Postmarketing surveillance of adverse drug reactions in general practice

II: Prescription-event monitoring at the University of Southampton

WILLIAM H W INMAN

Abstract

An independent, non-regulatory drug surveillance research unit has been established at the University of Southampton. Its first task will be to set up a prescription-event monitoring scheme in general practice to enable the pattern of adverse events, as distinct from suspected adverse reactions associated with new drugs to be compared with that of older medicines. Prescriptions for selected drugs will identify patients and a simple questionnaire, designed to be completed in under five minutes, will be used to obtain the required information. Medical opinions about causation need not be given, and the scheme will not interfere with normal prescribing practice.

Introduction

In my first article I defined what I believe to be a realistic target for a new surveillance system, suggesting that it should be possible to develop a method by which adverse events would be recorded in the first 10 000 patients who receive a new medicine and processed in such a way that events experienced by more than 0·1% of patients would be detected as soon as possible after a new drug had been granted a licence for marketing. Statisticians tell us that to be 95% certain of detecting a risk of 0·1% we would require a minimum of about 3000 observations. The larger figure of 10 000 is intended to allow for incomplete reporting; loss from study of patients who do not continue their medication, fail to report back to their doctors, or leave his practice; and various other contingencies.

I shall now describe a scheme, which has been launched by an independent unit in Southampton, and seek the co-operation of general practitioners, without whose help it cannot succeed.

Drug Surveillance Research Unit

In June 1980 the Drug Surveillance Research Unit was set up as an independent, multidisciplinary, non-Governmental, and non-regulatory group within the faculty of medicine at Southampton University. Its aims and objectives include developing new drug-monitoring methods, providing a suitable environment for training in drug-epidemiology, and working towards improving communications among patients, those responsible for health care, the drug industry, and the media. It is believed that by setting up this unit in a university environment we have created the optimum conditions to achieve these aims.

Drug Surveillance Research Unit, University of Southampton, Southampton SO2 3FL
WILLIAM H W INMAN, MRCP, FFCM, director

Prescription-event monitoring

Prescription-event monitoring will depend on identifying doctors and their patients as the prescriptions pass through the various divisions of the Prescription Pricing Authority. Relevant prescriptions will be photocopied and copies sent in strict confidence to the Drug Surveillance Research Unit. Each "test" drug will be matched with a "control drug," the test drug being one that has recently been granted a product licence and the control drug will usually be a chemically or pharmacologically similar drug already marketed for the same indications. An unknown proportion of the patients receiving the control drug will have been taking it for some time, though this will not be apparent from the prescription. Others will be "new" patients who have recently started treatment. The first task will be to process prescriptions for the control drug in such a way that *contemporary treatments* may be selected for comparison with the new product. In practice this will be done by monitoring the prescriptions for the control drug for several months until patients who are "new to the system" start to appear. These will be put on one side for further study and the remainder discarded. There would be little point, for example, in comparing patients starting treatment with a β-blocking agent marketed for the first time in 1981 with controls who might have been taking propranolol for ten or more years.

Having selected roughly equal numbers of patients receiving each drug, and after an interval depending on the nature of the drug (probably 6-12 months) a simple questionnaire, designed to be completed in under five minutes, will be sent to each general practitioner. Medical opinions will not be requested. The information could be copied from the patient's notes by a secretary or practice nurse.

The information required comprises only the age or date of birth and the answers to two questions relating to:

(1) New diagnosis or "events" that have come to the doctor's attention.

(2) Reasons for referral to a consultant or admission to hospital.

For the purpose of prescription-event monitoring an "event" is defined as any new diagnosis, unexpected deterioration or improvement in a pre-existing condition (whether or not related to the condition for which the drug has been prescribed), and any accident or any complaint of symptoms that were not present before the treatment was started. A recognised or suspected adverse drug reaction or referral to a hospital department is an event, and the words used to describe it will be those that the practitioner is likely to have used when writing on the patient's record card, such as "rash, looks anaemic, glycosuria, BP 170/110, fractured femur, pregnant—eight weeks, admission-congestive failure, jaundice, SVT left leg, lump in breast—referred to Mr Jones."

A fractured femur, for example, is an event that could result from drug-induced metabolic or central nervous system effects or simply from ice on the pavement. Either way it should be reported. If, for example, considerably more fractures occurred with hypotensive drug A than with drug B we might suspect that excessive hypotension or dizziness due to drug A was causing falls.

All processing of identified material will be conducted in house by the Drug Surveillance Research Unit, and identities will not be stored on the university computer used to process statistical material. Confidentiality will be absolute.

We do not believe that the work of completing the questionnaires will be burdensome. Given that four drugs were being monitored at the same time, on average a general practitioner might be asked to complete only two questionnaires each year.

Should comparison of event profiles disclose a potential safety problem, some doctors whose reports had contributed to a "warning signal" would be contacted. They would either be asked to complete a more comprehensive questionnaire or an interview could be arranged with a doctor employed by the Drug Surveillance Research Unit as a local field officer. A suitable fee would be paid for the time required to provide the detailed information. In practice the number of patients whose suspected adverse drug reactions will require detailed investigation should be small. Most drugs turn out to have a low incidence of serious adverse drug reactions. We hope that the minority that do not will show their dangers at a time when relatively few patients will have been exposed to risk.

Advantages of event reporting

Event reporting is quite distinct from reporting adverse drug reactions when the doctor notifies a monitoring centre that he suspects that the treatment he has prescribed may have caused such a reaction. Because no medical judgment is required to decide whether or not the event has been drug induced a lay person authorised by the practitioner could easily abstract relevant information from case notes and transfer them to questionnaires from the Drug Surveillance Research Unit.

With hindsight, if practolol had been subjected to prescription-event monitoring and the earlier marketed propranolol had been used as a control, the syndrome caused by the former should have been identified long before perhaps as many as 100 000 patients had been exposed to risk. The problem would have been identified by prescription-event monitoring because the number of diagnoses of psoriasis (or referrals to dermatologists) and of eye symptoms (or referrals to ophthalmologists) would have greatly exceeded the number linked with propranolol. Moreover, patients with both types of condition would have been encountered frequently. The fact of referral to a specialist rather than the actual diagnosis would have sufficed to alert the unit to this serious hazard.

Selection of drugs suitable for prescription-event monitoring

The number of drugs that may be included in prescription-event monitoring at any one time is limited by the ability of the pricing staff to memorise their names and set them aside during the coding procedure, and by the capacity of the unit to process them. During the pilot stage, two test drugs and two controls will be selected for study (see Addendum). They will probably be medicines containing a single active ingredient prescribed by one brand name for medium to long-term treatment of chronic diseases and used on a sufficient scale to yield an adequate number of event records. Prescription-event monitoring will probably not be used, at least in its initial stages, as a method for surveillance of antibiotics, parenteral drugs, topical preparations, or drugs used only intermittently. A study of product licences granted in recent years has suggested that prescription-event monitoring may only be appropriate for perhaps as few as four to six drugs released for marketing in an average year, and it should be emphasised that other surveillance methods should be developed for important drugs that do not fit the criteria for prescription-event monitoring. Many mixtures or reformulations or new indications for older remedies will not be included in the scheme, nor will non-prescribed medicines or those used predominantly in hospitals.

It is also important to appreciate that we would probably not use prescription-event monitoring to monitor a drug already known to be causing special concern because of adverse drug reactions. In such cases the procedure would need to be specially adapted to suit the problem that has been identified. Prescribing might be expected to be atypical and not comparable with that of the control drug. Although neither patient nor doctor will be aware that a particular drug is being monitored, at least until adequate numbers of prescriptions have been processed and the questionnaires despatched, they may be reassured that we would not be using the standard questionnaire if we had knowledge of any important hazard that had already been identified elsewhere —for instance, by the yellow card system. It should also be appreciated that the initial experiment is *designed to test the method rather than the drug*. Drugs will be selected for the experiment mainly on the basis of use. Prescribing rates should be large enough to given an adequate sample, but not so large as to swamp the system or overburden general practitioners.

Discussion

By participating in the pilot study of prescription-event monitoring, general practitioners will be helping to develop a new system that will help to detect previously unsuspected hazards more reliably and in less time than is possible with existing methods. Patients will benefit directly because prescription-event monitoring will help to limit exposure to harmful drugs. On the other hand, since most drugs will prove to have acceptable levels of toxicity, confidence in their safety may be assured more rapidly. The patient has everything to gain and nothing to lose through such monitoring.

Practitioners will be free to participate or not as they choose, and prescribing practice will not be modified because, until an adequate sample of prescriptions has been collected, no questionnaires will be sent out. Obviously, snags will be encountered. Some names may be illegible, some practices may have too many Smiths and Jones's, patients may move to another district, or insufficient events may be reported to generate "signals" of possible danger.

No monitoring system will ever prevent accidents entirely but prescription-event monitoring may help to prevent large-scale accidents. Its success lies in the hands of general practitioners.

ADDENDUM—Since writing this article we have selected four drugs and the collection of scrips has started.

Is a bran diet likely to have any adverse effect on arthritis?

I can think of no mechanism by which a bran diet could adversely affect any form of arthritis.

A woman of 24 will soon marry a young man of similar age. His elder sister has Down's syndrome, and she was born when her mother was 23. What is the risk of my patient having a child with Down's syndrome.

The risk depends on the type of chromosome abnormality present in the young man's sister. If it was a regular trixomy 21 then this couple have little or no increased risk of Down's syndrome in their children. If the chromosome abnormality was a translocation affecting 21 in the sister then, if his parents have not been tested and shown to be normal, it would be appropriate to examine the young man's chromosomes. If these are normal there is little or no extra risk. If he carries the translocation in balanced form then there would be a high risk, depending on just what the translocation was. If there is no information on the chromosome abnormality in the sister it would be a wise precaution to examine his chromosomes and again, if these are normal, there is little or no extra risk.