Pharmacovigilance in the 1990s

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Since the thalidomide disaster brought the risks of drug therapy into sharp focus, efforts have been made to establish observational systems for early detection of possible adverse effects of drug treatment. Initially, these efforts were collectively referred to by the terms Adverse Drug Reaction Monitoring Schemes, Drug Surveillance Programs, or simply Drug Safety Monitoring. The latest term to come into fashion is Pharmacovigilance. This is generally held to refer to the process of identifying and responding to risk-benefit issues arising with marketed medicines [1]. The process involves operating systems to generate hypotheses about new adverse drug effects—usually spontaneous reporting systems for suspected adverse effects—and subsequently evaluating such ‘alerts’ within a reasonable time-frame. Pharmacovigilance is thus part of the science of pharmacoepidemiology [2].

Pharmacovigilators tend to concentrate their primary efforts on finding ‘signals’ or ‘alerts’ from spontaneous reports of suspected drug reactions from journals or official reporting schemes such as the UK Yellow Card Scheme [3, 4]. Evaluating such ‘signals’ is then an important task both for the drug regulators themselves and for drug safety departments within the pharmaceutical industry. Signals can sometimes be evaluated by reference to premarketing trials and large randomized controlled clinical trials particularly if the ‘alert’ appears to have a pharmacological basis. In reality most such problems are not related to known pharmacological processes and appear more idiosyncratic in origin. In an effort to detect such types of adverse effects, there was a period in the 1980s when the pharmaceutical industry was encouraged to undertake careful prospective cohort studies of new chemical entities in order to gain more confidence in their safety profile [5]. These were mainly of a hypothesis-generating nature, although some had limited hypothesis-testing capabilities. Several such studies were published [6, 7] and the underlying methodology appeared to be evolving in a satisfactory manner. However, several costly, unpublished studies of inappropriate design were also in progress at that time, and concern was expressed by the Medicines Control Agency (MCA) and the Committee on Safety of Medicines (CSM) about the need to improve conduct of future studies [8]. In 1994, a joint working party of the MCA, CSM, Royal College of General Practitioners, British Medical Association and the Association of the British Pharmaceutical Industry published guidelines for company-sponsored Safety Assessment of Marketing Medicines [9]. This emphasized the urgent need for improved methodology in studies designed to assess the safety of marketed medicines. Subsequent to this report, few company-sponsored ad hoc cohort studies have been published in the medical literature.

It is therefore of great interest and importance that observational cohort studies can be conducted using pre-recorded information systems in which prescription details from an identified population are recorded in a systematic fashion, together with details of all ‘events’ of a medical nature occurring in members of this population. These events usually refer to general practitioner contacts, outpatient contacts, hospitalization or deaths. This approach was first mooted by Finney in Edinburgh as far back as 1965 [10], but had to await the advent of powerful computers before it became feasible. Several variants of these systems are available in UK and include MedPlus [11], the Medicines Evaluation & Monitoring Organisation (MEMO) in Dundee [12] and the General Practice Research Database (GPRD) currently belonging to the Department of Health [13].

Using one or more of these systems, drug regulators and safety officers have the facility for rapidly assessing whether or not an alert is likely to be of significance as a possible drug-related event and, if so, whether its frequency is likely to be of relevance to public health and so require regulatory action against the product in question, for example by changing its recommended dose or target population.

Great care must be taken in interpreting the information derived from such large record linkage schemes. They are used both for hypothesis-generation and hypothesis-testing. In both types, but particularly in hypothesis-generating studies, associations between drugs and events frequently can be explained on a non-causal basis. Such associations may be due to chance, bias or intervening variables (so-called confounders). Indeed, non-causal associations are far more frequent than causal associations in this area.

Large pre-recorded databases are ideal resources for testing whether a spontaneous report is likely to be a true adverse drug effect or to other causes. One such investigation appears in this issue [14]. Isolated case reports published in the Lancet raised the possibility that the widely used proton-pump inhibitor, omeprazole, was associated with the onset of acute gout. The manufacturers had also received notification of other cases of gout over the years and were anxious to obtain confirmation of whether or not this was a genuine drug-induced problem. GPRD, covering more than 4 million UK citizens over an average period which now exceeds 6 years, was an ideal resource to investigate the problem as it has been subjected to a series of validation exercises and is generally perceived as being a highly valuable resource for research. Using a cohort approach, the investigators reviewed over 53,000 subjects receiving over 185,000 prescriptions for omeprazole or two comparator drugs, cimetidine and ranitidine.

Within this overall large cohort of recipients of acid suppressant drugs, the investigators then conducted a review of all first-diagnoses of gout and related this to current or past exposure to the target drugs. They concluded that neither current nor previous use of omeprazole was associated with a greater frequency of acute gout than would have been expected by chance. Thus this large database was an ideal resource to test a signal generated from spontaneous reports of suspect adverse drug effects. Indeed, it is likely that the greatest value of this type of record linkage scheme, and others like it, will be their ability to generate accurate
and rapid information about the safety of drugs in widespread use in the community.

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References

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