

Editors' view

Adverse drug reactions – no farewell to harms

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This issue of the *Journal* is devoted to papers on adverse drug reactions. That these papers have all been spontaneously submitted to the *Journal* for peer review, rather than being commissioned or called for, testifies to the importance of the problem.

The commonly used term “adverse drug reaction” (ADR) excludes contaminants (such as are sometimes found in herbal medicines) or supposedly inactive excipients (bulking ingredients) in a formulation. Recognizing, therefore, that medicinal products contain ingredients other than active principles, we probably should talk about adverse reactions to medicines or medicaments, ARMs rather than ADRs. And we all surely want a farewell to ARMs. Or at least a farewell to harms. Especially since they are so common. In a widely cited paper Pirmohamed et al. have shown that the prevalence of adverse reactions among 18 820 patients aged over 16 years admitted to hospital over 6 months was 6.5%; adverse drug reactions directly led to admission in 80% of cases; and deaths occurred in over 2%, giving an overall death rate of 0.15% [1]. The projected annual cost of such admissions to the UK's National Health Service was calculated at £466m. To those who are familiar with the literature on this subject, these figures are not surprising.

Many adverse drug reactions are preventable, and in this issue of the *Journal* Howard et al., in a systematic review of 17 papers, identify the drugs that most commonly cause preventable admissions to hospital [2]. Four drug groups accounted for about 50% of drug-related admissions and 12 drug groups accounted for about 80%. The top four were antiplatelet drugs (including aspirin), diuretics, nonsteroidal anti-inflammatory drugs, and anticoagulants, all drugs

that doctors perceive as being among the most risky [3].

Other papers in this issue cover a wide range of topics, calling for comment on the classification and detection of adverse drug reactions.

The classification of adverse drug reactions in the 21st century

Any good classification system should begin by considering the components of the system to be classified. An adverse drug reaction has the following components:

1. A drug.
2. A patient.
3. Drug + patient → adverse reaction.

The next step is to consider what features of these components can be used to define them:

1. The *dose* (or concentration) of the drug determines its effects.
2. The *susceptibility* of the patient to the effects of the drug determines whether the individual suffers the adverse reaction.
3. The *time-course* of the adverse reaction describes how it occurs.

Several papers in this issue of the *Journal* illustrate some of the principles involved.

Relation to dose

The French chemist Claude Berthollet established the relation between the mass of a substance and the rate at which it undergoes a chemical reaction, an idea that he expounded in his 1801 treatise *Recherches sur les lois de l'affinité* and later developed in his *Essai de statique*

chimique of 1803. It was not until 1867, however, that the Law of Mass Action came of age, as propounded by the Norwegian chemists Cato Guldberg and Peter Waage in *Etudes sur les affinités chimiques*. Even then, the idea had to be rediscovered in 1877 by the Dutch chemist Jacobus van't Hoff, who classified chemical reactions and defined their orders. An idea that has survived intact for over 200 years can't be all that bad (although we can all think of obvious exceptions), and the pharmacological implications of the Law of Mass Action can be seen in the dose-response curve, better called the concentration-effect curve. In other words, it is a general expectation that a pharmacological effect should be related to the concentration of the substance that produces it.

However, the idea that certain adverse effects of drugs can be non-dose-related has persisted for over 50 years. As far as I am aware, it was first specifically suggested in 1973 by Levine, who distinguished dose-related ('toxic' and 'idiosyncratic') reactions from non-dose-related ('allergic') reactions [4], but was already implied in 1958 by Wayne, who distinguished predictable effects ('toxic effects . . . related to the main action of the drug or to its side effects') and unpredictable effects ('not related to the main or subsidiary pharmacological action of a drug') [5].

It is certainly the case that some adverse drug reactions appear not to be related to the dose or concentration in the therapeutic range of doses. There are two possible reasons for this. The first reason is that the relation between the dose, which is relatively easily determined, and the concentration at the site of action, which is not, is highly variable, and an absence of a dose-effect relation does not necessarily imply an absence of a concentration-effect relation; this may occasionally explain apparent non-dose-relatedness. The second, and more important, reason is that effects that appear not to be dose-related are saturated in the therapeutic range but are dose-related in the range of doses below the therapeutic range; in other words, they are hypersusceptibility reactions [6]. Most adverse reactions, however, are dose-related within the therapeutic range of doses (collateral reactions), and an elegant example of this is given by Law et al. in this issue of the *Journal*, in which they show that headache due to calcium channel blockers is dose-related [7]. That they have shown this by a meta-analysis of published data should encourage others to look for dose relationships elsewhere in the published literature. De Bruin et al. also show that cardiac arrest in hospital associated with the use of non-antiarrhythmic drugs that prolong the QT interval is dose-related [8].

Time course

In a book with the chilling title *Zur Geschichte des Gaskrieges* (1924) Fritz Haber, best known for fixing nitrogen, propounded Haber's Law, which states that the extent of an effect is a function of concentration and the time of exposure. In other words, the time-course of an adverse effect is as important as the concentration-effect relation. Six different time patterns have been identified – immediate, first-dose, early, intermediate, late, and delayed – and each has different implications for the diagnosis and management of adverse drug reactions [6]. In this issue of the *Journal* Atthobari et al. [9] provide evidence that suggests that the early form of adverse drug reaction may have two types, early-tolerant and early-persistent. In the former the adverse effect occurs early in therapy but is subject to tolerance and therefore does not persist – headache induced by glyceryl trinitrate is an example. However, an adverse effect can occur early in therapy and persist without the development of tolerance, as in the case of hypertension due to hormonal contraceptives [9]. Such effects do not have to be permanent – in this case, withdrawal led to resolution of the adverse effect.

Two spectacular examples of late adverse effects are reported elsewhere in this issue, both possibly related to cations. In one case a 62-year-old woman developed finger clubbing after abusing purgatives for several years [10]. This is a rarely reported adverse effect of purgative abuse – the authors cite four cases, and I have found only two others [11, 12]. Finger clubbing is rarely associated with causes of chronic diarrhoea, such as Crohn's disease, ulcerative colitis, and coeliac disease. The pathogenesis is unknown; could it be related to chronic potassium deficiency? In a second case, dysgeusia occurred in a 59-year-old man who had taken amlodipine for several years; it abated on withdrawal and rapidly returned on reintroduction [13]. The authors found only one other report of dysgeusia with a calcium channel blocker, nifedipine, but a case has also been attributed to diltiazem [14]. The beneficial effect of zinc salts in dysgeusias, in conjunction with which salivary calcium concentration rises [15], suggests a pathogenic role for calcium.

Susceptibility factors

The factors that increase an individual's susceptibility to an adverse effect can be remembered from the mnemonic GASPED – genetic, age-related, sex-related, physiological (e.g. pregnancy), exogenous (e.g. drugs, food), and disease-related.

Genetic susceptibility factors are highlighted in this issue by LaRocca et al., who report the effects of a

combination of nuclear and mitochondrial mutations in a 68-year-old woman who had adverse reactions to a wide variety of unrelated drugs [16], and by Shin et al., who report interethnic differences in the risk of QT interval prolongation due to quinidine in healthy Caucasians and Koreans [17].

Advanced age as an important susceptibility factor is highlighted by reports of an increase in the repeat rate of adverse reactions in older Australians [18], of other susceptibility factors in elderly residents of sheltered housing complexes in Scotland [19], of the inappropriate use of medications in elderly French patients [20], and of the factors that increase the risks of falls and fractures in elderly patients in the Netherlands and the USA [21, 22].

Pregnancy also features here, in a report that shows that the frequency of pregnancy in women taking isotretinoin is four times greater than has been published to date, that pregnancy prevention programmes have failed, and that the rate of elective abortions (84%) is much higher than previously reported [23]. It is disappointing that even when a susceptibility factor for an adverse drug reaction, in this case teratogenicity, is well known and easily identified, the associated risk of harm cannot be minimized.

Finally, polypharmacy can be a susceptibility factor for adverse drug reactions. In this issue of the *Journal* Viktil et al. show that the risk of an adverse effect increases linearly with the number of drugs being taken and that there is therefore no threshold at which polypharmacy can be clearly defined [24]. Researchers should conduct future studies in the light of this observation, rather than using a definition of say five or more drugs. They should also concentrate on the appropriateness or inappropriateness of therapy, rather than the mere numbers of medications used [25].

Detection of adverse effects – trials and anecdotes

One of the papers in this special issue does not deal with adverse effects at all – and that is the reason for including it. The dearth of information on adverse drug reactions in clinical trials is an important defect. Information may not be collected at all in trials [26]. If it is collected, it may not be properly reported. If it is properly reported, it may not be mentioned in the title or abstract of the paper or indexed in electronic databases, making retrieval difficult or impossible [27]. During 1999–2005, of 122 new active medicines introduced in the European Union, only 48% were reported to have been studied in randomized comparisons with other active compounds [28]. This in itself has implications for drug development, but we are not told anything about the quality of

Table 1

Reasons for publishing anecdotes of adverse drug reactions

To describe a newly recognised adverse reaction or interaction
To provide evidence of an association [30]
To generate hypotheses
To test hypotheses
To demonstrate diagnostic techniques
To elucidate mechanisms
To elucidate or suggest methods of management
To remind or educate
To enable systematic review

those trials and in particular whether information about adverse drug reactions was included. The authors of this report will doubtless want to follow up their preliminary investigation with information of this sort.

In striking contrast, anecdotal reports contribute a large amount of information on adverse drug reactions – about 30% of the world literature [29] – and several anecdotal reports are included in this issue. Although anecdotes can sometimes provide definitive evidence of cause and effect [30] they are generally regarded as being of poor evidential quality and are tolerated for other reasons, as listed in Table 1. Unfortunately, although they often provide hypotheses for testing, they are infrequently subjected to rigorous confirmation [31], perhaps because they are held in such little regard. These problems need to be tackled.

Spontaneous reporting systems, composed largely of anecdotal case reports that are not subjected to peer review, are currently the cornerstone of post-marketing signal detection. Recently in the UK patients have been invited to report adverse experiences spontaneously to the Medicines and Healthcare products Regulatory Agency (MHRA) on Yellow Cards. It is not yet clear whether this will have anything other than political value, but in this issue Blenkinsopp et al. conclude that evidence from patient reporting systems in other countries suggests that the potential benefits may outweigh the drawbacks [32]. However, there is currently too little information to be sure.

Conclusions

The papers in this special issue of the *Journal* contribute in many different ways to the study of adverse drug reactions. Some suggest ways in which reactions might be prevented or minimized. Some generate hypotheses for further study. And some show how future research could be fruitfully carried out. For example, there is a

shortage of systematic reviews in this field, an estimated 2.5% of the world literature [29]; many more are needed. A working group of the Cochrane Collaboration is being formed and hopes to stimulate work of this sort. We also need more formal studies to investigate signals that have been generated by anecdotal reports and data mining tools. And we need a pathogenetic classification to complement the DoTS classification, which is pharmacological and clinical. All this, and more, is necessary if we are going to achieve the much desired farewell to harms.

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Jacobus Henricus van't Hoff
(1852–1911; first Nobel Prize
in chemistry, 1901)