MEDICAL PRACTICE

Br Med J (Clin Res Ed): first published as 10.1136/bmj.283.6302.1305 on 14 November 1981. Downloaded from http://www.bmj.com/ on 18 April 2024 by guest. Protected by copyright.

Family Medicine

Prospective monitoring for adverse reactions to drugs in general practice

M DRURY, F M HULL

Interest in identifying the more serious adverse reactions to drugs was heightened by the problems produced by the use of thalidomide and practolol and worries about adrenergic inhalers and dicyclamine hydrochloride during the past ten years. There is a widespread belief that some intermediary system is needed in the United Kingdom between the early hospital-based drug trial and the voluntary notification system run by the Committee on Safety of Medicines.

Several proposals have been made for a postmarketing system of monitoring. Most have in common that they enable a cohort of patients receiving a new drug to be followed up retrospectively for a specified time with full recording of all adverse events. Inman[1] was first in the field when he advocated a scheme in which, for a limited range of drugs, the doctor would be obliged to send in a subsequent report on any adverse reactions sustained by the patient during the period of observation. Prescriptions for drugs under surveillance would be dispensed by a pharmacist only if written on a special prescription form that could be easily identified by the Prescription Pricing Authority. These prescriptions would then be sent to the monitoring centre, which would be responsible for issuing a subsequent follow-up form to identify any adverse events occurring. Skegg and Doll[2] reported a system in which all prescriptions and all morbidity occurring in a general-practice population were monitored for possible drug-effect associations, while Dollery and Rawlins[3] suggested a scheme consisting of registration documents produced by the drug manufacturer and issued to general practitioners in the intermediary phase. Copies of these, with suitable safeguards for confidentiality, would subsequently be followed up by a central agency, which would question both the prescriber and the patient.

Most authorities advocate retrospective monitoring of drugs because of the dangers of bias affecting the results if the doctor or patient is forewarned of the drug under scrutiny. The limitations of retrospective scrutiny of patient records are, however, considerable, and it is at least arguable that the benefits of improved quality of recording in prospective monitoring might more than outweigh the potential for avoiding bias in retrospective recording.

We report here a limited trial in which a method of prospective monitoring was carried out to determine feasibility. The questions we set out to answer were:

(1) Is it possible to recruit general practitioners to record adverse events occurring to patients taking specified drugs?

(2) Will such a method generate a hypothesis that an observed event is due to exposure to a drug?

(3) Is the prescribing and recording of a doctor seriously influenced by the extra work load or by knowing beforehand that a drug is under scrutiny?

Method

Three groups of general practitioners were invited to take part in the study: *group 1*—38 who were known by virtue of their publications or participations to be interested in this topic; *group 2*—all 14 general practitioners in one town who could be personally visited and invited to participate; and *group 3*—a one-in-ten sample of 510 practitioners in one city. Six test drugs were observed including one prescribed generally for short-term treatment and two that were relatively new additions. Two systems of documentation were tried out, and follow-up of patients was maintained for 12 months. Only patients having first prescriptions for the drug under scrutiny were recruited.

In the first method a carbon copy of the prescription was made on a special sensitive paper. The paper bore a unique number but the patient's name and address were obscured. The doctor inserted the

General Practice Teaching and Research Unit, Department of Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TJ

M DRURY, MB, FRCGP, professor of general practice
F M HULL, MB, FRCGP, senior clinical tutor

Hogben number (first three letters of surname, first initial, and date of birth) on this recruitment form. He then affixed a yellow sticker bearing the same unique number on to the back of the prescription given to the patient, which allowed identification by the pricing bureau. The completed form was then sent to us. This method maintained confidentiality, tested whether the use of a specially identified prescription caused problems to any person handling it, and allowed concurrent medication to be recorded.

Follow-up forms inquiring about adverse events in the subsequent period were sent to the doctor at intervals of six and 12 months.

Difficulties produced by the size and nature of the pad led to a change in the recruiting documentation after six months. Each participating doctor was given a pad of forms the same size as a prescription pad. Each pad consisted of pairs of forms bearing a number unique to the pair. The first sheet was made of pressure-sensitive paper which recorded a copy of the prescription given to the patient. The top segment of this, with the name and address of the patient and the number, was detached and kept by the doctor, thereby making a register of patients recruited. The lower part with details of the prescription and bearing the same number was sent to us. The second sheet, of stiff yellow card, was inserted into the notes to record details of subsequent events. In the event the second system proved easier for all participants to handle.

Follow-up forms from both systems were coded by a secretary using a constructive disease coding system[4 5] and were analysed to answer the three questions.

Results

IS IT POSSIBLE TO RECRUIT GENERAL PRACTITIONERS TO RECORD ADVERSE EVENTS?

A letter was sent to the doctors in all three groups (table I). Twenty-eight doctors (74%) in group 1, eight (57%) in group 2, and 23 (45%) in group 3 recruited patients into the system. A higher percentage of doctors from group 1 recruited patients, but several doctors in group 3 recruited large numbers of patients, and this group consequently had the greatest number of patients recruited per doctor. A total of 1771 prescription copies were returned by the 59 doctors taking part, and follow-up forms were subsequently returned for 1099 patients.

TABLE I—*Results of recruiting general practitioners to record adverse events*

	Interested doctors (group 1) (n = 38)	Doctors in same town (group 2) (n = 14)	Random sample (group 3) (n = 51)	Total (n = 103)
No who recruited patients	28 (74%)	8 (57%)	23 (45%)	59 (57%)
No of prescription forms returned	752	120	899	1771
Mean No of prescription forms per doctor	27	15	39	30
No of doctors returning follow-up forms	28	8	16	52
No of follow-up forms returned	619	54	426	1099

TABLE II—*Number (and percentage) of prescription copies returned for each drug in study*

Test drugs	No of prescriptions	% of all prescriptions
Co-trimoxazole	705	39·8
Propranolol	336	19·0
Chlordiazepoxide	159	9·0
Cimetidine	413	23·3
Oxprenolol	88	5·0
Diflunisal	70	3·9
Total	1771	100·0

WILL THE METHOD GENERATE HYPOTHESES ABOUT ADVERSE DRUG REACTION?

Table II shows the number (and percentage) of prescription copies returned for each drug in the study. There was considerable variation between the doctors in the type of drugs reported on. For example, one doctor prescribed cimetidine in one-third of his test scripts and another prescribed it on only two occasions. Completed follow-up forms were returned for 1099 patients (74·7%). Doctors in group 1 returned 619, group 2 (54), and group 3 (426). Listed in table III are the number of deaths, admissions to hospital, and symptoms or problems subsequently reported during the 12-month follow-up period for each drug. In 24 there was a well-recognised adverse effect reported and in a further 43 we thought there was a possible side effect. Attribution of cause and effect is notoriously difficult, and such a method of monitoring can only generate hypotheses. In this study most problems occurred only once or twice with each drug, but skin problems were noted in six of the 241 patients taking cimetidine and 17 of the 275 patients taking diflunisal.

TABLE III—*Number of deaths, admissions to hospital, and symptoms or problems subsequently reported during the 12-month follow-up period for each drug*

Test drug	No of first prescriptions	Recorded events		
		Death	Admission	Symptoms
Co-trimoxazole	705	0	2	62
Propranolol	336	2	4	8
Chlordiazepoxide	159	0	0	8
Cimetidine	413	7	0	241
Oxprenalol	88	1	0	8
Diflunisal	70	14	16	275

DOES THE METHOD INFLUENCE THE WORK OR PRESCRIBING PATTERN?

Receptionists reported some minor difficulties in identifying patients by the Hogben number, which does not include a patient's sex. In a busy general practice any procedure that complicates retrieval of notes from the files is intolerable.

Follow-up questionnaires about the study were submitted to all participating doctors, their receptionists, the pharmacists in the town in which an attempt had been made to obtain the participation of all doctors, and the pricing bureaux.

No adverse comments by patients on the tagged prescription were made to receptionists or pharmacists, but two doctors reported that a patient had been concerned that his prescription was different.

The pricing bureaux reported no problem in identifying tagged prescriptions.

Thirteen doctors commented adversely on the need to carry a different type of prescription pad on home visits and one doctor on the increased work load. Sixteen thought that they avoided prescribing some of the study drugs, while two believed they prescribed them more often and 41 that it made no difference to their prescribing habits. Most doctors believed that they failed to include some of their prescriptions for drugs in the study (under 5% by 39 doctors, 5-30% by nine, 31-70% by nine, and over 70% by two). If we had used a "new" drug only in the study it would have been possible, by collecting prescriptions issued by the doctor from the pricing authority, to measure compliance more accurately. In our study we recruited into the system only patients receiving a test drug for the first time. Collecting scripts from the pricing authority would have included many from patients who had been taking the drug for some time so this method of measuring compliance was not available to us.

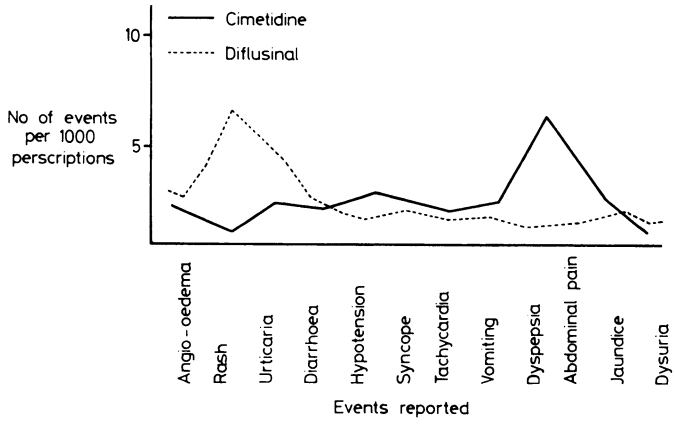
Discussion

This study has shown that it is possible to recruit doctors to monitor prospectively for adverse events to drugs that they have prescribed. That there is some resistance is shown by the fact that of doctors randomly selected only about half recruited patients and one-third followed them up for one year. This recruitment might have been much higher if more intensive methods had been used.

It is generally accepted that a minimum of 10 000 patient/script combinations would be required to generate a hypothesis about an adverse event that occurs at a frequency of one per thousand. In this study, when two drugs were compared, there was a three-fold difference in one type of event (skin problems) shown that was unexplained. If such a difference had been shown after sufficient patients had been recruited it would have suggested a need to test it by using a more sophisticated method.

The hypothesis can be most easily seen by plotting associate

Br Med J (Clin Res Ed): first published as 10.1136/bmj.283.6302.1305 on 14 November 1981. Downloaded from http://www.bmj.com/ on 18 April 2024 by guest. Protected by copyright.



Events (per 1000 prescriptions) associated with taking cimetidine and diflunisal.

events graphically (figure). The misfit between two drugs can then be clearly seen: differences may be due to known association between dyspepsia and cimetidine but others, such as that between skin problems and diflunisal, may lead to the generation of a hypothesis of adverse reactions.

One-third of doctors thought that their prescribing was affected by their participation in the study. Such an effect would delay the accumulation of data. The quality of recording on follow-up forms was of a high standard, but no validation of its completeness was carried out. We believe that if large-scale postmarketing surveillance is to be introduced prospective recording is a method that should be considered.

We wish to express our gratitude to the Department of Health and Social Security for financing this project and to the general practitioners, their staff, the pharmacists, and members of the pricing bureaux who co-operated in data collection.

References

1 Inman WHW. Assessment of drug safety problems. In: Gent M, Shigematsu I, eds. *Epidemiological issues in drug-induced illnesses, 1976.* Proceedings of an International Symposium 19-21 January 1976. Hamilton, Ontario: McMaster University Library Press, 1978.
2 Skegg DC, Doll R. Frequency of eye complaints and rashes among patients receiving practolol and propranolol. *Lancet* 1977;ii:475-8.
3 Dollery CT, Rawlins MD. Monitoring adverse reactions to drugs. *Br Med J* 1977;i:96-7.
4 Hull FM. Disease coding. *J R Coll Gen Pract* 1971;**21**:581-5.
5 Clark EM. Disease coding in a problem oriented general practice. *J R Coll Gen Pract* 1974;**24**:469-75.

(*Accepted 14 September 1981*)

Contemporary Themes

A psychogeriatric survey of old people's homes

M G CLARKE, A J WILLIAMS, P A JONES

Abstract

An assessment of mental impairment and behavioural disabilities in 289 residents in six old people's homes indicated that 50·6% were probably demented and 54% needed considerable help in daily living, 74% were taking prescribed medication, and 11% were taking four or more prescribed drugs. There was a wide variation between homes in those rated as behaviourally disabled, and in the amount of medication prescribed. A follow-up of 60 mentally impaired residents showed few remediable psychiatric disorders or psychotoxic drug effects. A community psychiatric nurse working with the psychogeriatric team would provide a useful support service to old people's homes, particularly where there is a high proportion of disturbed residents and where the staff lack nursing experience.

Department of Psychiatry, University of Leicester, Leicester LE2 7LX
M G CLARKE, MRCP, MRCPSYCH, lecturer (present appointment: consultant psychiatrist, Lister Hospital, Stevenage, Herts)

Towers Hospital, Leicester LE5 0TD
A J WILLIAMS, MB, MRCPSYCH, consultant psychiatrist (present appointment: consultant psychiatrist, Parc Hospital, Bridgend, Mid-Glamorgan)

Leicestershire Area Health Authority, Leicester
P A JONES, MB, MRCPSYCH, senior registrar in psychiatry

Introduction

About 105 000 elderly people live in local authority homes in England and Wales.[1] The age of admissions to these homes is increasing, and the proportion who are mentally infirm and behaviourally disturbed appears to be rising.[2] The role of the homes is not completely clear, as they evidently cope with many old people who seem as sick or dependent as those in hospital.[3] Psychiatric referrals from homes indicate that a range of problems is being managed in the homes, particularly disturbed, interfering, and aggressive behaviour.[4] As residents become more difficult to manage they may be referred for long-stay hospital care, but beds are scarce and their name may just be added to a waiting list.

If the residents of homes are becoming more demented, dependent, and disturbed the role of the staff will also be changing, and the services providing support to these homes needs to change. To become more familiar with the problems encountered we conducted a survey of six old people's homes in the City of Leicester. These were in the district in which two of us (AJW and PAJ) provided a psychogeriatric service. The objectives of the study were: (*a*) to screen the residents for

Br Med J (Clin Res Ed): first published as 10.1136/bmj.283.6302.1305 on 14 November 1981. Downloaded from http://www.bmj.com/ on 18 April 2024 by guest. Protected by copyright.