Monitoring adverse reactions to antibiotics in general practice

CEDRICK R MARTYS
From Darley Dale, Derbyshire, UK

SUMMARY In a general practice in Derbyshire 298 patients who had been given antibiotics were questioned about possible adverse reactions to the drug prescribed. Four methods of assessing adverse effects of drugs in the community were used, and a comparison was made of the replies elicited from patients by doctor and health visitor respectively. Significant differences were shown to occur in the way in which each investigator completed the questionnaires. If ancillary staff are to be employed in monitoring adverse effects of drugs in the community on a large scale then they will have to use a method less reliant on the differentiation of incidental symptoms from drug side effects than is required in the present survey.

The incidence of adverse reactions to drugs in the community is not known\textsuperscript{2-4} despite the survey of hospital outpatients by Bulpitt and Dollery\textsuperscript{5} and Kellaway and McCrae.\textsuperscript{6}

In a practice of 5200 patients in South Yorkshire Mulroy\textsuperscript{7} found that 3\% of all consultations were the result of ill effects of treatment. A survey of 477 patients in a hypertension clinic by Bulpitt and Dollery\textsuperscript{4} using a self-administered symptom questionnaire showed that up to 68\% of patients had one or more side effects to the drug or drugs administered. In a study of 200 outpatients by Kellaway and McCrae\textsuperscript{8} 31\% had an adverse drug effect compared with their series of 500 hospital inpatients where the incidence was 17\%.

The detection of adverse drug reactions requires careful observation of the patient taking the drug and the recording of any adverse event not part of the clinical picture of the illness and not intended in the course of treatment. Close surveillance of a patient on a daily or indeed hourly basis is possible only in a hospital environment. The methods used in the community must necessarily differ from those used in hospital surveys, where the patient is available for interview and observations as and when required. In the community there are two basic ways of obtaining information.

Patient initiated response—The patient is left to report voluntarily any reaction that he thinks may have been a result of his treatment. Mulroy\textsuperscript{9} collected information on adverse drug reactions in his practice in this way. This method of data collection suffers from the drawback that only serious or unusual reactions are likely to be reported, and any figures of the incidence of reactions must be regarded as a minimum. The Birmingham Research Unit of the Royal College of General Practitioners have been monitoring patient initiated consultations of 60 general practitioners on a weekly basis since 1966 in an attempt to measure the incidence of adverse drug reactions in the patients they see. The total rate of reporting is low. Crombie\textsuperscript{10} reported that the rate for recording practices in the Royal College of General Practitioners' survey was 34 per 100 000 patients at risk, illustrating again the difficulty of obtaining a true measure of the burden of adverse reactions to drugs in the community by this method.

Doctor initiated response—The patient is specifically invited to return to the doctor (or ancillary staff worker) in order that information on the nature and incidence of adverse drug reactions can be elicited, either by using a questionnaire or by other means. Kellaway and McCrae\textsuperscript{8} used this method. Bulpitt and Dollery,\textsuperscript{4} measuring the incidence of adverse drug reactions to hypotensive agents using a self-administered questionnaire, either posted a questionnaire to the patient or had him complete one while attending the outpatient clinic.

Subjects and methods

In a general practice survey of 298 patients given antibiotics the way in which a general practitioner or his health visitor recorded information on adverse drug effects was compared by using the same data sheet to record suspected drug reactions.
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The survey was divided into two parts:

TRIAL A
The first 125 patients entering the survey were placed on a random basis in one of the following four groups.

Group 1—The patient was asked to return to surgery one week after starting treatment. No reason for this request was given.

Group 2—The patient was asked to return to surgery one week after starting treatment and was told that he would be asked if he had developed any reactions to the drug he had been prescribed. No specific reactions were indicated.

Group 3—The patient was asked to return to surgery one week after starting treatment and was told that he would be asked if he had developed any reactions to the drug he had been prescribed. Six specific reactions were indicated—sickness, dizziness, drowsiness, diarrhoea, itching, and a rash.

Group 4—The patient was told nothing, but one week after starting treatment the health visitor went to see him at home to complete the questionnaire.

Patients were allocated to the group under consideration by random number tables in such a way that for every five patients given a particular antibiotic, one patient was allotted to groups 1, 2, and 3 and two patients to group 4.

Since trial A indicated that the manner in which the doctor and the health visitor completed their questionnaires might differ, a second stage was designed to examine further these differences with respect to the general question, the specific questions, and the effect of suggesting several specific reactions to the patient at the start of treatment.

TRIAL B
The remaining 173 patients in the survey were subsequently allocated to two groups corresponding to groups 2 and 3 in trial A.

Group 1—The patient was asked to return to surgery one week after starting treatment and was told that he would be asked if he had had any reactions to the drug he had been given.

Group 2—As group 1, but the patient was also given the same six specific reactions to look out for as in trial A.

Members of each of these two groups were seen by the general practitioner or health visitor respectively in order to complete their questionnaires. They were not told in advance who they would see. Throughout the survey, only one doctor and health visitor interviewed patients.

The patient was asked initially to state, in his own words, if he had developed any unexpected symptoms, signs, or reactions of any description since starting treatment. This gave him the opportunity to cite, without prompting or suggestion, any unexpected events that might have occurred during the course of his treatment. He was then asked if he had developed any of the symptoms or signs specified on the checklist below. The terminology was such that the patient would be expected to be familiar with the symptoms elicited—for instance, “vomiting” or “headache”—then he was asked simply if this particular event had occurred while he had been taking the drug. Where he could not reasonably be expected to understand the terminology used then the interviewee had to convert to equivalent lay terms—for instance, he was asked, “Have you had a sore tongue or mouth,” “Have you had glossitis or stomatitis?” and “Have you had any difficulty in breathing,” not “Have you had any respiratory obstruction.” The checklist used in this survey was based on the categories of adverse events tabulated by Hurwitz and Wade, which had been modified somewhat for use in a general practice setting. The patient was also asked several general questions, including details of whether treatment was discontinued when the reaction developed and if not the subsequent ill effects.

Results

Of the 298 patients entering the survey, 104 (35%) replied in the affirmative to one or more questions on the data sheet. Twenty (19%) of the 104 patients had discontinued treatment when a suspected side effect occurred. Of those who had continued treatment, three (4%) thought that they were made worse by doing so.

TRIAL A
Significantly more patients replied to questionnaires in groups 2 and 3 than in groups 1 and 4 (table 1). The health visitor obtained no reply in nearly half the homes she visited among the patients in group 4, thereby accounting for the low response rate for this group.

Apart from determining the best method for collecting information the survey was intended to investigate the effect of suggestibility on the patients taking part. Were the patients in group 3, who were

<table>
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<th>Group</th>
<th>Total No in group</th>
<th>No replied</th>
<th>%</th>
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<td>1</td>
<td>24</td>
<td>17</td>
<td>71</td>
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<td>25</td>
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<td>24</td>
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<tr>
<td>4</td>
<td>49</td>
<td>26</td>
<td>57</td>
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χ² = 11.06, p < 0.05.
asked to note six specific reactions, more likely to report side effects than patients in the other groups (table 2)?

In response to question 1 there was no significant difference between the four groups ($\chi^2 = 1.83$, $p > 0.05$), indicating that suggestibility was not an important factor in the members of group 3, although a larger experience might have shown consistently higher positive answers in group 3. Neither was there a significant difference between groups 2 and 3 in response to the specific questions ($\chi^2 = 6.39$, $p > 0.05$).

Of those patients seen at home by the health visitor, 61% replied Yes to one or more of the specific questions, almost three times as many as those replying Yes to question 1 (21%). The patients in group 4 were seen by the health visitor only, and although here they were given no particular symptoms to be on the alert for, she nevertheless recorded more side effects in this group than were recorded in any other. In fact, she listed over twice as many "specific" side effects as the doctor found in the comparable (unwarned) patients in group 1 that he interviewed.

**TRIAL B**

Altogether 173 patients entered this part of the survey, and 168 (97%) returned a reply to the questionnaire (table 3). Once again, the health visitor obtained a much higher percentage response to the specific questions than to question 1 for patients in both groups, whereas for those patients seen by the doctor the difference was less pronounced (table 4). There was no significant difference within either group 1 or group 2 between doctor and health visitor in the number of patients answering Yes to question 1 (group 1: $\chi^2 = 0.06$, $p > 0.05$; group 2: $\chi^2 = 0.45$, $p > 0.05$).

In groups 1 and 2, however, the doctor and health visitor had significantly different proportions answering Yes to one or more specific questions (group 1: $\chi^2 = 5.98$, $p < 0.05$; group 2: $\chi^2 = 16.95$, $p < 0.001$).

These figures showed that, regardless of whether or not the patient was given several specific reactions to look out for, there were consistent differences in the way in which the doctor and health visitor elicited symptoms that might be adverse reactions from the patients they saw, the health visitor recording twice as many symptoms as the doctor in the patients she interviewed.

**Discussion**

When monitoring adverse reactions to drugs in the community it is important to know whether ancillary staff can be usefully employed in obtaining information from patients about possible side effects of their treatment by using a standard questionnaire, as surveys of this nature entail a single investigator in a considerable workload. From the results presented earlier, it may be argued that the doctor’s questionnaires were incomplete in elucidating all the specific adverse reactions and that, of the two, the health visitor was more thorough. There may have been a difference in rapport achieved between the patient and health visitor or doctor respectively. It is well known that patients will often talk more freely to health visitors or nursing staff but are inhibited in the presence of the doctor. In this case it may be that they were more willing to divulge information on possible side effects to the health visitor than to the doctor, not wishing the latter to think that the drug he had given them had caused more harm than good. If this is so it contrasts with the report\(^\text{a}\) that indicated that investigators who personally detect and record adverse drug reactions get a much higher yield than do those who rely on others for their recording. In the present survey, however, a close scrutiny of individual questionnaires showed that the health visitor on some occasions had marked down as adverse reactions symptoms that were probably due to the illness from which the patient was suffering rather than a reaction to the drug he had been given.
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On discussion and reflection she agreed that this may have been the case, and that this accounted for the relatively high number of adverse reactions she had sometimes noted for drugs that from general experience were believed to be relatively free from such effects.

There is, however, a possibility of bias in the other direction. The doctor indicated as probable adverse reactions on the data sheet of patients he interviewed only those symptoms or signs that were thought to be drug induced, not those that might be expected to occur in the natural history of the illness that was being treated. Hence any symptoms or signs occurring in this category in patients seen by the doctor would not be recorded, and the list of side effects consequently would be incomplete. This could explain the differences in response rate for the six specific questions.

It is difficult to avoid this problem entirely. If the questionnaire used in this survey is used as a symptom checklist and all symptoms that the patient reports are recorded then an unreliably high incidence of adverse effects may be reported. On the other hand, if the only symptoms recorded are those thought to be drug induced a false low incidence rate may result, since side effects corresponding to symptoms expected in the course of the patient's illness may be omitted from the checklist.

To obtain information on a large scale about adverse effects of drugs in the community the help of paramedical or ancillary staff workers would be essential. In such a survey it would be necessary to design a questionnaire less reliant on the differentiation between symptoms and adverse reactions important in accurate completion of the questionnaires used in this survey. Other comparable surveys in hospital have used a doctor alone or ancillary staff trained specifically for the purpose. In another investigation the doctor completed the questionnaire, but written notes by nursing staff were used if it was thought they had recorded an adverse reaction. Yet other surveys do not indicate whether or not ancillary staff help to complete questionnaires.

Although Huskisson and Wojtulewski have suggested that checklists actually interfere with the collection of information concerning drug side effects, many workers do in fact use a checklist of some type. These authors have also indicated that side effects not on the checklist may be missed. The general question at the beginning of the questionnaire used in the present survey should be of value in avoiding this difficulty. What is clear is that this method of intensive surveillance is much more likely to obtain total incidence figures of adverse drug reactions than any method relying on spontaneous reporting and the problems of bias that make these figures difficult to interpret. Inman and Price-Evans, however, found that 91% of all reactions in a random sample received by the Committee on Safety of Medicines were "probably" or "possibly" drug-related—a reassuring figure.

Requests for reprints to: Dr C R Martys, "Stonecroft", Whitworth Road, Darley Dale, Derbyshire.

References

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C R Martys

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