REVIEW ARTICLE

Monitoring of drugs after marketing

ROYAL COLLEGE OF GENERAL PRACTITIONERS' MEDICINES SURVEILLANCE ORGANIZATION*

Introduction

THE need for a regular formalized scrutiny of drugs used in the community has been recognized for a long time, but practical problems have generally delayed the implementation of appropriate systems. This paper reviews some of the methods which might be applied in order to exploit the major opportunities for this type of research to be conducted in general practice in the British National Health Service. The relevant services which are offered by the Royal College of General Practitioners are also discussed.

All drugs are subjected to prolonged and vigorous testing before national drug regulatory bodies will grant a licence for marketing for subsequent use in the community. In spite of pre-marketing development, which rarely takes less than 10 years, experience has repeatedly shown that important unexpected effects—beneficial as well as adverse—may become apparent only after marketing has occurred. There are two main explanations for this phenomenon.

First, only after marketing can the experience of a large enough number of users be analysed for rare events to have occurred with sufficient frequency for associations to be recognized. Second, in the course of normal medical practice it is usual for a drug to be used for a wider range of indications than would be considered appropriate during formal pre-marketing testing and assessment. For example, the drug may be used in poor-risk subjects, in the elderly, in those with multiple pathology, concurrently with other drugs, and in patients subjected to a variety of environmental influences. In these circumstances, effects may become apparent that could not have been revealed before marketing. Since the purpose of post-marketing surveillance of drugs is to study them in the normal circumstances of their use in clinical practice, the experimental techniques of the clinical trial—with randomization of drug usage and the 'blinding' of subject and observers—are inappropriate. Biases are inescapable and observations have to be interpreted with great care.

Reporting of adverse reactions

Drug regulatory bodies have so far concentrated on collecting information on 'adverse reactions' to drugs as they are supposedly recognized by clinicians. A major disadvantage of this approach is that most side effects of drugs (and it is again important to emphasize that they may be beneficial as well as adverse) are manifested in users by a change of frequency of particular diseases or syndromes which also naturally occur in non-users of the drug. Thus, unless effects are dramatic or highly unusual, they cannot be recognized by clinicians as 'adverse reactions'. Moreover, an understandable reluctance to present as a 'drug reaction' an eventuality which the doctor may, even subconsciously, associate with his own prescribing, possibly explains in part the known low level of reporting. Only by comparing the frequency of occurrence of particular conditions in users with that in an appropriately matched group of non-users, or users of another comparable drug, can the drug-associated changes in frequency be assessed.

Although the reporting of 'adverse reactions' may occasionally be helpful in raising suspicion of unexpected occurrences, and undoubtedly must be continued, the inadequacies of the system have been widely recognized. There is need for more formal and structured drug monitoring.

General practice studies

If most side effects of drugs cannot be recognized as such when they occur, it becomes essential for all occurrences reported by patients to their doctor to be most carefully recorded, so that they are available for subsequent analysis. Two features of the organization of general practice in the British National Health Service provide an opportunity for drug monitoring which is not available elsewhere in the world.

First, all patients register with the general practitioners of their choice, and so each practice has a defined list of patients for whom it is responsible. It is appropriate for control subjects to be drawn from this defined population. These controls are valid because

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they will be reporting their illnesses to the same doctors who are collecting comparable information about the users of the drug under surveillance.

Second, there is a strong tradition, which is rarely abused, that specialist or secondary care is arranged by and on the advice of the general practitioner to whom the specialist will subsequently report his findings and opinion. The general practitioner's medical record therefore contains a substantially complete account of total morbidity reported by each patient to any health service agency. This ensures that comprehensive surveys of total reported morbidity and mortality can be based on general practitioner records. This facility has been successfully exploited, for example in the Royal College of General Practitioners' Oral Contraception Study[1] conducted by its Manchester Research Unit, and in the national morbidity surveys[2] organized through the Birmingham Research Unit.

Assessment of risk

The word risk in normal English usage is associated with undesirable events. However, in epidemiological investigations, risk is used in a special sense which includes the assessment of the 'risk' of a beneficial effect.

Relative risk (risk ratio) is the statistic most frequently determined. It is calculated directly by dividing the incidence of an observed event in drug users by the incidence of the same event in the control subjects who do not use the drug under investigation. In a case-control study (see below) it is calculated indirectly by a different method. Relative risk is a useful expression of the *strength* of the association between the drug and the event. It gives little indication, however, of the *magnitude* of the association and its consequent effect on the public health or the individual patient. A tenfold increased risk of a rare event may be clinically unimportant, but a mere doubling of risk of a common and serious condition will have grave implications.

The importance of the association can be determined only by considering the actual incidence of the event in the user and control populations (that is, the absolute as distinct from the relative risk). This is expressed as the excess (sometimes called attributable) risk and is the *difference* in incidence of a particular event between the users and the controls.

An example from the College's Oral Contraception Study will illustrate the crucial value of the absolute risks. Oral contraceptive users aged 35 to 44 years who smoke cigarettes have a relative risk of 4.2 of dying from a circulatory disease, while non-smoking users of the same age have a comparable relative risk of 3.3.[3] These two relative risks do not appear to be materially different, but in fact the clinical importance of these observations can only be determined from the absolute risks which are one in 2,000 per year for the smokers and one in 6,700 for the non-smokers—a dramatic difference.

Table 1. Methods for post-marketing monitoring of drugs.

	New data	Existing data
Cohort	Prospective drug-based Prospective disease-based	Retrospective drug-based Retrospective disease-based
Case control	Disease based	Disease based

Absolute risk can be calculated directly only in studies incorporating a cohort design.

The acceptability of a demonstrated adverse association depends upon the magnitude and the severity of the effect and the seriousness of the condition being treated. For example, a high risk of a serious side effect may be wholly acceptable in the treatment of an otherwise fatal condition, whereas it would be intolerable if it were associated with the use of (for example) a mild analgesic.

Study design

The methods which will now be discussed vary in the speed and economy with which projects can be completed. It must be emphasized that in one important respect they are identical. They all require the same size of population as a basis for their observations, and this statistic is determined solely by the postulated frequency of the side effect to be assessed and the prevalence of usage of the drug to be investigated.

In a cohort study the experience of a group of subjects (for example users and a matched group of non-users) is analysed from a given date or from a specified event. If the date is today or in the future, and the data are to be subsequently collected as the events occur, the design is known as prospective. It is also possible—by using exisiting records—to set the starting date in the past and analyse events as they have been recorded subsequent to that date. This type of design can be described as a retrospective cohort study.

A classical case-control is also retrospective in nature, but it is not a cohort design. Because of the confusion associated with the term 'retrospective' it is clearer and more practical to consider available methods grouped into two main categories—those requiring the collection of new data and those making use of existing records. An attempt has been made to give a readily understood and distinctive name to each of the available methods (Table 1).

1. Methods requiring collection of new data

a) Prospective cohort study

i) Drug based. This is conceptually the simplest design, and it is also the most reliable and informative. A group of users of the drug under investigation is identified, and for each

subject recruited for subsequent observation an appropriately matched control subject is also required. The control must be a patient with the same disease as the user, but on alternative treatment. Total reported morbidity and mortality is recorded prospectively for all subjects, and all treatment is also recorded.

The advantages of this method are substantial. Because it is prospective, record forms can be designed that ensure that all relevant data are systematically recorded as they occur. The inevitable errors and omissions can be corrected relatively easily because they refer to recent events. The design is capable of testing multiple hypotheses simultaneously, but in addition it is capable of revealing unsuspected associations, that is, it can also generate hypotheses. Both relative risks and absolute risks can be determined directly.

The disadvantages are quite simply cost and time—it will inevitably take several years to collect reliable data on the presence or absence of rare associated events. A negative cannot be proved. Therefore, in determining the logistics of a study an arbitrary decision has to be made about the lowest frequency of occurrence of a drug-associated event it is practicable to detect. Demonstration of a difference in frequency of an event between the users and controls of one in 1,000 users per year is often quoted as realistic. This will usually require the recruitment of 10,000 users and the same number of non-users for observation over at least one year. Because each general practitioner is unlikely to have more than 10–20 patients using the investigated drug, a large number of doctors will be required. We estimate that at least 3,000 College Members would be willing to take part in such studies so that the required number of subjects can be readily recruited.

ii) Disease-based. In this design a group of drugs of similar therapeutic activity can be studied by recruiting subjects when they are diagnosed as having a disease for which the drugs would be used for treatment. For example, a range of antidepressants can be compared if all subjects with depression are recruited for prospective observation. The occurrence of events associated with each drug can be evaluated and the relative risk of side effects determined. Absolute differences in risks can also be calculated. About 10,000 users of each drug would probably be required.

b) An immediate post-marketing evaluation

This type of project has much more limited objectives than a formal prospective study. It is designed to collect data associated with the first widespread clinical use of a drug. Information of considerable value to the marketing company, and to prescribers, will be the indications for the use of the drug perceived by clinicians, the apparent efficacy and acceptability of the drug in routine clinical practice, and the identification of side-effects which may not have become apparent during the necessarily rigorous conditions of pre-marketing clinical trials. A control group, though ideal, is not necessarily required.

2. Methods using existing data

The College's Birmingham Research Unit coordinates morbidity recording by 147 practitioners, with a total practice population of 300,000. These practices maintain full diagnostic registers of all conditions presented using (at present) manual registers developed by the Unit which are now used worldwide. Diagnoses are coded using the College Disease Classification, which is a short list of the *International classification of diseases.*

Although simple analyses of these registers may be informative, their real value lies in their use as a cross-index enabling access to the clinical records of patients who have suffered particular diseases which are the subject of specific investigations.

This existing and continually accumulating data base may be exploited in several ways, which will now be described.

a) Case-control study

This is an inversion of the cohort method (as a result of which the Americans call it a trohoc study!). Instead of starting with the drug users and observing them for the occurrence of a suspected effect, the case-control study starts with the subjects diagnosed as having the suspected effect ('cases'), and their prevalence of use of the drug is compared with that of a matched group of control subjects who do not have the suspected effect nor any other disease which might be associated with the drug. The suspicion may arise as a result of notifications using the 'Yellow Card' system, cases reported to medical journals, from the Drug Surveillance Research Unit at Southampton,[4,5] or from pharmaceutical companies.

Suppose an antidepressant drug called Euphoramine is suspected of causing alopecia. The Birmingham Research Unit will request all the practices maintaining full diagnostic registers to identify all their patients reporting alopecia. Using the age–sex registers, which are always kept by these practices, each alopecia case will be matched by age and sex with another member of the practice. Various exclusions must be exercised in order to obtain a control group which is as free as possible of potential biases. Subject to these conditions being fulfilled, the use of Euphoramine is determined among the cases up to the time of diagnosis of alopecia, and up to the same date in the control subjects. Comparison of the overall prevalence of the use of Euphoramine in cases and controls determines the relative risk of cases of alopecia having been prescribed the drug, and with a subsequent inversion of the argument this is assumed to give an estimate of the relative risk of Euphoramine users developing alopecia.

It is important to note that absolute risks cannot be directly calculated, but if there are accurate estimates available of the real incidence of alopecia in the community (which is unlikely) an approximation can be determined. Only a single hypothesis can be tested.

The case-control study is a widely used technique, and has already been effectively employed by the Birmingham Research Unit.[6] Its advantages and disadvantages have been extensively discussed.[7] The latter arise predominantly from the difficulty in selecting wholly comparable control subjects, and for this reason many studies incorporate two independent sets of controls—for example in general practice a second control may be selected from the immediate neighbourhood of the home of the case. Cases may then be compared with each set of controls in turn. If this results in two similar estimates of risk, the two control groups may be combined, and this increases the statistical power of the study.

Because the data already exist in the clinical records of the participating doctors, a case-control study may be carried out quickly. Nevertheless, cases and controls may require to be interviewed, and additional relevant data collected. It is probably realistic to expect that a study can be completed and analysed within three months of its inception.

It should be noted that a case-control study can also be conducted prospectively. This technique is often applied in hospital practice when cases occurring uncommonly in the community present fairly frequently at a specialist unit which has a large catchment area. In this way an adequate number of cases may be investigated over a reasonable period of time. This advantage is clearly lost in general practice.

b) Disease-based retrospective cohort study

With this design, the method of access to the data is the disease or diseases for which the drug is normally prescribed.

Using the same example as previously, participating general practitioners would be asked to identify all their patients in whom depression had been diagnosed. The date of diagnosis should be as early as possible after Euphoramine has been marketed. In each case of depression, the treatment used and all events reported subsequent to the diagnosis are abstracted from the records. The incidence of alopecia can be determined in association with Euphoramine users and compared with the incidence in subjects prescribed other antidepressant drugs.

Appropriate standardization techniques or multivariate analysis will be required in order to control for confounding variables. Both relative and absolute risks can be determined. Multiple hypotheses may be tested and new hypotheses generated. The data can be collected and analysed quickly.

Though the cost may be lower, the logistics will be similar to a prospective study. To a certain extent this will limit the investigation of rare events, since the number of users is obviously related to the limited number of doctors who maintain full diagnostic registers. On the other hand, their registers extend over many years, so that a prolonged duration of use can be evaluated in a long-established drug.

The theoretical disadvantage is that the records may be incomplete in respect of important variables. Because doctors who keep diagnostic registers are generally meticulous record keepers, this problem is likely to be substantially mitigated.

c) Drug-based retrospective cohort study

There are various ways in which general practitioners could obtain directly a list of all their patients who had used a particular drug. The subsequent experience of these patients could then be compared with that of other patients using an appropriate comparison drug.

In general, the same advantages and disadvantages would apply as in the disease-based study. However, there would be no limitation to doctors who maintained disease registers.

The most convenient method of identifying drug users would be through a practice drug register. This is barely feasible using manual records, but will become entirely practicable when computers are widely introduced into general practice. Until then, it will be possible to obtain the cooperation of the Prescription Pricing Authority, which can return to the volunteer doctors copies of the prescriptions they have issued for the two comparison drugs. This procedure is similar to that employed by the Drug Surveillance Research Unit[5] at Southampton. However, because in the College study the prescriptions will be returned to the doctors rather than the research unit, any problems of confidentiality will be avoided.

One advantage of studies using existing data bases is that the participating doctors generally would not know which drugs were to be investigated at the time that they were recording information about the users. This eliminates some potential observer biases.

Administration of College studies

Large-scale prospective cohort studies will generally be conducted by the Manchester Research Unit which has the necessary special experience.[1,8] The Birmingham Research Unit will be concerned with all studies depending on disease registers. Both units could carry out the drug-based retrospective cohort studies. Other College units and University Departments of General Practice may well undertake particular projects.

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Traveller's diarrhoea

Traveller's diarrhoea can be prevented with bismuth subsalicylate or doxycycline, but neither is suitable for children. Trimethoprim-sulphamethoxazole is effective for prophylaxis and treatment in adults. It is also safe for children and may prove to be efficacious. It may be possible to avoid widespread prophylaxis and to give medication only if diarrhoea develops.

Source: Weiss BD. Traveler's diarrhoea: update 1983. *Am Fam Physician* 1983; April: 193-195.

Undiagnosed neurological symptoms

Two of 25 patients attending the Institute of Neurological Sciences in Glasgow with 'funny turns' were found by means of glucose and insulin assays to have an insulinoma. Both recovered after surgical removal of the tumours. Patients with intermittent undiagnosed neurological symptoms should be screened for insulinoma.

Source: Harrington MG, McGeorge AP, Ballantyne JP. A prospective survey for insulinomas in a neurology department. *Lancet* 1983; **1:** 1094-1095.