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Editorial

Spontaneous reporting of fatal adverse drug reactions

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Many countries run schemes which encourage physicians and other health care professionals to report suspected drug reactions (ADRs). The aims of these spontaneous reporting schemes (SRSs) are to identify previously unsuspected reactions, to elucidate the relevant risk factors, and to evaluate the comparative toxicity of drugs within the same therapeutic class [1,2]. By their nature these schemes have significant shortcomings. Only a fraction of all adverse drug reactions are reported, and only a minority of physicians submit reports [3]. Moreover, the causal link between previously unrecognized reactions and a suspect drug may be difficult to establish, particularly if there is a long latency between the prescription and the onset of the event. Reporting is also biased in favour of reactions that have been recently recognized but against reactions that have been known about for many years. Finally, reports are often difficult to interpret because reliable information on prescription volume, and on the demographic characteristics of the population receiving the drug, may be hard to obtain.

Recently Kromann-Anderson et al. [4] have described 590 reports of fatal ADR's received by the Danish Committee on Adverse Drug Reactions between 1968 and 1988. The data are of special interest as they are the first review of fatal reactions since the Swedish experience (up to 1975) was published [5]. They also highlight the particular difficulties involved in evaluating serious and fatal adverse drug reactions. As with other national SRSs [6,7], fatal reactions constituted less than 3% of all reactions reported and the total number was very small, even though the Danish reporting rate of suspected ADRs is amongst the highest in the world.

There are several reasons why so few reports of fatal ADRs are received. Fatal reactions directly and unequivocally caused by drug therapy using normal therapeutic doses are mercifully rare. The time interval between prescription and death may be long, for example with drug-induced cancers, and it may be more difficult

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for the physician to establish the link. Fatal reactions may be more common in elderly patients, especially in the presence of multiple pathology, and in this group sudden death is probably less likely to be ascribed to drug therapy. Reactions are perhaps also less likely to be suspected in patients with serious pre-existing disease: sudden death associated with flecainide treatment of ventricular arrhythmias after myocardial infarction was for example not detected by SRSs but during a randomized clinical trial demonstrating an excess mortality in patients given active therapy [8]. Finally even serious and clearly drug-related reactions are underreported by physicians. Only 15% of fatal episodes of thromboembolism associated with oral contraceptives and 11% of fatal blood dyscrasias caused by phenylbutazone or oxyphenbutazone were reported to the British Committee on Safety of Medicines [9,10]; in the Danish series only 22 reports of fatal complications of peptic ulceration associated with non-steroidal antiinflammatory drugs were submitted between 1968 and 1988 against a background of increased usage. SRSs would also be expected to be poor at detecting drug-induced increases in the frequency of common fatal disorders such as cancers, unless the relative risk was very large [11].

In spite of these shortcomings the Danish data demonstrate the value of SRSs. Notification of deaths due to bone marrow aplasia were dramatically reduced following the recognition, or clarification, of the role of chloramphenicol, phenylbutazone, oxyphenbutazone and dipyrone. A similar effect was also observed in Sweden [5]. The withdrawal of phenformin led to an 18-fold reduction in reports of drug-induced lactic acidosis. Reporting rate for fatal thromboembolism with oral contraceptives was reduced by over half following the withdrawal of high oestrogen containing preparations in 1974. The recognition of repeated exposure to halothane as a risk factor for halothane-induced hepatic failure resulted in a 5-fold reduction in annual fatality reports.

It is clearly of paramount importance that potentially fatal ADRs are identified as soon as possible so that appropriate action can be taken. Continued monitoring to ensure that the anticipated effects have occurred, and have been maintained, are critical. In the light of the Danish results, how can this best be achieved? A priority must be to encourage fuller reporting of suspected serious ADRs. These must include those ADRs that are well-recognized, or those involving long established drugs, because of the invaluable information this gives on risk factors and comparative toxicity. Any plan which increases the total number of reports should be welcomed and a number of strategies have been assessed. Continuing education and encouragement is obviously of prime importance. The experience from Rhode Island, USA, where a concerted campaign increased reporting seventeen-fold [12] is testimony to this. Regular feedback to clinicians of the results of spontaneous reporting has increased reporting rates in the UK as has the insertion of reporting forms into prescription pads and data sheet compendia. Allowing access to data and the electronic reporting of reactions using Viewdata or other electronic systems may also be effective. In some countries, such as the UK, hospitals present a particular problem and any mechanism to improve reporting from hospitals should be welcomed. Strategies include using specially designed forms for report-

ing reactions to anaesthetics, and either encouraging pharmacists to prompt doctors into making reports or allowing them to report reactions themselves. A statutory obligation for doctors to report ADRs, as exists for pharmaceutical companies, has been difficult to enforce and, judging by the experience of the statutory reporting of communicable diseases in the UK, and experience in Sweden, would probably be ineffective.

SRSs, although fallible, remain a cheap and flexible way of detecting adverse reactions to drugs and their value has been underlined by the experience of the Danish Committee on Adverse Drug Reactions. The value of such schemes should be increased by persuading doctors and other health care workers to report all serious suspected ADR's to their national authorities. This will become of even greater importance with the emergence of a single market for pharmaceuticals throughout the European Community.

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