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The burden of adverse drug events

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Drug safety should be considered as part of the balance between benefit and risk, and represents a burden to the patient, the healthcare professional, the regulator and industry. Each of these has a different view on adverse drug reactions and these are discussed in this article.

Commentaries on the burden of adverse drug events are usually limited to an account of the number of patients seen at healthcare centres or admitted to hospital on account of suspected adverse drug reactions. Occasionally, attempts are made to estimate the morbidity and mortality due to such events, but if such calculations are made from retrospective rather than prospective studies, their value is diminished.

Important as such discussions may be, they can only give a partial picture of the burden of adverse drug events. In the current jargon, there are more stakeholders in this process than the public and patients; in addition, this is a burden that is shared with healthcare professionals, regulators and the pharmaceutical industry. The responsibility of each of these parties is different, but unless one can appreciate their respective roles, an incomplete picture emerges.

The first general point is that drug safety, however defined, cannot be considered in isolation. As modern biopharmaceutical medicines become more effective in diseases which have hitherto been considered untreatable, the price to pay may be greater toxicity; but provided the balance between effectiveness and safety remains positive, the regulator will often grant such products marketing authorization. Safety alone is not an issue; it is the balance between benefit and risk. Unfortunately, sections of the press, the public and many politicians do not appreciate this. Many modern anticancer, anti-infective and anti-inflammatory drugs exhibit horrendous safety profiles, but such is their effectiveness that they are widely and successfully prescribed by expert physicians to the benefit of patients.

Burden on the patient

Many studies, both retrospective and prospective, have been conducted on the epidemiology of adverse drug events and adverse drug reactions. Lazarou *et al.* [1] performed a meta-analysis of prospective studies of adverse reactions in hospitalized patients in the USA and suggested that these caused over 100 000 deaths in the USA in 1994 and was the fourth most common cause of death. This conclusion has been criticised because of logistic differences in the studies included in the meta analysis. Pirmohamed *et al.* [2] conducted a prospective observational analysis of 18 820 patients admitted over a period of 6 months to two large general hospitals in the UK. They calculated that some 6.5% of admissions were due to adverse drug reactions, the most common of which was gastrointestinal bleeding from nonsteroidal anti-inflammatory drugs, including low-dose aspirin. The overall fatality rate was 0.15% and the annual cost to the National Health Service was estimated as some £466

million. The figure of 6.5% approximates to the 5% estimate on pooled data from several worldwide studies.

Burden on the healthcare professional

Pharmacovigilance is the study of the safety of marketed medicines. There are two approaches to pharmacovigilance, which are finding evidence of harm and extending knowledge of drug safety.

Documenting the harm caused by medicines is usually carried out by passive surveillance, which is the spontaneous reporting of adverse events by healthcare professionals or by industry to regulatory authorities. The problems associated with such systems are well known, the most important being under-reporting and incompleteness of reports, making further analysis difficult. On the positive side, passive surveillance allows continuous assessment of the safety of a medicine over its life-cycle; moreover, reports can be made not only by healthcare professionals but also by patients. The most valuable outcome of passive surveillance is to generate a safety signal, which is information on the possible relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented.

Such signals are used to extend knowledge of drug safety by active surveillance, defined as a systematic approach which seeks to ascertain completely the number of adverse events by means of a continuous pre-organized process, namely observational studies or clinical trials whose end-point is drug safety. Clinical data for observational studies are collected from patient registers or from patient clinical records; patient registers can be for individual drugs [e.g. Tysabri (natalizumab), used for the treatment of multiple sclerosis], for classes of drugs (e.g. anti-tumour necrosis factor-α drugs used for the treatment of inflammatory forms of arthritis) or they can be condition specific (e.g. orphan diseases).

To be useful for active surveillance of drug safety, patient medical records should contain details of drug exposure and records of outcomes in individual patients. Clinical record databases, such as the UK Clinical Practice Research Datalink (CPRD) and the US Sentinel programme, are examples which will be increasingly valuable in assessing the burden of adverse drug events.

But both registers and databases as described here have limitations. These will usually contain data on drugs which have been prescribed for the patient but not necessarily taken by him. Frequently, they do not contain data on over-the-counter medicines, such as herbal remedies purchased by the patient. The most important drawback is, of course, that the drugs under investigation have not been randomly prescribed as in a clinical trial.

Hence, the concept of a large, simple trial with safety as an end-point may seem attractive. Such studies are, however, expensive, take a considerable time to execute and are thus rarely conducted.

There are a variety of methods which can be used to find evidence of harm from medicines and extend knowledge of drug safety. The concept of a pharmacovigilance toolkit whereby different methodologies can be used appropriately in different situations may be helpful [3].

Burden on the regulator

The history of the regulation of medicines is the history of drug safety. The wilful contamination of an elixir of sulfadimidine with diethylene glycol predicated the Food Drugs and Cosmetic Act of 1938 in the USA. The untested use of thalidomide in pregnant women led to modern drug regulation as we know it today. More recently, the results of the administration of the monoclonal antibody TGN 1412 in a phase 1 clinical trial led to new regulations for 'first in man' studies. These are landmark events defining the burden of drug safety for the regulator.

In recent times, the Institute of Medicine was invited by the US Food and Drug Administration (FDA) in 2005 to review the regulatory governance processes for drug safety in the USA [4]. Among the recommendations of its 2007 report was that safety of medicines should be monitored throughout the life-cycle of a medicine by appropriate methodology. The 2007 US Food and Drug Administration Amendments Act defined the postmarketing requirements that a company had to fulfil once marketing authorization for a product had been obtained and it outlined the methods which could be used to achieve this, namely adverse event surveillance, observational studies or clinical trials. The Act also proposed that the FDA could impose a Risk Evaluation and Mitigation Strategy on any new product, be it a chemical or biological medicine. It also set in motion a new active surveillance system for drug safety, which has become known as Sentinel.

In Europe, new pharmacovigilance regulations were enacted in 2007 and became operative in 2012. At the core of these regulations is the creation of a risk management plan for all newly approved products. It also created the legal basis for requesting postauthorization studies of both safety and effectiveness, and sought to improve transparency of and access to safety data, which had hitherto been the preserve of the regulator alone. Thus, both the FDA and European regulators envisaged greater postauthorization surveillance of drug safety and drug effectiveness, increasing their own burden but aiming to improve public health.

Another regulatory milestone was the publication in 2007 of a meta-analysis of clinical trials on rosiglitazone (Avandia). Rosiglitazone had been approved by both the USA and Europe in 1999 for the treatment of type 2 diabetes mellitus. Its efficacy was based on the surrogate end-

points of fasting blood sugar and glycosylated haemoglobin (HbA_{1C}) levels. But rosiglitazone also causes increases in low-density lipoprotein–cholesterol and in weight, and the meta-analysis of clinical trials showed that its administration led to an increase in myocardial infarctions, rather than a decrease [5], and raised the question of its benefit–risk balance.

The FDA and other US Agencies approached the Institute of Medicine again in 2010 for advice on how to improve the postauthorization safety of medicines further. Among the proposals put forward by the Institute of Medicine was that a submission for marketing authorization for each new medicine should contain a Benefit Risk Assessment and Management Plan, which should be updated over the life-cycle of the medicine. This plan would define the public health question posed by a medicine, would require a formal benefit–risk assessment and would give the rationale for the type of any postmarketing study of safety or effectiveness proposed [6].

Regulators realize that new measures such as these are expensive and time consuming for other stakeholders, but the risk to public health of imbalances in benefit and risk occurring at any time in the life-cycle of a medicine can be considerable.

Burden on industry

Apart from the obligatory notification of all adverse events reported to a company (see previous discussion), industry must provide regular cumulative reports of drug safety to health authorities. These are variously entitled Periodic Safety Update Reports (PSURs) in Europe or Periodic Adverse Experience Reports (PADERs) in the USA, but they are essentially the same; they are interval data reviews of safety, covering one product, and have to be submitted at fixed times set by the regulator, more frequently early in the life-cycle of the product. They provide an analysis of adverse drug events and also lack-of-efficacy reports, as well as safety data from ongoing studies. They may also lead to a change in the label of the product.

Since 2013, PSURs and PADERs have evolved into Periodic Benefit Risk Evaluation Reports (PBRERs) which, as their name implies, comprise a review of risk in the context of benefit and the seriousness of the condition being treated. Unlike PSURs and PADERs, they provide both interval and cumulative data, and their frequency of submission is decided by the National Competent Regulatory Authority.

It is unclear how many countries will adopt PBRERs as the chosen method of industry safety reporting, but they illustrate the change from consideration of safety to that of benefit–risk balance.

Conclusion

The burden of adverse drug events not only comprises the public health impact of medicines on the patient, but also includes the responsibility of the healthcare professional to report these events, the role of the regulator in ensuring that lessons from previous safety disasters have been learned, and industry's part in contributing to a meaningful programme to ensure the safety of its products. Only by a concerted effort to share the burden of adverse events can therapeutic progress be made.

Competing Interests

I have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work.

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