Occasional Reviews

Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms

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Abstract

Suspected adverse drug reactions first reported in 1963 in the "British Medical Journal," the "Lancet," the "Journal of the American Medical Association," and the "New England Journal of Medicine" were reviewed 18 years later to assess their initial validity and subsequent verification. Of 52 first reports, five were deliberate investigations into potential or predictable reactions, and in each case causality was reasonably established; the other 47 reports were essentially anecdotal. Of these 47 reports, 14 related to categories of adverse reaction where false-positive reports were unlikely: immediate reactions, local reactions, and known reactions caused by a different mode of administration or a brand previously thought or claimed to be safe. The problem of false alarms rose in the remaining types of reactions: general reactions that did not occur immediately after administration and arose for the first time with a new chemical entity. Of 33 reports of such suspected adverse reactions, validity was satisfactorily established in 14 cases on the basis of rechallenge, predictability from known pharmacology, or the unique nature of the reaction. Of the remaining 19 reports, further verification still has not been satisfactorily established in 12. Seven of these possible false alarms were haematological reactions.

Although 35 of the 47 anecdotal reports were clearly correct, of the 19 reports that were not reasonably validated at the time of the report, only seven were subsequently verified. This suggests that agencies monitoring adverse drug reactions should adopt criteria for assessing the validity of first reports of suspected adverse reactions. Such criteria should include: reactions on rechallenge, a pharmacological basis for the adverse reaction, immediate acute reactions, local reactions at the site of administration, reactions with a new route of administration of a drug known to provoke such reactions by another route, and the repeated occurrence of very rare events.

Introduction

From time to time the validity of anecdotal reports of suspected adverse drug reactions is challenged, and not only by representatives of the pharmaceutical industry. Despite various mechanisms for identifying adverse drug reactions, however, the anecdotal report (perhaps of a single case) is often the first means of alerting doctors and regulatory agencies to a serious adverse reaction to a new drug. Unfortunately there is often a substantial time lag between the first alert and subsequent verification and further delay before any regulatory action occurs. A systematic policy of investigating first alerts, at any rate of serious reactions, might reduce the delays that occur. Any consideration of such a policy should, however, take into account the possibility of false alarms. It would be useful to know how often these occur, and the present review was undertaken to investigate this problem.

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Methods

Four journals were reviewed for reports of adverse drug reactions in 1963. The journals reviewed—the *British Medical Journal*, the *Lancet*, the *Journal of the American Medical Association*, and the *New England Journal of Medicine*—were chosen because they publish anecdotal reports of adverse reactions and are widely read internationally. The year 1963 was chosen, firstly, because the adverse reaction yellow-card system was started in 1964, and, secondly, to allow as long a time as possible for verification. Reports were selected for further study where there was reason to think that these were the first alerts to the suspected reaction.

Each report was assessed for internal evidence of validity. When any reasonable doubt remained an attempt was made to assess whether or not each suspected reaction had been verified in the subsequent 18 years. For this purpose three text books of adverse drug reactions were consulted: D'Arcy and Griffin's *Iatrogenic Disease*, Davies's *Textbook of Adverse Drug Reactions*, and Meyler's *Side Effects of Drugs*.[1-3] A search of published reports was also made using the computerised data base BLAISE (British Library Automated Information Service). This data base covers 3000 journals from 1966 onwards. A further search was made using the Excerpta Medica computerised data base. Finally, the adverse reaction files in the Medicines Division of the Department of Health and Social Security were studied. These include all yellow cards and all death certificates in which a drug is mentioned. They cover the period 1964 to the present time, and for the period 1975-80 information is also available on the extent of general practitioner prescribing.

Results

SYSTEMATIC STUDIES

There were 52 "first alert" reports in 1963 in the four journals reviewed.[4-55] Of these five were deliberate scientific studies to confirm suspected unwanted actions of new drugs not previously reported but related to known pharmacological actions of the drugs. These were: (*a*) the action of morphine on diverticulosis of the colon[17]; (*b*) the effect of rectal betamethasone on pituitary-adrenal function[16]; (*c*) the histological effects of spironolactone on the adrenals—so called spironolactone bodies[31]; (*d*) the action of oral contraceptives on thyroid function values[42]; (*e*) the occurrence of paralytic poliomyelitis after the use of Sabin vaccine.[47]

ANECDOTAL REPORTS

Reports with internal evidence of validity

Forty-seven reports were essentially anecdotal clinical reports. A review of these for internal evidence of validity showed that they fell into various categories.

Obviously valid reports—Table I lists 14 adverse reactions belonging to categories in which causality is not in doubt. There were five immediate adverse reactions, four local reactions at or near the site of administration, and five general reactions after a new form of dosage or route of administration of a drug already known to provoke that reaction in another form. This category included a report of a well-known adverse reaction to aspirin that occurred with the use of a proprietary preparation which had been claimed (falsely) to be safe in this respect.

TABLE I—*Fourteen adverse reactions where causality was not in doubt*

Type of reaction	Drug	Adverse drug reaction (and reference)	No of cases	Type*
Immediate	Dichloralphenazone	Anaphylaxis[7]	1	B
	Saline emetic	Pulmonary oedema[20]	1	A
	Griseofulvin	Anaphylaxis[21]	1	B
	Local lignocaine	Collapse[22]	2	A
	Parenteral reserpine	Collapse[39]	7	A
Local reactions	Hydrocortisone	Hypopigmentation[9]	8	A
	Condom emulsion	Peritonitis[35]	1	A
	Renacidin	Chemical pyelitis[44]	1	A
	Intradermal vaccine	Granuloma[48]	9	A
Known reaction with new form of dosage or brand	Topical corticosteroid	Diabetic state[19]	4	A
	Oral neomycin	Apnoea[25]	1	A
	Rectal corticosteroid	Peptic ulcer[33]	1	A
	Caprin (aspirin)	Gastrointestinal bleeding[12]	5	A
	Topical penicillin	Convulsions[28]	1	A

*Rawlins-Thompson classification.[56]

The remaining 33 reports were of general adverse reactions that did not occur immediately after administration and had not been previously reported after administration by a different route.

Reasonable criteria of validity—In 14 the arguments presented at the time were sufficiently convincing to establish causality with a reasonable degree of certainty. Rawlins and Thompson[56] have divided adverse drug reactions into two types. Type A reactions are consequent on the pharmacological action of a drug, are relatively frequent and often dose-dependent, and may be predictable. Type B reactions are "totally aberrant effects that are unrelated to a drug's normal pharmacology." They point out that most but not all adverse reactions may be classified into one of these two types on clinical grounds alone. The criteria of validity supporting the assessment of these reactions as convincing were as follows: rechallenge data in five reports, known pharmacological or therapeutic evidence in eight, and the repetition of a rare event in one (table II). In general pharmacological predictability was important for most of the type A reactions and rechallenge and other criteria for most of the type B reactions. The case of hepatotoxicity with the monoamine oxidase inhibitor phenoxypropazine was perhaps anomalous. This drug is a hydrazine derivative, thus related chemically to five previous hydrazines with monoamine oxidase inhibitor activity, each of which had previously been associated with hepatotoxicity, and cross reactivity had also been shown.[57] Phenoxypropazine was withdrawn from the market for this reason so that subsequent verification was not possible. Rechallenge data provide the most satisfactory basis for establishing causality when available, either by chance or as a result of deliberate intervention when this is felt to be ethically justifiable. There were various pharmacological criteria of validity with these suspected adverse reactions. Psoriasis as a result of chloroquine treatment was convincing as there was already therapeutic evidence that existing psoriasis was often aggravated by the drug. Presumably the first appearance of psoriasis after the use of chloroquine was also attributable and related to unknown factors predisposing this patient to psoriasis. Hepatotoxicity after phenoxypropazine was convincing in view of the known propensity of related hydrazines to cause this reaction. A similar argument applies to chlorthalidone, a drug with a slightly different chemical structure from that of the thiazides but with essentially identical pharmacological action. Brain damage as a sequel of penicillin-induced anaphylaxis with prolonged loss of consciousness due to anoxia was unusual but convincing. The remaining adverse reactions were based on pharmacological effects known at the time. Fanconi's syndrome with degraded tetracycline was convincing because both the syndrome and the use of degraded tetracycline are unusual and the association noted in five patients left no reasonable room for doubt.

TABLE II—*Fourteen first reports of adverse drug reactions with reasonable criteria of validity at time*

Criterion of validity	Drug	Adverse drug reaction (and reference)	No of cases	Type*
Rechallenge	Streptokinase	Henoch-Schonlein purpura[6]	1	B
	Methyldopa	Lactation[14]	5	A
	Sulphamethizole	Pancreatitis and meningitis[38]	1	B
	Tetracycline	Myopia[59]	1	B
	Cyclopentelate	Psychosis[51]	4	A
Pharmacologically predictable or logical	6-Azauridine	Chromosome damage[4]	3	A
	Amitriptyline	Ileus[13]	1	A
	Griseofulvin	Pigmentation[24]	4	?A
	Chlorthalidone	Hepatic coma[40]	1	A
	Oxytocin	Water intoxication[41]	1	A
	Chloroquine	Psoriasis[49]	1	B
	Penicillin	Brain damage (following acute anaphylaxis)[55]	2	B
	Phenoxypropazine (hydrazine MAOI)	Hepatotoxicity[24]	2	B
Repetition of rare events	Degraded tetracycline	Fanconi syndrome[45]	5	?B

*Rawlins-Thompson classification.[56]

Reports needing verification

Of the 47 anecdotal reports in 1963 28 were convincing as described above and the other 19 were not and could have been classified at the time as "requiring verification."

Validated reports—Seven of these 19 reactions have been satisfactorily verified and are now generally accepted as caused by the drugs suspected. These reactions were (with their Rawlins-Thompson types): (*a*) oral contraceptives causing changes in clotting factors (A)[5]; (*b*) oral contraceptives causing myocardial infarction (A)[27]; (*c*) methyldopa causing Parkinsonism (A)[11]; (*d*) amitriptyline causing peripheral neuropathy (B)[15]; (*e*) haloperidol causing (rarely) a hypersensitivity jaundice (B)[37]; (*f*) amiphenazole causing a lichenoid skin eruption (B)[26]; (*g*) oral contraceptives causing depression (when pyridoxine deficiency occurs) (A).[54]

Unvalidated reports—The 12 suspected adverse reactions that still have not been verified are listed in table III. Most of these have been included in the table because there have been no further reports. The reactions fell into two categories. Eight were rare clinical syndromes of which there have been no published reports in association with these drugs in the subsequent 18 years. Seven of these were haematological reactions, which are often idiosyncratic. These may have been false alarms, or they may indeed have been true idiosyncratic adverse reactions with an exceptionally low incidence. There have been no subsequent publications of agranulocytosis after amitriptyline treatment but some yellow card reports have been received at the DHSS; these have not been validated and have been few in relation to the widespread use of the drug. Haematuria after iron sorbitol may have been related to the disease for which the drug was given rather than caused by the drug. Alternatively it may have been a manifestation of a recrudescence of latent urinary tract infection as described by Briggs *et al.*[58] The other four suspected reactions were relatively common clinical syndromes that may have occurred

TABLE III—*Twelve adverse drug reactions suspected in 1963 but still not verified*

Drug	Adverse drug reaction (and reference)	No of cases	Type*
Rare clinical syndromes			
Methaqualone	Aplastic anaemia[9]	1	B
Nitrofurantoin	Megaloblastic anaemia[30]	1	B
Novobiocin	Haemolytic anaemia[43]	1	B
Clofibrate	Agranulocytosis[32]	1	B
Promethazine	Agranulocytosis[29]	1	B
Amitriptyline	Agranulocytosis[36]	1	B
Chlorthalidone	Agranulocytosis[46]	1	B
Iron sorbitol	Haematuria[10]	1	B
Common clinical syndromes			
Oral contraceptives	Alopecia[53]	3	A
Hydrallazine	Cancer[58]	5	B
Gammaglobulin	Abortion[23]	3	B
Phenylbutazone (maternal)	Fetal hepatitis[18]	1	B

*Rawlins-Thompson classification.[56]

coincidentally in patients receiving the suspected drugs. In some of these cases there were plausible arguments for suspecting the drugs but in the absence of factual evidence, which would need to be of an epidemiological nature, such arguments remain unconvincing. In three cases there were possible pharmacological or other arguments for accepting these reports as convincing either at the time or later. Nitrofurantoin as a cause of megaloblastic anaemia was a particular possibility as the drug is chemically related to hydantoin which is known to produce this reaction; oral contraceptives have demonstrable effects of small magnitude on the phasing of hair growth; and hydrallazine has been shown to cause benign tumours in animal toxicity studies. In the case of nitrofurantoin the absence of subsequent reports supports the classification of this adverse reaction report as a false alarm. In the case of alopecia with oral contraceptives and of cancer with hydrallazine there have been further anecdotal reports, but as these are common occurrences in the general population such further reports cannot be accepted as verifying suspected reactions of this type.

Discussion

In assessing the significance of these findings there are two possible conclusions. It might be argued that 35 out of 47 anecdotal reports were clearly correct and that some of the remaining 12 unverified reports may also have represented true adverse reactions of an idiosyncratic nature that are so infrequent that they have not occurred again often enough to be reported. Others of the unverified reports, relating to common clinical syndromes (such as alopecia with oral contraceptives), may not have been satisfactorily verified simply because the necessary epidemiological studies are not easy. Thus as an argument in favour of accepting all anecdotal reports as a good basis for adverse reaction early warning systems operated by regulatory agencies, or as a form of post-marketing surveillance, it might be suggested that 35 validated reports out of 47 represent more than 70% true positives, with no absolute proof of any false positives.

A better way to approach the problem, however, may be to insist on an informed, commonsense evaluation of each new anecdotal report of a suspected adverse drug reaction. The criteria for assessing validity should include those used in tables I and II. On this basis many anecdotal reports may be classifiable as convincing at the time, and these could indeed form a sound basis on which a regulatory agency could operate an early warning system. This would leave many reports that still need verification. In the 1963 publications there were 19 such reports, of which only seven were verified in the ensuing 18 years. At its worst this means that about two-thirds of such anecdotes are false alarms—and this cannot represent a logical basis for any regulatory action. Regulatory agencies need to develop operating guidelines for classifying anecdotes as convincing. This preliminary study of the problem suggests that the following criteria should be considered: (*a*) data from rechallenge; (*b*) a pharmacological basis for the adverse reaction; (*c*) immediate acute adverse reactions; (*d*) local reactions at the site of administration; (*e*) a first report of reactions with a new route previously recognised with another method of administration; and (*f*) the repeated occurrence of rare events. There are certainly other important criteria which could constitute convincing evidence in an anecdotal report. For instance, suspected adverse reactions in an anecdotal series arising mainly or entirely with doses at the top end of the range normally prescribed would suggest a dose-response relationship —a feature of type A reactions, which are unlikely to be false alarms.

Clearly it would be useful to review the outcome of a larger series of first reports—for example, those published in 1964-6—and to see whether these criteria have predictive value for subsequent verification of suspected adverse reactions, and whether there are other important criteria. These or similar criteria could perhaps be used by journal editors in considering anecdotal reports submitted for publication. The problem is related to but not identical with that facing a regulatory agency evaluating reports of individual adverse reactions or a doctor assessing a suspected adverse reaction in a patient. The DHSS uses various criteria, including some of those mentioned above, in an algorithm when it categorises yellow card reports for subsequent evaluation. For individual doctors Kramer *et al*[59] have proposed another algorithm.

So far as suspected adverse reactions requiring verification are concerned two separate problems have been identified. Rare clinical syndromes commonly include haematological adverse reactions, and this category of suspected adverse drug reaction might perhaps be tackled as a problem in its own right. Perhaps some form of registry, organised by haematologists or with their co-operation, would be needed, similar to that operated by the American Medical Association in the 1960s. Such a registry based on reporting of cases by participating haematologists and physicians would provide a larger data base for evaluating drug reactions that can be achieved by reviews of published reports, as currently incorporated into textbooks of adverse drug reactions. It would also avoid selection bias, by including all cases of each type of blood dyscrasia rather than merely those suspected of being attributable to a drug.

The second problem is that of common clinical syndromes; this is an epidemiological problem. When the syndrome is serious—for example, myocardial infarction after oral contraceptive use—it is important that verification should be initiated promptly. This particular suspected adverse reaction was verified by Inman *et al*[60] only after seven years had elapsed and was not generally accepted until further confirmation had been obtained from controlled epidemiological studies by Mann *et al*[61] 13 years after the original report.

Conclusion—Although the 12 reactions suspected in 1963 but still not verified satisfactorily are a minority of the 47 adverse reactions reported in 1963, they are a large proportion of the 19 reports which lacked valid evidence at the time of publication. Any regulatory agency using anecdotal reports of suspected reactions as a basis for an early warning system will need to develop criteria for assessing the validity of such reports.

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How good are articles on adverse drug reactions?

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Abstract

A study was carried out of the quality and completeness of articles on adverse drug reactions: 5737 articles from 80 countries published between 1972 and 1979 were studied. Only 61% of the articles included information on the number of patients treated and the number with adverse drug reactions, yet these are essential for calculating the incidence of adverse reactions. In only 55% could the incidence of a particular adverse reaction be calculated.

Great importance is placed on articles on adverse reactions, particularly those that report on many patients. Authors and editors should ensure that articles include the following information: drug regimens, numbers of patients treated, numbers of patients developing adverse reactions, and nature and incidence of adverse reactions.

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Introduction

Published articles on adverse drug reactions are considered to be important, particularly for regulatory agencies and drug companies, as both have to rely heavily on worldwide experience by independent investigators in "daily life." It is important to know not only what adverse reactions occur but how often they occur, and this cannot be determined from individual case reports. Studies of large groups of patients are therefore especially important in providing quantitative information. But how good are articles at giving information on adverse drug reactions?

One review of 23 papers on adverse drug reactions published in a reputable medical journal showed serious shortcomings in most of them: in 14 articles the number of patients affected by particular symptoms was missing, and nine articles contained no information on dosage or duration of treatment.[1] Similar inadequacies were found in 1600 clinical trials submitted by drug companies to licensing authorities[2]: in 80% of the trials adverse reactions were referred to, but in only 44% was the number of different types of adverse reactions given and in only 13% was