

General Policy Topics

Adverse drug reaction monitoring: new issues

When a new drug reaches the market, patients expect it to be safe and effective. During development, preclinical and clinical studies usually provide sufficient evidence of the product's effectiveness, but this is not the case for its safety. Normally, no more than 3000 patients have been treated with the drug during the clinical trial phase, making it likely that adverse drug reactions with an incidence of less than one in 10 000 will remain undetected. Indeed, several examples serve to prove that pre-marketing clinical trials may fail to detect side effects that later manifest themselves as adverse drug reactions.

Adverse drug reactions can cause severe suffering, and are probably more frequent than many people think. They are estimated to cause 3–5% of all hospital admissions (1), and a survey carried out in 1971 (2) found that they may be responsible for 160 000 deaths each year in US hospitals alone. A more recent study has concluded that adverse drug reactions significantly prolong the length of hospitalization — which may double the cost — and are associated with an almost twofold risk of death (3).

Reporting of adverse drug reactions is therefore essential to obtain the necessary information on the safety of products. In addition, many subpopulations, such as young children, the old, pregnant women, and patients using other medicines concomitantly, or with complicated disease conditions, are not normally exposed to the drug in clinical trials during the development phase.

The origin of adverse drug reaction monitoring lies in the often-quoted thalidomide catastrophe (4), which created a new perception of drug control, accelerating the enforcement of already established, but sometimes dormant, regulatory systems in many countries. In 1967, the World Health Organization reacted to these events by setting up a project on the international monitoring of adverse reactions to drugs (5). Within a few years, this project was extended and developed into the **WHO Programme on International Drug Monitoring**.

Originally established by ten highly developed countries, the WHO Programme currently numbers fifty members. All of these countries possess a national centre for adverse drug reaction monitoring and a national programme. These national centres collect reports from health professionals and pass them on for entry into the international data base housed at the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden.

Over the last five years, some twenty new countries have joined the programme, and almost all of them are from the developing world. Several other countries have expressed the wish to join, and are currently in contact with the WHO Collaborating Centre, which offers the guidance necessary for setting up a national monitoring programme.

Development of a national programme requires special approaches, since these new centres often do not have an infrastructure that allows them to collect and follow-up large numbers of reports. In developed countries, however, people can build on the experience of others and the importance of adverse drug reaction monitoring can be emphasized in professional education. Specific training in drug safety can be more easily organized.

Reports of adverse drug reactions are traditionally collected from health professionals, mainly physicians — at the national level. Many countries, however, are now in the process of **decentralizing** their reporting systems, with the consequent establishment of regional centres for adverse drug reaction monitoring (6, 7). A regionalized system permits closer contact with the reporter, and is particularly suitable when pharmacists are also included in the monitoring process.

The WHO Collaborating Centre plays an essential role in the WHO Programme since it is responsible for maintaining the data base of reports received from those countries participating. At the present time, there are some 1 600 000 reports on file, and each year almost 200 000 new reports are added. The data base can, under certain conditions, be interrogated by third parties (8). It may also generate signals of potentially severe drug toxicity and provide confirmation of signals generated in

specific countries or regions. The Centre also acts as the guardian of the standardized terminology of adverse drug reactions in computerized systems (WHOART).

The **terminology** currently in use within the context of the programme was developed at an early stage, and has been continuously updated. It is used by national centres and by many pharmaceutical companies. None the less, it has become evident that the terminology no longer covers all areas of drug monitoring such as premarketing, clinical trial, or social history data. As a result, terminology that addresses the needs of the majority of drug regulatory authorities is now under development. The ultimate goal of this activity is to develop a truly global terminology with relevance for all countries. This would lead to considerable savings in terms of staff and resources, both within industry and regulatory authorities.

National and regional differences in medical culture and tradition, and availability of resources, result in different diagnostic and, consequently, pharmacotherapeutic practices (9). Because of the substantially different conditions in developing countries in terms of endemic diseases, overcrowding, poverty, malnutrition, and health services, the benefit-risk ratio for drugs determined in developed countries is often not relevant. In general, the benefits to be obtained from effective treatment or prophylaxis within developing countries may be so huge that the benefit-risk ratio is strongly positive, even when there is a substantial incidence of adverse reactions. For example, in a country with a high mortality rate associated with reproduction, the benefits of avoiding pregnancies are large, and will more than offset the risk associated with oral contraceptives. Moreover, many diseases, such as tropical diseases, are only prevalent in developing countries and the safety of innovative treatments can only be tested there.

In spite of budgetary constraints, several developing countries have set up well-organized, well-run adverse drug reaction monitoring programmes. These are often driven by the strong motivation of a handful of health professionals (10). Monitoring of adverse drug reactions in developing countries is of great importance. A good programme may detect signals that are specific for that country, but also for drugs — such as those used in tropical diseases (11) — that have often been on the market for many years in countries where there is no way of providing information on the potential risks.

Traditionally, the use of **herbal medicines** has been high in developing countries and is now taking up an increasing share of the health care market of the developed world. One explanation may be the popular belief that they do not cause adverse reactions. None the less, some herbal medicines are quite active and may even contain toxic compounds. For example, cases of hepatic veno-occlusion attributed to pyrrolizidine alkaloids in tea made from *Senecio* and *Symphytum* (comfrey) species have been reported in several countries, and patients have died of hepatic necrosis following overuse of herbal medicines derived from these plants. Attention must also be paid to possible interactions when administering other drug treatments. These safety aspects have resulted in restrictive regulatory measures in a number of Member States (12, 13).

Naturally occurring compounds may not be the only cause of toxicity from herbal products. Sometimes herbal drugs are dangerously adulterated or enriched by the addition of potent synthetic pharmaceuticals such as anabolic steroids, sedatives and nonsteroidal anti-inflammatory agents. Severe adverse effects have been reported in patients after consumption of such adulterated medication (14, 15). Continuous vigilance remains essential, but registration of adverse reactions to herbal medicines is complicated because of the lack of consistency in the composition of a product consisting of the different parts of several different herbal species.

Recently, the world was shocked by reports of many young children in Haiti dying after consumption of a cough mixture which proved to contain glycerol contaminated with diethylene glycol (16). This incident was not isolated; other cases involving diethylene glycol have been reported in the USA, India, Nigeria and Bangladesh, claiming the lives of uncountable numbers of children, and intoxicating many others (17, 18, 19). Other instances of **counterfeit or substandard medicines** have been reported such as antimalarials containing a trace amount of chloramphenicol, or eye drops manufactured using tap-water instead of sterile water (20). In view of the huge amounts of money involved and the relative ease of manufacture, transport and sale of medicinal products — in particular in insufficiently controlled markets — a decrease in the prevalence of counterfeits on the drug market is not to be expected. Efforts are needed to curb the problem, and drug monitoring programmes can be instrumental in this. For

example, an unexpected lack of efficacy may be spotted in a product which is then found to have no active ingredient, or unusual toxic effects may be caused by cheap adulterants inappropriately used by unscrupulous manufacturers. Patients reacting in an unusual way to relatively standard treatment should be reported as this can lead to the detection of counterfeit or substandard drugs.

Often, counterfeit drugs do not contain sufficient amounts of the active substance. Apart from providing unsatisfactory treatment, this may also lead to underdosing. In the case of infectious diseases, this can also contribute to the **emergence of antibiotic resistance**. Monitoring of the development of resistance is of vital importance, and national drug monitoring programmes can play an important role in this regard. Many other mechanisms may lead to antibiotic resistance and this can pose a threat to public health. Alarming outbreaks of tuberculosis in the USA have lately stirred public interest and concern. In 1993, the World Health Organization declared tuberculosis a global emergency (21) and cited the danger of multidrug resistance. Once again, reporting the absence of effect of long-established therapies may provide a clue to detection of a resistant strain.

Malaria kills between one and two million children every year. However, the number of drugs available for treatment is remarkably small and multidrug resistance diminishes the already not so rich armamentarium even further. Almost all tropical countries are now faced with the problem of an increasing number of ineffective antimalarials and even travellers returning from affected areas sometimes fail to respond to medication (22). Simple and sustainable systems for identification and evaluation of adverse reactions as well as reporting on lack of efficacy associated with antimalarial drugs are needed, but many tropical countries do not have the public health infrastructure to allow reporting (23).

Generally, **vaccines** are considered as safe and no major disasters have been reported. Since vaccines are administered to healthy people, mostly children, the impact of a perceived problem can be tremendous. Many will remember the scare when pertussis vaccine was reported to be associated with brain damage. Vaccination coverage decreased in the United Kingdom from 96% to 60% and only rose again when further studies demonstrated the absence of a causal relationship (24). It is consequently important to

collect information on the safety of vaccines to provide sound reference data in the event of a problem.

Because of these considerations, many countries have established a specific programme for the monitoring of adverse events following vaccination, and a field guide for vaccination programme monitors has been published by WHO (25).

In line with the general trend in our society to autonomy and the need to keep public health costs under control, more and more countries are allowing prescription-only drugs to be shifted to **over-the-counter (OTC)** status. This may result in a different rate of reporting of adverse effects, or even lack of reporting altogether, and monitoring centres should be on their guard.

Control of prescription medicines is the responsibility of the physician, or at least the dispensing pharmacist, whereas OTC drugs escape this kind of control (27). The possible risks associated with a switch from prescription-only to OTC include unexpected interactions when the product is used in combination with other treatments, and the missed opportunity for diagnosis of a possible serious ailment. This situation has primarily economic advantages, but it also provides the public with easier access to medication which is non-prescription (28). Consequences for drug monitoring programmes have not been sufficiently investigated, but initiatives are in hand to start the discussion.

A number of issues in adverse drug reaction monitoring have thus been identified that deserve more attention than received so far. It is fortunate that many developing countries are beginning to realize that they need to become active and collect information on the potential adverse effects of the drugs in their markets.

Although these initiatives may not avoid another disaster with absolute certainty, it is through effective monitoring and application of WHO guidelines that the risk associated with the use of medicines will be reduced to a minimum.

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