugs causing severe morbidity in South Africa. This problem will increase as the ARV roll-out expands.

### Lessons learned from recent drug withdrawals due to ADRs

A number of recent medicine withdrawals have raised concerns regarding drug safety. Current methods of pharmacovigilance, responsible for recognition, assessment, understanding and prevention of ADRs, have failed to detect some serious adverse effects, and under-reporting can result in long delays in the detection of ADRs.[1] The development of strategies to prevent ADRs requires identification of relevant risk factors, while signal detection requires ongoing, systematic review of ADR reports and assignment of priorities to potential signals. Statistical methods can be used to aid the detection of causal links between adverse effects and drugs, although clinical skills and judgement remain critically important in this analysis.[1]

A review of the list of drugs withdrawn from the market can provide useful insight into the importance of post-marketing surveillance, as well as the drug approval process. A review of drug withdrawals for safety reasons in the USA revealed that 75 drugs/drug products were removed during the 33-year period 1969 - 2002.[1] A further 11 drugs had special requirements for prescriptions or had restricted distribution programmes.[1] Numerous other drugs required the addition of a 'black box' safety warning. During a similar period, 41 products were identified that had been withdrawn from the Canadian market for safety reasons.[14] Examples of international drug withdrawals have included fulminant liver failure with troglitazone, QT prolongation and ventricular arrhythmias with cisapride, haemolytic anaemia, coagulopathy and renal or hepatic dysfunction with temafloxacin, and fatal rhabdomyolysis with cerivastatin.[1,15]

**The annual number of drugs withdrawn for toxicity has increased over time.**

The annual number of drugs withdrawn for toxicity has increased over time. There are three possible explanations for this increase in drug withdrawals, i.e. the expanding number of marketed drugs; more sophisticated methods for identifying safety issues; and increasing availability of international safety data or less stringent approval criteria.

The most well-known recent example of drug withdrawal due to toxicity is the selective COX-2 inhibitor, rofecoxib (Vioxx), which increased the risk of cardiovascular disease. Both the manufacturer and the Food and Drug Administration were said to have 'failed the public health systems'.[16-19] Rofecoxib was aggressively marketed in 1999 as an effective, safer alternative to conventional non-steroidal anti-inflammatory drugs (NSAIDs). Despite rofecoxib's potential for

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increasing the risk of adverse cardiovascular effects by altering the ratio of prostacyclin to thromboxane, which enhances platelet aggregation, none of the studies that constituted its new drug application were designed to evaluate cardiovascular risk. A cautionary flag was raised in 2001 when an excess number of myocardial infarctions were associated with rofecoxib in the Vioxx Gastrointestinal Outcome Research (VIGOR) trial.[17,19] This led to the recommendation that it was 'mandatory to conduct a trial to specifically assess cardiovascular risk and benefit'.[18] However, such a trial was never conducted. Excess numbers of myocardial infarctions or strokes were reported in a second rofecoxib trial designed to assess whether rofecoxib was effective in preventing the recurrence of colon polyps.[19] This resulted in Merck's withdrawal of rofecoxib from the market in 2004. While Merck continued aggressive marketing and withheld or misinterpreted data, the FDA took a passive position of watchful waiting, despite strong signals that there was a problem and that large numbers of patients were exposed. Of note was that spontaneous reporting systems played no part in the identification of the rofecoxib cardiovascular toxicity. An increased incidence of a common event such as myocardial infarction can only be detected by statistical analysis of cohorts or in randomised controlled trials.[1] Data on the adverse effects of newly marketed drugs are limited, because at the time of marketing only approximately 1 000 trial participants have been exposed. Once drugs are approved they are used in a much wider group of people and often for much longer periods. The characterisation of the full safety profile of drugs relies on the clinician's careful observation of their effects in 'real-world' practice, which is far removed from clinical trial conditions.

Limitations of the current drug regulation process include pre-marketing trials that are underpowered to adequately determine safety, lack of long-term safety data, absence of systematic post-marketing surveillance, under-representation of special populations in pre-marketing studies, lack of information on off-label use, frequent use of surrogate outcomes, and lack of data on relative efficacy.[1] Drugs are often rapidly evaluated before approval, which may be at the expense of safety. The design of pre-marketing studies allows uncommon, serious adverse effects to go unnoticed. Subsequent under-reporting of adverse events reduces the ability to quantify risk accurately.

Clearly, the pharmaceutical industry has an important role in setting up surveillance systems for drug safety. In the past, it appears that the industry was reluctant to perform observational safety studies proactively or to propose drug-utilisation studies designed to determine to what extent usage in ordinary practice differs from that in pre-marketing trials.[1] Agreeing on common approaches world-wide in therapeutic risk management should bring benefits. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (www.ich.org) recognises the importance of constructive dialogue between regulatory authorities and the pharmaceutical industry. While the main focus is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines, it may also contribute to improved drug safety and the protection of public health from an international perspective.

## Pharmacogenomics – a way forward?

Pharmacogenomics, the study of how variation in the human genome affects response to drugs, has in recent times been added to the armamentarium of the clinical pharmacologist. Interest in predicting the individual's response to drugs by assessing genetic differences has accelerated in the last 5 years since the completion of the Human Genome Project and with the decreasing costs of sequencing genes of interest. The idea of being able to distinguish, by appropriate genetic tests, individuals who may be harmed by certain drugs from those who may benefit from them is very attractive to clinicians.[20] However, the initial enthusiasm of this leading to tailored therapy for all has been replaced with the more realistic view that pharmacogenomics will be of benefit for a limited number of drugs.

There are several examples of pharmacogenetic tests to predict toxicity in genetically predisposed individuals. The polymorphisms in the cytochrome P450 isoenzyme 2B6 that impair metabolism of efavirenz, resulting in more frequent neuropsychiatric ADRs, occur far more often in blacks than whites.[21] Severe drug hypersensitivity reactions can also be predicted by genetic testing, e.g. abacavir hypersensitivity and *HLA-B*5701*, and carbamazepine-induced Stevens-Johnson syndrome and *HLA-B*1502*.[22-25] The clinical uptake of pharmacogenetic testing has been rather poor. Part of this may be related to the poor evidence presented to date regarding the clinical utility of testing.[26,27] This seems to be particularly true for CYP2D6, perhaps the most widely studied polymorphic enzyme, as pointed out in a recent systematic review of the use of CYP2D6 testing in patients prescribed selective serotonin re-uptake inhibitors for depression.[28] Even when there is relatively good evidence for the risk of severe toxicity and an enzyme deficiency, the uptake of testing is patchy. For instance, with thiopurine methyltransferase testing to prevent azathioprine toxicity, a survey in Europe showed that uptake was generally low, while a more recent study in the UK showed that testing varied enormously between different specialties.[29-31] Part of the reason for this may be the unresolved debate as to whether phenotyping or genotyping is superior and the relative lack of availability of genotyping tests in accredited laboratories.

By contrast, pharmacogenetic testing for abacavir hypersensitivity has really taken off in developed countries, which have reported a drop in the frequency of abacavir hypersensitivity after the implementation of pre-prescription genotyping.[32] Testing for *HLA-B*5701* has such a high negative-predictive value and the hypersensitivity associated with abacavir is severe – therefore the test is cost effective.[33] Also important is the willingness of HIV physicians to rapidly adapt their clinical practice to new evidence.

Although the advancement of pharmacogenetics in clinical practice has been slower than predicted, pharmacogenetics has a definite place in new drug development and an emerging role in clinical practice, e.g. the recent report of morphine poisoning in a breastfed neonate of a mother who was prescribed codeine for pain after an episiotomy.[34] Codeine is metabolised to morphine by CYP2D6 and neonates are known to have impaired capacity to eliminate morphine. The mother was genotyped for CYP2D6 and found to be an ultra-rapid metaboliser. The baby's death has

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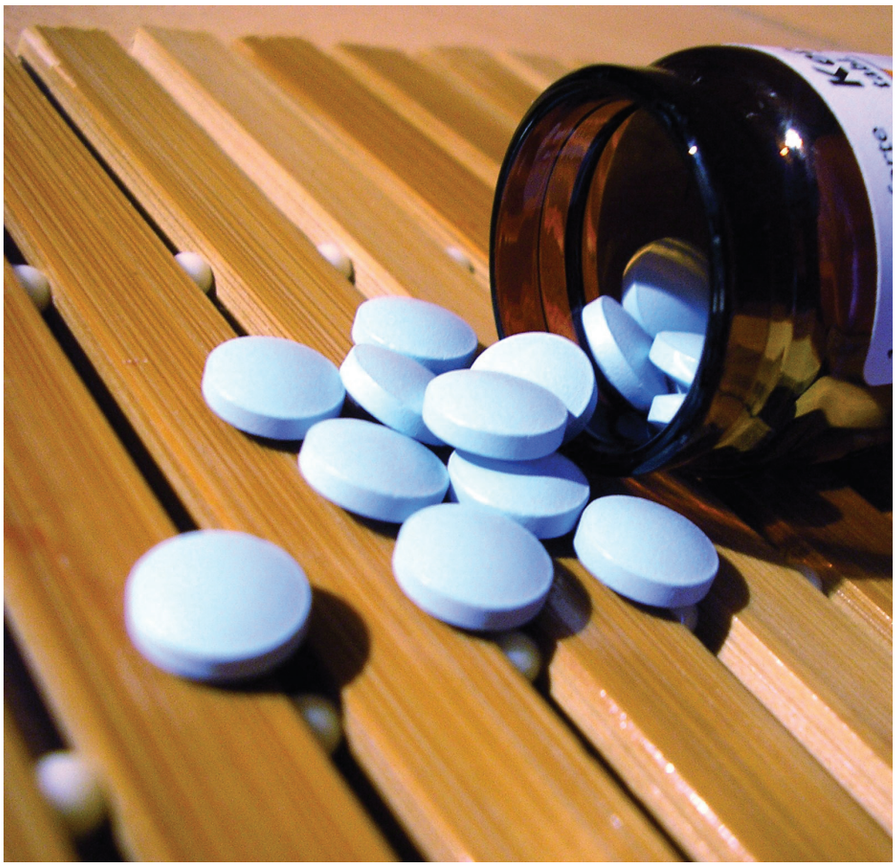

triggered a series of new clinical strategies and recommendations for mothers who breastfeed while on codeine for postpartum pain relief and has also led to a change in the information provided in the majority of package inserts for codeine-containing medicines across the world.[34]

## Conclusion

It is important to understand that the risks of a drug change over its marketed life as new safety data emerge with the exposure of very large numbers of real-world patients. Increased emphasis on education is required at all levels. Drug safety and pharmacovigilance should be included in undergraduate medical and pharmacy curricula and postgraduate educational programmes, and medical students should be taught how to communicate risk-benefit issues to patients. While prescribing is a core skill that should be taught to every medical student, reporting and participation in ADR monitoring schemes must also be promoted as a fundamental professional responsibility.

Epidemiological studies provide an observational method for detecting and quantifying the frequency of adverse drug effects. Over the past two decades, technological advances have increased the availability of automated databases and the capacity of epidemiologists to analyse them. Observational health care data can describe health care encounters, including doctors' visits, medicine dispensing, hospital admissions and deaths. Ultimately, it should be possible to develop complete population databases, with well-documented exposures to medicines, outcomes and potential risk factors. This, combined with appropriately structured randomised clinical studies and pharmacogenomic research into the risk of ADRs, would extend the knowledge of safety, such that emerging changes in risk-benefit are effectively communicated to clinicians and patients.

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## In a nutshell

- A series of recalls of high-profile prescription medicines has aroused serious concerns regarding the safety of medicines.
- ADRs can involve any organ system, can present clinically in many different ways, and are important disease mimics.
- ADRs have been separated for ease of reference into type A and B reactions.
- Type A reactions are expected exaggerations of a drug's known pharmacological effects. Therefore they are usually dose dependent, predictable, and preventable.
- Type B reactions are idiosyncratic and tend to be unrelated to the known pharmacological action of the drug. They are usually not related to dose, unpredictable, uncommon, and potentially more serious than type A reactions.
- The incidence of ADRs varies between 2% and 6.7%.
- The elderly account for the majority of cases.
- The development of strategies to prevent ADRs requires identification of relevant risk factors, while signal detection requires ongoing, systematic review of ADR reports and assignment of priorities to potential signals.
- Data on the adverse effects of newly marketed drugs are limited, because at the time of marketing only approximately 1 000 trial participants have been exposed.
- Pharmacogenomics may be of benefit in determining patients at risk of adverse drug reactions.
- There are several examples of pharmacogenetic tests to predict toxicity in genetically predisposed individuals, e.g. pharmacogenetic testing for abacavir hypersensitivity.
- Drug safety and pharmacovigilance should be a critical aspect of the education of future health care professionals.

## Single Suture

### *Europe exporting measles*

Europe may become a significant source of 'exported' measles, particularly in poor countries that have had more success with vaccination programmes.

A study, published in the *Lancet,* found that the World Health Organization is unlikely to meet its goal of eliminating measles in the European region by 2010 because vaccination rates in many countries, including Germany, the UK and Italy, are too low to stop the virus from spreading.

As a contrast, Latin America eliminated measles in 2002, but since then there have been outbreaks that have come from Europe.

Measles rarely kills in Europe, but in poorer countries malnutrition and limited health care make the virus potentially lethal.

Muscat M, *et al. Lancet* 2009; 373: 383-389.