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General Practice Observed

Adverse reactions to drugs in general practice

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Summary and conclusions

Of 817 patients in a general-practice survey of adverse reactions to drugs, 41% were thought to have "certainly" or "probably" had a reaction to the drug prescribed. Adverse effects on the gastrointestinal and central nervous systems were the most frequently reported, and 90% of reactions had occurred by the fourth day of treatment. More patients given drugs acting on the central nervous system and antihistamines reported reactions than those in other categories.

A higher incidence of adverse drug effects is shown in this general-practice survey than in other, mainly hospital-based, surveys. Further intensive surveillance for adverse effects of drugs is recommended to provide additional information on the burden of drug-induced disease in the community.

Introduction

An adverse reaction to a drug has been defined as "any unintended or undesired consequence of drug therapy,"[1] or alternatively as any effect of a drug that is "noxious and unintended and occurs at doses used in man for prophylaxis, investigation, or therapy."[2]

Since the thalidomide disaster several intensive hospital monitoring systems have been set up to measure the incidence of drug-induced disease during inpatient treatment.[1 3-8] Adverse reactions to drugs present at the time of admission or occurring while the patient was in hospital have been investigated and recorded in a systematic manner. The Boston Collaborative Drug Surveillance Programme has for over 10 years run a multicentre survey of hospital patients using specially trained monitors stationed on wards to record adverse effects of drugs. Reports are issued at regular intervals,[9 10] and a comprehensive picture is now emerging of the incidence and severity of drug-induced disease in hospital patients.

Although the frequency of adverse effects reported from hospital-based surveys varies between 1%[11] and 28%,[12] most of the work cited earlier gives a rate of detection of adverse drug effects of 10-20%. The burden of drug-induced disease in the community is not known,[13-15] but reaction rates can vary from 3% to 68%.[16-18] This wide variation in incidence rate probably reflects different methods of data collection.

As there are no intensive monitoring systems in the community comparable to those established in some hospitals for measuring the incidence of adverse effects of drugs the incidence of reporting in a voluntary system is likely to be low.[19 20] The present survey was undertaken to obtain a more accurate measure of the incidence of drug-induced disease in the community.

Methods

To measure the incidence of adverse drug reactions in the community a two-year prospective study was undertaken in general practice. The practice of about 3300 patients is part urban, part rural in Darley Dale at the edge of the Derbyshire Peak District. All patients who had been given a drug for the first time were asked to complete a questionnaire. The usual details of name, date of birth, and sex were recorded, followed by treatment, dose administered, and diagnosis. Patients were asked to state in their own words whether any symptoms occurring since starting treatment might have been a side effect of the drug prescribed. They were then questioned about specific symptoms that could be drug-related (table I) and asked whether the severity of the reaction had led to discontinuation of treatment, and also questioned about self-medication.

After a pilot survey had been completed, all patients entering the main survey were asked at the end of their consultation to make an appointment for one week later (except those given oral contraceptives, who were seen after one month), when they would be asked about any unwanted effects or side effects of the drug prescribed. Details of the pilot survey and the questionnaire are given elsewhere.[21]

Except for some patients in the pilot survey who were seen by the health visitor, all patients in the survey had to see the doctor to complete their questionnaires. Since these additional interviews had to be conducted within the existing appointments system of the practice, reactions could not be investigated at the same time for all drugs. In the first year the two major drug groups (antibiotics and analgesics) were investigated concurrently, and all other groups of drugs in the second year. Nevertheless, a considerable strain was thrown on the efficient working of the appointments system at times.

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TABLE I—*Frequency of specific reactions*

Type of reaction	No reported	% incidence in total no of respondents
Gastrointestinal system		
Nausea	94	11·5
Vomiting	19	2·3
Diarrhoea	68	8·3
Glossitis/stomatitis	14	1·7
Dyspepsia/flatulence	38	4·6
Dry mouth	44	5·4
Melaena	1	0·1
Central nervous system		
Excessive wakefulness	10	1·2
Excessive sleepiness	98	12·0
Confusion	17	2·1
Hallucinations	7	0·9
Tremors	6	0·7
Convulsions	0	0·0
Headache	46	5·6
Dizziness	75	9·2
Cardiorespiratory system		
Fainting	10	1·2
Palpitations	3	0·4
Respiratory obstruction	3	0·4
Asthma	1	0·1
Chest pain	1	0·1
Skin		
Rash	24	2·9
Itching	22	2·7
Other systems		
Vaginal discharge (thrush)	1	0·1
Paraesthesia	4	0·5
Haematemesis	2	0·2
Sweating	5	0·6
Constipation	12	1·5
Depression	7	0·9
Hot flushes	4	0·5
Impotence	1	0·1
Double vision	1	0·1
Blurred vision	6	0·7
Dry eyes	1	0·1
Tinnitus	1	0·1

The survey was restricted to all patients given single-drug treatment for the first time in a given year for several reasons.

(1) Most patients in general practice present with relatively straightforward clinical problems, for which treatment with a single drug is entirely appropriate.

(2) Those patients needing two or more drugs at the start of treatment of a particular condition are often the more-severely ill. They may be removed suddenly to hospital, and the opportunity for follow-up of possible adverse drug reactions is lost. Although the likelihood of a reaction is increased the more drugs the patient is given, the actual measure of morbidity in the practice is not likely to be greatly affected by omitting patients on multiple treatment, as they constitute only a small minority of the total undergoing treatment at any one time.

(3) In a relatively small survey such as this, particular adverse reactions can be shown to occur with a given drug only if this is the only drug that the patient is receiving. If a patient is on combined treatment it is much more difficult to say unequivocally that a reaction he suffers is due to one and not another of the drugs he is taking. Often in this case only large surveys of many thousands of patients will make the picture clear and show unambiguously which drug is causing the reaction.

Patients on long-term treatment—for instance, digoxin, diuretics—who during the two years were given a new drug were included in the survey so long as drug interaction between old and new treatment was unlikely. We could then reasonably conclude that any adverse reaction developing was probably due to the drug they had been given.

Results

During the two years of the survey 872 of the 998 patients who were asked to return to complete the questionnaire did so, a reply rate of 87%. The health visitor saw 55 of the patients given antibiotics; these are not included in the following results, so that 817 questionnaires were analysed. Table II shows the number of patients and the response rate for each group of drugs monitored in the survey.

Forty-one per cent of patients had a reaction thought to be "certainly" or "probably" due to the drug prescribed (table I). The commonest adverse effects affected the gastrointestinal and central nervous system—that is, nausea, diarrhoea, dry mouth, drowsiness, headache, and dizziness. Many classes of drugs cause gastrointestinal intolerance. In this survey these side effects were not serious and were usually self-limiting, but nausea and vomiting were a frequent reason for stopping treatment. Three per cent of patients complained of confusion or hallucination, reactions that caused immediate cessation of treatment. Pentazocine and dihydrocodeine were most often associated with these symptoms. Rash occurred in 3% of patients, half of whom were receiving or had just completed a course of ampicillin. None of these patients had been suspected of suffering from glandular fever before treatment began. Other reactions, not on the check list but volunteered by the patient, are also listed. Probably the most serious of these was depression, mentioned by seven patients, but no case of attempted suicide due to side effects of drug treatment occurred.

TABLE II—*Number and type of drugs prescribed*

Drug group	No in group	No replying to questionnaire	Response rate (%)
Antibiotics	405	348	86
Drugs acting on central nervous system	366	323	88
Drugs acting on cardiorespiratory system	68	63	93
Drugs acting on gastrointestinal system	43	36	84
Antihistamines	39	33	85
Nutritional, hormonal, metabolic, and misc	77	69	89
Total	998	872	mean = 87

Table III shows the time interval between onset of treatment and onset of adverse reactions. The peak incidence of reactions was one to three days after starting treatment; 90% occurred by the fourth day.

TABLE III—*Time to onset of reaction*

	Time to onset of reaction (days)				Total
	<1	1–3	4–6	⩾7	
No of patients	118	182	22	12	334
% of total with reactions	35	54	7	4	100

Table IV shows the number of patients with one or more reactions in each drug group. More patients reported adverse reactions to drugs acting on the central nervous system (51%) and to antihistamines (45%) than to drugs in other categories, and more patients who were taking analgesics and antihistamines discontinued treatment than did those who were taking other types of drugs (34% and 47% respectively) (table V).

TABLE IV—*No of patients with one or more reactions in each drug group*

Drug group	Total No on drug	No with one or more reactions in each group	Incidence of reactions in each group (%)
Antibiotics	293	104	35
Central nervous system	323	166	51
Cardiorespiratory system	63	25	40
Gastrointestinal system	36	11	31
Antihistamines	33	15	45
Nutritional, hormonal, metabolic, and miscellaneous	69	15	22

TABLE V—*Number discontinuing treatment after reaction developed*

Drug group	Total	No in each group discontinuing treatment due to side effects	% of total with reactions
Antibiotics	104	20	19
Central nervous system			
Analgesics, anti-inflammatory agents	119	41	34
Others	47	7	15
Cardiorespiratory system	25	5	20
Gastrointestinal system	11	2	18
Antihistamines	15	7	47
Metabolic, nutritional, and misc	15	0	0

Patients were asked if they had taken any self-medication during the course of treatment. More young adults and children took medication in addition to their prescribed treatment than patients in other age groups (table VI). Mothers treated their children with various proprietary cough linctuses and aspirin preparations in all their different guises. Adults took a wide variety of self-prescribed medicines, polycombination analgesics of various kinds being most common but closely followed by proprietary cough linctuses, laxatives, and other gastrointestinal preparations. Herbal preparations and "kidney pills" were also popular. One of the most serious adverse reactions occurred when a teenage patient took two aspirin tablets to alleviate a bout of epigastric pain. He had a haematemesis shortly afterwards.

TABLE VI—*Number in each age group admitting to self-medication*

	Age group										Total
	0–	10–	20–	30–	40–	50–	60–	70–	80–	90–	
No in each age group admitting to self-medication	16	16	25	33	25	18	10	3	0	0	146
% of total in each age group	22	17	18	24	23	16	10	9	0	0	17

Discussion

During one year 19 general practitioners in practice in Oxfordshire prescribed at least one drug to 60% of their patients.[22] On the strength of the findings in the present work, at least 40% within the first week, or about 25% of the practice population, may have had an adverse drug effect of some kind. There is as yet no large-scale, in-depth survey of the total burden of drug-induced disease in the community. General practice has lagged far behind hospital workers, and the difference in the type and severity of medicine practised, the drugs administered, and the availability of inpatients for review at daily or more frequent intervals should all be remembered when the incidence, type, and severity of hospital-based and community-based adverse drug effects are compared.

Many large hospitals now undertake intensive monitoring of adverse effects of drugs. Different centres use different methods of collecting information, and any comparison of results should be treated with care. Consistent criteria about what constitutes an adverse reaction are not easy to achieve.[23] Over the past few years different monitoring centres have used specially trained nursing staff,[12] pharmacists,[24 25] physicians with a special interest,[26–28] drug-reaction reporting cards completed by the patient's physician,[29 30] and postal questionnaires.[31] Mulroy[16] has undertaken a patient-initiated survey of adverse effects of drugs in his practice. For several years now in Britain the Committee on Safety of Medicines has had a "yellow card" reporting system in which practitioners are invited to report to its central office in London any suspected adverse drug effects, particularly to new or recently introduced drugs.

Most of the hospital-orientated studies mentioned use intensive monitoring for adverse drug reactions—the patient is seen on a daily basis and closely questioned about unexpected "events" that may be drug-induced. These are often classified as "definite," "probable," "possible," or "don't know" when cause-effect relations are being considered,[12 24 28] according to the degree of certainty that the particular event is drug-induced. Sometimes events are classified as "minor," "moderate," "severe," or "contributed to death."[24 25] In a general-practice setting every patient given a drug cannot be reviewed every day, and the present survey used an interview with the patient one week after starting treatment as a reasonable compromise. This does not provide day-to-day information on unexpected "events" but merely elicits the patient's recollection of these events, often after several days have elapsed. Also, of course, no information is available on any events occurring after, say, two or three weeks of treatment. Again, this survey made no attempt to grade reactions either by severity or by the likelihood of a cause-effect relationship, although as described earlier only those reactions thought to be either probably or possibly drug-induced were recorded as such.

Most surveys use a data sheet or questionnaire for recording suspected adverse drug effects. In the Boston Collaborative Drug Surveillance Programme this is particularly detailed.[12] Except where postal questionnaires are used, there is direct contact between the monitor (physician, nurse, pharmacist) and the patient in all cases. When paramedical staff act as monitors, the investigating doctor reviews their reports before finally assigning a particular event to the "drug-induced" category, or not.[12] When medical staff interview the patient they make a direct assessment of the nature of the event or side effect—the method used in this survey.

Altogether 41% of patients in this survey had some type of adverse drug effect. This is higher than the quoted incidence rate from intensive hospital surveillance, and comparable figures are not available from general practice. The wide variation of incidence of adverse drug reactions shown in these hospital-based surveys may be explained by the classification system used by the particular investigator. Some may record only serious and life-threatening events, others every suspicious untoward effect, however trivial, that may be associated with the drug prescribed. The figure of 41% obtained in this survey represents the incidence of all adverse effects thought to be certainly or probably due to the drug administered. Mulroy[16] found a patient-initiated consultation rate of only 3%; here only reactions that the patient voluntarily brought to the doctor's attention were recorded.

Gastrointestinal intolerance is well known to occur with many classes of drugs.[32] In this survey as in others[6 33] gastrointestinal side effects were a frequent cause of morbidity, followed by central nervous system effects, particularly drowsiness, headache, and dizziness. A detailed analysis of reactions to individual drugs is given elsewhere.[21]

In this survey 90% of reactions had occurred by the fourth day. Hurwitz and Wade[6] found that 88% of reactions had occurred in the first eight days of treatment with a drug. Kellaway and McRae[18] in a survey of adverse drug reactions in hospital outpatients found that unwanted effects occurred most commonly one to two weeks after discharge from hospital. The time at which data are collected may be important. Patients seen only once after starting treatment (seven days in this survey—excepting patients on oral contraceptives, who were seen after one month—and 14 days in the Kellaway study) are more likely to recall reactions occurring immediately before being interviewed than in the more distant past, unless something novel or totally unexpected has occurred. Nevertheless, all seem to agree on the general time-scale to onset of reaction from start of treatment, and the first week needs the greatest vigilance.

Patients on long-term treatment are in a different position. This survey did not attempt to measure the incidence of side effects in patients on treatment for many months or years, but such work is undoubtedly important and could well form the basis for a further study.

Drugs acting on the central nervous system were responsible for a greater incidence of more severe reactions than drugs in other groups and also a greater overall incidence of adverse drug reactions of all grades of severity, followed closely by the antihistamines and drugs acting on the cardiorespiratory system. Mulroy[16] found antibiotics caused more reactions than other groups of drugs, as did Macdonald and Mackay[3]—but again these differences may reflect the ways in which the different surveys obtained their information. Both these studies found the next greatest incidence of reactions in the central nervous system and cardiovascular groups of drugs.[3 16]

The figures quoted for self-medication must be regarded as a minimum incidence, depending as they do on a voluntary admission by the patient of tablets he had taken on his own initiative. At least one in six patients for whom a prescription is written will take additional treatment of their own; in some age groups the figure is as high as one in four. These patients

may well suffer an adverse effect of their own treatment, and an interaction with the prescribed drug is also possible. Law and Chalmers[34] have provided a more detailed analysis of self-medication and the occasional disaster with self-administered aspirin is well known.[35]

In the present survey the general rule was used that any event occurring or any symptoms or signs developing during the course of treatment that was not a usual concomitant of the patient's illness and not intended in the course of treatment was an adverse drug reaction or side effect. The two terms are used almost synonymously throughout this survey (as indeed they are in other works), though the term "adverse drug reaction" might better be reserved for the truly unpredictable allergic or idiosyncratic reaction, and the term side effect used to describe well-known concomitants of treatment with certain drugs—for instance, drowsiness with antihistamines and dry mouth with tricyclic antidepressants. Nevertheless, from the patient's and the doctor's point of view they are both "unwanted effects of drugs" and are regarded as such.[36]

The application of this rule in all cases can create difficulties. The patient who develops nausea and diarrhoea 48 hours after starting a course of ampicillin may have developed an intercurrent gastrointestinal infection, and these symptoms are wrongly described as side effects of the drug concerned. Reidenberg and Lowenthal[37] have shown that a positive history of many symptoms commonly considered drug side effects can be elicited from healthy people who are not taking any medication. Green[38] has emphasised the importance of the doctor's being aware of all pre-existing symptoms and signs before starting treatment, so that symptoms and signs the patient's attention is drawn to after treatment has started may not be erroneously labelled side effects. He has also, along with other workers, measured the incidence of side effects to placebos, obtaining the curious result that side effects to a placebo-controlled treatment were similar to the active drug. This suggested that the investigator may have been inadvertently recording adverse effects that he was expecting the drug under study to have. This is important work, and underlines the danger of placing too much reliance on the cause-effect relation between a drug and a side-effect if only one or two exposures to the particular drug constitute the sample space. If, however, of 40 patients given a particular drug, 20 develop nausea and drowsiness, this finding is unlikely to be due to chance alone. Copeman[39] has emphasised that an apparently drug-induced rash may be provoked by concomitant infection or other factors.

One central difficulty is to know what weighting to give to symptoms elicited from the patient during completion of the questionnaire. How is one to decide whether a particular symptom is an adverse effect of the drug, an incidental symptom that is part of the patient's illness, or an event that is neither of these? In this survey, as in those quoted, no attempt was made to indicate what pre-existing symptoms were present before the start of treatment. An improvement in future surveys might be a separate symptom check list for use before the patient starts his treatment, providing a baseline of known presenting symptoms against which any events occurring during the course of treatment may be compared.

This survey has shown that intensive surveillance for adverse effects of drugs in general practice shows a high incidence of symptoms that are probably drug-induced, higher than that found in comparable hospital surveys or previously suspected in the community. Further work of this nature, in other practices and in other areas, is needed to confirm and extend the results presented here.

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What is the place of antibiotics in the treatment of acne in young people?

The evidence relates the development of adolescent acne to overproduction of sebum with secondary colonisation of the sebaceous glands and ducts with the acne bacillus. The notion that blockage of the sebaceous duct is important and that the inflammation is due to breakdown of sebum is primarily conjectural. As would be expected, therefore, acne responds partly to antibiotics and completely to blocking sebaceous lipogenesis. Drugs that block sebaceous lipogenesis, however, are not yet for general use, although they should be used for severe cases. The exception is in women, in whom a contraceptive pill with low progesterone content will partially inhibit sebum production. (In very bad acne cyproterone acetate can be considered; other inhibitors of sebaceous lipogenesis are the new 13-Cis ritinoic acid and, most recently, cimetidine.) Of the antibiotics, the most effective systemically is tetracycline. It must be given long term: short, sharp courses with high doses are not satisfactory. It is also important to be certain that the patient is taking the tetracycline on an empty stomach and is not taking calcium-containing drinks concomitantly because of the problems with absorption. Used in this way 250 mg once or perhaps twice daily is usually adequate. Trials of topical antibiotics are being done but are still at the "promising" stage. At the moment the most effective topical antimicrobial appears to be benzoyl peroxide as a gel. Many patients also respond well to ultraviolet radiation, although the effect lasts only for the duration of the treatment. In summary, the average patient will respond moderately well to tetracycline 250 mg once a day taken continuously plus topical benzoyl peroxide gel and intermittent courses of ultraviolet radiation. In a woman, a low progesterone contraceptive pill is a possible additional treatment.