Spontaneous reporting of suspected adverse drug reactions

The recent article by Tubert and colleagues (1991) makes interesting reading. A superficial reading of their paper might leave the impression that identification of meaningful signals from 'spontaneous' reports of suspected drug reactions is a relatively straightforward procedure, but such is not the case.

The method of estimation of observed and expected events used by Tubert and colleagues (1991) makes the assumption that patients treated with the drug of interest differ little from the general population. Axiomatically, patients treated with a drug are not a randomly selected subset of the general population (unless one makes particularly nihilistic assumptions about medical care). To a greater or lesser extent, due to selection bias, patients being treated may differ from the general population in factors such as age or sex and so the incidence or prevalence of the event of interest (the suspected adverse drug reaction) is likely to differ from that in the general population even if the drug had no adverse effects. If, for example, the oral anticoagulant fluindione which Tubert *et al.* (1991) use to illustrate their methodology were being used to a significant extent by cardiac surgeons following heart valve replacement the incidence of hepatitis would be likely to be higher than in the general population whether due to post-transfusion hepatitis, halothane exposure or other factors. This confounding by indication (Hartzema & Perfetto, 1991) or selection bias, must be carefully considered when interpreting apparent ADR signals whether by Tubert's technique or by other methods.

The example of fluindione also illustrates potential detection biases. Patients being treated with any prescription medication are likely to see a doctor more often than do the general population. Patients being treated with oral anticoagulants in addition regularly attend a doctor so that their degree of anticoagulation may be measured and any appropriate dose adjustments made. Symptoms or signs of hepatitis, if present at the time of visits to the anticoagulant clinic, would be more likely to be detected in such patients than in the general population. In addition liver injury itself might be more easily detected by alteration in the control of anticoagulation.

Knowledge of the natural history in the community of many diseases is poor. The use of 'expert' groups to estimate the likely spontaneous incidence of the event of interest (Bégaud, 1991; Tubert *et al.*, 1991) is fraught with uncertainties. We are told nothing of the expertise of these groups nor the data (or lack of it) on which their estimations were made. The uncertainties of the assumptions made in that crucial aspect of the overall process are important.

The Poisson parameter 'm' is given as the product $I * T$. Strictly, m is not an incidence rate nor a prevalence rate in that context but a reporting rate. This may be more appropriately represented as $m = I * T * P$, where P is the proportion of events occurring which are detected and reported. P is unknown and may differ for the general and treated populations. The authors are aware (Bégaud, 1991) of the sensitivity of their conclusions to assumed values of P.

The authors assert that 'spontaneous reporting remains the best method of detecting new ADRs'. This is a commonly held but unsubstantiated assumption. The sensitivity and specificity of 'spontaneous' reporting systems, e.g. yellow cards, is unknown since little or no audit has taken place of regulatory decisions based on such data. It is the careful, critical and intelligent use of 'spontaneous' reports of suspected ADRs and awareness of the limitations of the data which allows new ADRs to be detected and false signals to be rejected.

The term 'spontaneous' as applied to ADR reporting systems is inaccurate. They cannot be said to be 'without any external stimulus'. In the United Kingdom the Committee on Safety of Medicines requests doctors to send in reports; for example, for new drugs 'All suspected reactions, that is any adverse or unexpected event, however minor, which could conceivably be attributed to the drug' (Committee on Safety of Medicines, 1991) are sought. This is an ongoing background stimulus to reporting but there are specific stimuli designed to elicit additional reports, for example the rise in the number of suspected ADRs with terodiline from 24 in July 1991 to 69 by October 1991 (Committee on Safety of Medicines, 1991) can hardly be considered to be 'spontaneous' but rather was elicited by the stimuli of a 'Dear Doctor' letter from the CSM and attendant media publicity. A more appropriate title for the Yellow Card system and the comparable French pharmacovigilance system would be an 'elicited' reporting system.

As a result of the uncertainties in assumptions including, but not confined to, those mentioned above the 'critical values' discussed by Tubert *et al.* (1991) may be misleading. The effort to quantify signals of adverse drug reactions is a worthy one but a reliable technique must make due allowance for confounding and bias which are likely to occur.

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‘Spontaneous’ reporting of suspected adverse drug reactions— a reply

We totally agree with the comments of Watt (1992) but we would like to add the following remarks:

It is obvious that the risk of a given reaction may greatly differ among subgroups of patients treated. A drug may be used preferentially by patients with a particular pathology or certain characteristics leading to a much higher risk.

Unfortunately it is extremely difficult to evaluate the baseline risk associated with a given pathology, as is the case with formal epidemiology (a cohort study for instance) without a precise analysis of subgroups. An incidence rate of 5/10,000 is often an uninformative mix of various values of risk according to patient characteristics and exposure.

Statistical models and probability approaches in pharmacovigilance require to calculate the expected number of cases, knowledge of the value of i , which is the background incidence of the symptom in patients similar to those treated.

When no reliable epidemiologic data are available it is possible to test conclusions from the model, to reject or not the null hypothesis of independence, under several values of i . In the example in our paper non-rejection of the null hypothesis of independence when 11 cases were notified and 2,000 patients were treated would have required an annual incidence of at least 1/200 for acute liver injury, a very improbable value.

This model was proposed only to generate hypotheses and alerts, not for decision making or to prove causal relationships. In our example the value of 1/200 could have several explanations, including a strong causal association between drug and symptom or a background risk particularly high in patients treated with the drug (for instance, if as Watt (1992) suggests the drug was prescribed after cardiac surgery leading to a marked risk of liver injury due to ischaemia). Both explanations are important and whichever is correct the observation still merits investigation.

We agree that the expected number of cases, $m = i \times n$, should be corrected for the proportion of events

which are not detected and reported. Unfortunately this proportion is unknown. In a paper to appear in the *Journal of Clinical Epidemiology* (Tubert *et al.*, 1992), we show the influence of underreporting on the probability of identifying a new adverse drug reaction. As discussed in our paper (Tubert *et al.*, 1991), underreporting decreases the power of the statistical test and reduces the probability of concluding that an association is present.

Finally it is true that reporting is rarely ‘spontaneous’. Most regulatory agencies and manufacturers try to stimulate reporting of cases, or even make it mandatory. Nevertheless it seems best to retain the term ‘spontaneous reporting’ to describe pharmacosurveillance techniques in large populations which identify only a proportion of ADR cases and give no precise information on the whole population treated.

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