Post-marketing surveillance or drug acceptability study?

Ever since the thalidomide and practolol 'disasters' there has been considerable interest in the concept of post marketing surveillance of drugs. It is an uncomfortable but unalterable truth that the human toxicology of any drug can only be established fully when large numbers of individuals have been exposed to it for a prolonged period. Animal studies and controlled clinical trials, though essential, cannot be relied upon to reveal the rare idiosyncratic reaction which may radically alter the risk-benefit relationship of the drug in question. This fact places upon the pharmaceutical industry and the medical profession a duty of vigilance so that unanticipated drug effects will be detected at the earliest possible time. There is, however, no agreement as to the best strategy for achieving this.

Observational cohort studies, such as have been carried out on the oral contraceptive pill (Royal College of General Practitioners, 1974), can be used to examine a wide range of possible drug effects but are expensive and time-consuming to perform and have limited statistical power to detect rare events. In addition, the suggestion of monitored release made a decade ago (Dollery & Rawlins, 1977) has not been taken up primarily because the realities of current patent law gives pharmaceutical companies relatively little time in which to achieve volume sales if development costs are to be recouped. At present spontaneous reporting by the 'yellow card' system is the mainstay of adverse reactions detection, but since only a minority of such reactions get reported large numbers of patients may be exposed to a new agent before the existence of a problem is recognised. Such was the case with benoxaprofen (Editorial, 1982). Furthermore, the absence of an accurate denominator (patient-years of exposure) makes it very difficult to quantitate risk from yellow card reports.

This month in the Journal the first of what may be a long line of 'post marketing surveillance' studies using computer technology appears (Chalmers *et al.*, 1987). The study by Dr Chalmers and colleagues deals with the assessment of captopril for the treatment of hypertension in general practice. Some 2000 general practitioners were recruited into the study and data on blood pressure changes and reported events were collected (using a Viewdata system) in patients

treated with captopril for moderate hypertension. Each doctor was provided with a keyboard, monitor and a Prestel jack connected via British Telecom allowing direct entry of patient data into a central mainframe computer. The authors argue that this technology would avoid delays in collecting data and offer a large database for long term analysis. There can be no doubt that the number of subjects (13295) enrolled in the study over a period of 18 months is impressive by comparison with almost any other post marketing surveillance exercise. In a large study of this type, however, there is the inevitable trade-off between rigorous scientific method and the benefits of observations made on a large population. The cohort study design requires the inclusion of a comparable control group in order to enable statistical evaluation of both efficacy and adverse effects of the drug in the reference population. Thus, as no control group was included, the present observations represent only one half of a true cohort study. The questions which must be asked, therefore, are whether anything meaningful can be derived from this kind of evaluation of a recently marketed drug and does the study design offer any significant advantage over spontaneous reporting.

Assessment of efficacy in the present study is of debatable validity. Thus the results of treatment with captopril are obscured not only by the absence of a control group for comparison but also by the lack of restriction on the use of concurrent therapy which varied widely. The improvement in blood pressure control during the study may be attributable to captopril but may also relate to the use of other drugs as well as the recognised tendency of recorded blood pressure to fall with time even on placebo. One possibly useful piece of information which can be gleaned is the number of patients who were withdrawn because of poor blood pressure control but this statistic is itself difficult to interpret as the majority of patients ended up on multiple therapy so that the role of the ancillary therapy (as compared with captopril alone) cannot be assessed easily.

What of the assessment of adverse events? Most probably the large number of patients from which this information is derived gives the study and the Viewdata approach its greatest strength. The well recognised 'side effects' of captopril were identified including taste disturbance, rash, cough and hypotension with an interesting excess

prevalence of suspected adverse reactions leading to withdrawal of therapy in female recipients. The authors feel that this latter observation was highly unlikely to have arisen by chance but concede that confounding by selection or reporting bias cannot be excluded. This identifies drawbacks of the absence of a control group in this study design for the evaluation of the significance of uncommon or unexpected findings. Thus adverse drug effects may not be easily distinguishable from complications of the condition treated.

This novel approach as reported by Chalmers *et al.* (1987) represents a useful addition to existing data sources for detecting drug toxicity. The methodology of data collection offers more than 'augmented spontaneous reporting' in that measurement of person-years of exposure are possible so that numerical estimates of risk can be made. However, two important limitations have to be acknowledged. The design cannot evaluate efficacy of treatment except in the most general sense of 'acceptability' to both doctor and patient, and the evidence for a cause and effect relationship between drug exposure and

an adverse event must be interpreted in the absence of a reference population. In view of the size of the database produced by this technique, it is theoretically possible that as other drugs are studied using this methodology for similar or different indications, the background 'incidence' of reporting for various 'events' will become apparent. Between drug comparisons might then provide a better indication of drug related effects. This would, however, require rigid standardisation of the format of reporting and considerable interaction between pharmaceutical companies compiling individual databases.

At this time, therefore, the viewdata technique should be seen as a hypothesis-generating rather than a hypothesis-testing exercise, but is nevertheless a considerable advance on spontaneous reporting for an individual agent. It is likely that studies of this type may become a regular feature of the post-marketing evaluation of new drugs.

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