

General Policy Topics

Postmarketing surveillance: what is being achieved?

It has long been recognized within national drug regulatory authorities that at the time a newly-developed drug is accorded a product licence, there is need for further investigation of its performance under routine conditions of use. This arises because premarketing clinical studies are typically undertaken for relatively short periods of time on a cumulative total of no more than one or two thousand carefully selected patients (1).

Whereas the resulting data provide a satisfactory basis for assessing efficacy and dose-related toxicity, other important aspects of the drug's performance remain to be explored. There may be need to review the consequences of long-term treatment, the potential for abuse and the management of overdosage in the light of extended experience. It is also imperative to institute some form of monitoring to ensure that rare but potentially serious adverse reactions and drug interactions are identified or excluded with reasonable certainty, not only in the target population of patients as a whole but in specific groups such as the very old and the very young. In particular, insofar as pregnant and lactating women are treated, the implications of fetal and perinatal exposure may have to be assessed.

Earlier this year, a working group of representatives of major drug regulatory authorities and multinational research-based pharmaceutical companies, meeting under the aegis of the Council for International Organizations of Medical Sciences, published proposals intended to harmonize requirements for the submission of these supplementary data (2). At present, some 12 national authorities formally require manufacturers to reassess periodically the safety of their licensed products. The debate is still engaged on how meaningful data can best be generated, and the value of company-sponsored postmarketing surveillance studies has attracted particular attention.

The conclusion recently drawn in the United Kingdom is that such studies "have made little contribution to regulatory monitoring of drug safety"

(3). Two-thirds of 27 prospective studies that were reviewed were judged to be unsatisfactory as a basis for evaluating adverse events; they were uncontrolled; selection bias was not effectively excluded; and no study met the target of extending the number of patients in whom the drug had been formally studied by 5-fold or more. In general, it was felt that companies had been slow to provide the generated information and that existing national guidelines on what is required are too vague (4).

The changes now being considered within the United Kingdom invoke issues of fundamental principle. There is recognition that refinement of observational cohort studies is necessary if the prevailing inadequacies in experimental design are to be overcome, and that the scale of the studies must be substantially increased if meaningful information is to be gained on infrequent events. It is also accepted that an array of independent studies may be required to examine all aspects of safety inherent in a particular drug, and that each needs to be selected with regard to signals of possible toxicity generated within preclinical and clinical studies.

The hope must be that these changes can be implemented using computerized data storage and retrieval facilities without a burdensome increment in drug development costs. Logistics suggest that the whole gamut of activities embraced within post-marketing drug safety assessment will soon have to be addressed on a broader international basis.

References

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4. Joint Committee of the ABPI, the BMA, the Committee on Safety of Medicines, and the Royal College of General Practitioners. Guidelines on postmarketing surveillance. *British Medical Journal*, **296**: 399-400 (1988).