Occasional Survey

Death after Taking Medicaments

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Summary

A register of reported adverse reactions, recently made available to major hospitals and medical schools gives an indication of prescribing habits under the N.H.S. in England and Wales. An analysis is made here of the chief medicaments allegedly leading to death. Such data are incomplete because of lack of knowledge of the total use of each drug in the United Kingdom and because reporting of adverse reactions is very incomplete. Nevertheless, data about various groups of drugs do draw attention to some hazards and should encourage more widespread reporting of reactions to drugs and other medicaments.

Some therapeutic agents are so toxic to the human body that an excessive dose may cause death. If the disease being treated is itself very serious, the risk may be justifiable. Sometimes, however, the illness is trivial and the danger is not from an overdose but because of a congenital or acquired abnormal response by the individual. Occasionally the route of administration is an important factor, or perhaps one drug may interact in the body with another and lead to a fatality.

The Committee on Safety of Drugs, which first met in 1963, organized in the United Kingdom the system in which medical practitioners are asked to fill up a standard card to report serious or unusual reactions, or, for new drugs, all reactions. This system of reporting has been continued by the Committee on Safety of Medicines, which came into being in 1971, and in 1973 they made available to large hospitals and to medical schools a two-volume register of the reported adverse reactions; usually the period covered June 1964 to October 1971, though for newer drugs this was necessarily shorter. In many instances the register also estimates the number of prescriptions issued by general practitioners in England and Wales on Form E.C. 10 during 1968, 1969, and 1970.

Obviously, the figures given are at best a rough guide to some possible dangers: only half the reports come from general practitioners and about a quarter of the information is obtained from sources other than the yellow report cards (including reports in major medical journals). Undoubtedly, only a fraction of the adverse reactions are reported and this is likely to be greater if the medicament is new or of current interest. Inman¹ showed that only six reports of deaths of asthmatics were reported as possibly being due to overuse of pressurized aerosol bronchodilators in 1965 and 1966, whereas it has been estimated that over 1,700 deaths may have been

attributable to such preparations. If such events were occurring now, the rate of reporting would be very much higher because doctors know of the hazard.

The report cards are constructed so that the doctor may indicate all the medicaments the patient was receiving before an adverse reaction. Thus, if a patient was receiving two drugs that might be responsible, the reaction will be shown in the register against each of them. Where the relationship is palpably improbable, it will not be shown in the register against the unlikely cause. Thus it would not be suggested that folic acid may have caused an intestinal perforation if the patient was receiving potassium chloride and folic acid simultaneously: clearly if a drug was responsible it would be the potassium chloride.

In 1970 I obtained permission from the Committee on Safety of Drugs to use data from the register and to publish figures that included the number of deaths reported as possibly being due to certain drugs.² This article brings this information up to date and emphasizes some points. Nevertheless, the figures of numbers of prescriptions do not include those of Scotland or Northern Ireland and private prescriptions are not shown. Figures are not available for drugs used in hospitals.

Deaths from an overdose of established drugs are not reported, and if a patient is being treated for a fatal disease, such as cancer with a cytotoxic drug, little purpose would be served by including the inevitable in a register of adverse reactions.

Preparations Reported Most Often

The number of drugs reported to have possibly caused over 50 deaths in seven and a half years or less is small (table I).

TABLE I—Numbers of Deaths Reported as Possibly due to Drugs in seven and a half Years or less

Oral contraceptives	332	Acetylsalicylic acid	72
Phenylbutazone	217	Oxyphenbutazone	69
Chlorpromazine	102	Indomethacin	68
Corticosteroids	94	Halothane	57
Isoprenaline	84	Amitriptyline	50
Phenacetin	77		

Oral contraceptives come first on the list, but the figures relate to pills used before October 1971. It does not follow that there is an equal risk if the now more commonly used low-oestrogen/progestogen preparations or any alternative oral contraceptive is considered. The register lists over 40 oral contraceptives, all of the oestrogen/progestogen type, and 313 of the 332 reports of possibly associated deaths refer to thrombotic episodes. The number of oral contraceptives

taken between March 1964 and October 1971 is not known, but the dangers of pregnancy are probably greater than those of taking contraceptive pills.

Relation of Deaths to Prescribing Habits

Unfortunately no precise figures can be obtained for the number of drugs prescribed. Nevertheless, the three-year analysis of E.C.10 prescriptions for England and Wales shown in the register at least indicates whether or not a preparation is very commonly used, unless its use is considerable in hospital practice. A rough guide to relative dangers may be obtained by dividing the average number of deaths reported annually by the average number of millions of prescriptions per year (R/M). It must be remembered that the latter has been derived from only a three-year period, but this is better than referring to reports without any indication of the extent of prescribing. Since figures of prescriptions for contraceptives or halothane are not available, and those for salicylates, phenacetin, or paracetamol are not meaningful, these substances are not included in table II.

TABLE II—*The ratio of: Reports per Annum of Deaths/millions of Prescriptions*

Sodium aurothiomalate ..	164.3	Indomethacin ..	4.4
Phenindione ..	30.0	Imipramine ..	3.6
Warfarin ..	28.3	Chloramphenicol ..	3.6
Phenelzine ..	17.2	Phenytoin ..	3.0
Oxyphenbutazone ..	14.3	Chlorpromazine ..	3.0
Tranlylcypromine ..	13.7	Amiriptryline ..	2.3
Adrenaline ..	9.6	Trifluoperazine ..	2.0
Chlorpromazine ..	8.6	Methaqualone diphenhydramine	1.9
Isoprenaline ..	7.9	Frusemide ..	1.3
Propranolol ..	7.4	Methyldopa ..	1.3
Phenylbutazone ..	7.1	Corticosteroids ..	0.84
Orciprenaline ..	6.2		

This table shows that there is a considerable change in the apparent order of danger, and it contains preparations not included in table I. At the head of the list is sodium aurothiomalate, a gold preparation formerly used more extensively for the treatment of rheumatoid arthritis. During the three-year period there were only 14,000 prescriptions annually, with 16 fatal reactions in a seven-year period. These were usually blood dyscrasias, but if the prescriptions gave a true indication of its use the death rate would be 1.6 per 10,000 prescriptions. For all corticosteroids the figure is 0.008 per 10,000 prescriptions.

The figures for warfarin and phenindione are virtually meaningless since most of these are used in hospital. The use of phenelzine as a monoamine-oxidase inhibitor type of antidepressant is not outstandingly extensive, but it was possibly the cause of death on 26 occasions in seven and a half years, the reported cause of death being jaundice in 15 instances. With 21 reported deaths tranlylcypromine caused death attributed to jaundice only twice, but there were five reports of death after taking cheese. Despite the concern about excessive use of high-dosage isoprenaline inhalers, there were only 21 reports of death from cardiac arrest, 29 from heart failure, and 17 from overdose, the complete total being 84 in just over seven years.

Possible Deaths from Various Types of Drugs

In the register the drugs are arranged by groups and it is usually possible to comment briefly on the degree of usage and extent of danger in each group.

GENERAL ANAESTHETICS

As has been indicated, figures are not available for how much general anaesthetics are used.

HYPNOTICS, SEDATIVES, AND ANTICONVULSANTS

The number of hypnotics, sedatives, and anticonvulsants listed is 32, and over more than seven years there have been 155 reports of death, 24 from overdose. It is exceptional for an expected death from an overdose to be reported. The drugs most commonly implicated are shown in table III.

TABLE III—*Hypnotics, Sedatives, and Anticonvulsants*

Drug	No. of Deaths (usually in 7½ years)	Annual Prescription Rate in millions (England and Wales)	R/M (as defined in text)
Methaqualone with diphenhydramine ..	31	2.74	1.9
Phenytoin ..	21	0.93	3.0
Phenobarbitone ..	20	7.86	0.34
Nitrazepam ..	10	2.38	0.70

So far as methaqualone with diphenhydramine is concerned, the most frequent report of a single alleged cause of death was overdose (nine instances). With phenytoin the commonest suggested cause was macrocytic anaemia (seven instances). Megaloblastic anaemia from this drug should respond to folic acid or perhaps to folic acid. There is no particular cause of death attributed to phenobarbitone and it is so widely used that some of the patients will have been receiving other drugs. There is no indication that nitrazepam is likely to cause death, but two reports suggest that a fatal termination may have been from an overdose. This does not exclude the possibility that other drugs were concerned.

TRANQUILLIZERS

The number of agents listed is 26, and there are 257 reported deaths. The drugs most commonly reported as possibly causing fatalities (table IV) were those most often used, except that few reports relate to prochlorperazine or meprobamate. Fifty-four patients who had received chlorpromazine were said to have died from jaundice, and this is about a quarter of the cases reported as being jaundiced after taking this drug. Nevertheless, most patients with chlorpromazine jaundice recover and abnormal liver function tests are not rare. There were only three reports of abnormal hepatic function tests in seven and a half years. Possibly also a patient with hepatic failure may have been given a tranquilizer. Chlordiazepoxide was given as a possible cause of 13 cases of fatal jaundice and of nine cases of fatal coronary occlusion. Certainly the latter is unlikely. There was no striking relation between either diazepam or trifluoperazine and any cause of death.

TABLE IV—*Tranquillizers*

Drug	No. of Deaths (usually in 7½ years)	Annual Prescription Rate in millions (England and Wales)	R/M (as defined in text)
Chlorpromazine ..	102	1.59	8.6
Chlordiazepoxide ..	42	6.34	0.93
Diazepam ..	25	4.35	0.76
Trifluoperazine ..	22	1.43	2.0

ANTIDEPRESSANTS

There are 19 antidepressants listed, and 164 deaths reported. The drugs most often recorded are shown in table V. Of the deaths after the taking of tricyclic antidepressants, jaundice was recorded on 20 occasions for amitriptyline, on seven for imipramine, and twice for nortriptyline. With this group of drugs cardiac arrest, coronary occlusion or heart failure was recorded on 24 occasions.

TABLE V—*Antidepressants*

Drug	No. of Deaths (usually in 7½ years)	Annual Prescription Rate in millions (England and Wales)	R/M (as defined in text)
Amiriptryline	50	2.92	2.3
Imipramine	36	1.35	3.6
Phenelzine	26	0.21	17.2
Tranlycypromine	21	0.21	13.7
Nortriptyline	11	0.47	3.1

STIMULANTS

No particular hazard emerges from stimulant drugs.

ANALGESICS AND ANTITUSSIVES

Unfortunately, the same is not true of this group. The number of preparations listed is 38, with 592 deaths. In table VI no effort has been made to relate the deaths attributed to aspirin, phenacetin, and paracetamol to figures for prescriptions as these preparations can be readily obtained over the counter; moreover, the combinations of analgesics taken by a patient are so many that the true cause of death may not be apparent, certainly in relation to renal failure. For what the statement is worth, death from nephropathy was reported on five occasions after aspirin, and there are two reports of death from renal failure, six from necrotizing papillitis, and two from uraemia. For phenacetin the corresponding figures are 15, 16, 24, and 12, but with paracetamol there is but one report of death from renal failure and two from necrotizing papillitis.

TABLE VI—*Analgesics and Antitussives*

Drug	No. of Deaths (usually in 7½ years)	Annual Prescription Rate in millions (England and Wales)	R/M (as defined in text)
Phenylbutazone	217	3.60	7.1
Phenacetin	77	4.12	—
Acetylsalicylic acid	72	6.24	—
Oxyphenbutazone	69	0.65	14.3
Indomethacin	68	2.19	4.4
Paracetamol	19	12.19	—

Only two cases of death from jaundice were attributed to paracetamol and in seven instances the cause of death was considered to be an overdose. There were 25 reports of aspirin causing death from gastrointestinal haemorrhage.

Obviously under-reporting is a serious reason for lack of data. Nevertheless, as any haematologist knows, blood dyscrasias such as aplastic anaemia, pancytopenia, agranulocytosis, or thrombocytopenia may follow taking pyrazolone derivatives such as amidopyrine, phenylbutazone, or oxyphenbutazone and it has been claimed that, with the last two, recovery is likely if the course of treatment has been short. Such data cannot be obtained from the register.

Of the deaths said to follow phenylbutazone, 166 were reported as blood dyscrasias. After oxyphenbutazone 61 of the reports of fatalities were related to such conditions, but it should be noted that the company marketing this produce in the United Kingdom actively encourages the reporting of adverse reactions. In nearly seven years there has been only one report of a fatal blood dyscrasia from amidopyrine, which is marketed in combination with phenylbutazone as Irgaprin. After indomethacin there were 17 reports of blood dyscrasias, but 23 of deaths from peptic ulcer or haemorrhage from the gastrointestinal tract.

Obviously there are dangers from almost any analgesic, but it is perhaps reasonable to suggest that a patient being trea-

ted for arthritis should know that there is some risk, and should be allowed to decide whether the benefit justifies taking it.

The register shows that the antitussive drug pholcodine, which had an average of 3,880,000 prescriptions per annum in England and Wales, was not reported as causing any fatalities in seven and a half years.

AUTONOMIC DRUGS (INCLUDING HYPOTENSIVE AGENTS)

The 54 agents listed were considered to have possibly caused 245 reported deaths. The more prominent ones appear in table VII.

TABLE VII—*Autonomic Drugs (including Hypotensive Agents)*

Drug	No. of Deaths (usually in 7½ years)	Annual Prescription Rate in millions (England and Wales)	R/M (as defined in text)
Isoprenaline	84	1.52	7.9
Orciprenaline	40	0.86	6.2
Methyldopa	24	2.46	1.3
Propranolol	23	0.62	7.4
Adrenaline	17	0.29	9.6
Ephedrine	16	7.32	0.31

Reference has already been made to the serious under-reporting of deaths of asthmatics who had used pressurized aerosol bronchodilators, and it is easy to understand that the fatal termination might be attributed to the disease itself. Of the reports relating to isoprenaline, the alleged causes of death, with the numbers of instances, were: cardiac arrest (21), heart failure (29), bronchospasm (1), dyspnoea (1), asthma (13), anaphylactic shock (1), and overdose (17). For orciprenaline the comparable figures were 10, 11, 4, 0, 9, 0, and 6. Other drugs of this type included in table VII were considered to have similar hazards, and even with salbutamol there were five reports of cardiac arrest. Methyldopa was reported as causing haemolytic anaemia on 132 occasions, with 12 deaths, and to have led to jaundice 50 times with four deaths.

DRUGS ACTING ON THE VASCULAR SYSTEM

Though 33 drugs are listed, reports of fatalities are few. Only seven deaths were attributed to digoxin in over seven years despite 3,220,000 prescriptions annually. Quinidine, sometimes considered hazardous, was only once reported to have caused death in seven years: the prescription rate was 86,000 annually.

ANTI-HISTAMINES

The use of anti-histamines was extensive, but there are only 21 reported possible fatalities, no particular pattern being evident.

CORTICOSTEROIDS

The number of corticosteroids listed is 13 and there are 94 deaths in over seven years with an annual prescription rate of 15,558,000. Of the deaths, 42 were from alimentary disturbance such as perforation or bleeding.

DIURETICS

There were 80 possible deaths from the 26 diuretic prepara-

tions listed, blood dyscrasias being the likely factor in 31 instances.

ANTIBACTERIAL AGENTS

With antibacterial agents there is always the possibility that the patient had a potentially fatal infection and that this was the true cause of death. Nevertheless, the surprising feature is perhaps how few deaths have been reported as possibly due to antibacterial substances.

Penicillins

Twelve penicillin preparations are listed, but in nearly seven and a half years there are reports of only 27 deaths, with death from anaphylaxis in only nine. Phenoxymethyl penicillin (about eight million prescriptions per annum) was reported as causing only one death in seven and a half years. The number of prescriptions for benzylpenicillin are not given.

Chloramphenicol

When the American Medical Association issued a table of reports of drug-induced blood dyscrasias in 1965 chloramphenicol was the one most commonly listed. In the British register it was reported as being the likely cause of death from a blood dyscrasia on 26 occasions in seven and a half years. It is difficult to give an indication of the extent of its use since the number of prescriptions for systemic use had fallen to 58,000 in 1970, while the prescriptions for topical use had risen to 1,299,000.

Tetracyclines

The number of tetracyclines listed is eight, and deaths reported 22, the cause recorded being jaundice in 10 instances. Prescriptions were about 16 million per annum, so the ratio R/M was low at about 0.18. Oxytetracycline, with an annual prescription rate of 8,452,000 in England and Wales, was reported as having possibly caused only two deaths in seven and a half years.

Sulphonamides

With the sulphonamide group reports were more numerous. Nineteen sulphonamides are listed and there are 35 reports of deaths over the whole period against an annual prescription rate of just over five million. There were 20 deaths from blood dyscrasias, 10 of these being attributed to co-trimoxazole. This may indicate that doctors more readily submit reports about new drugs; indeed, there was not a single report in seven years of a death after sulphamethoxazole, one of the constituents of co-trimoxazole.

Some claim that sulphonamides should be avoided because they may cause serious skin reactions or renal failure. It is perhaps merely an indication of poor reporting that in seven and a half years there were only five reports of death from skin reactions in relation to sulphonamides considered together and this includes only one patient said to suffer from the Stevens-Johnson syndrome. Only one patient was reported to have died from uraemia and another from renal failure.

MISCELLANEOUS SYNTHETIC ANTIBACTERIALS

Fourteen miscellaneous synthetic antibacterials are listed, with 56 deaths. Jaundice was the fatal event reported in 37 instances, the drugs blamed being isoniazid with para-aminosalicylic acid on 11 occasions, and sodium aminosalicylate on 12. These drugs have not been included in table II, however, because the diminution in their use in the period 1968 to 1970 suggests that meaningful figures for the number of prescriptions over a seven-year period cannot be given.

Discussion

These data have been quoted to give some information, but without any suggestion that they have scientific accuracy. All that they can convey is that some modern drugs have serious side effects which can on occasion be fatal. The data do not provide information about interactions between drugs, or between drugs and other substances such as alcohol. It is impossible and indeed psychologically undesirable for a doctor to tell his patients of all the possible adverse reactions that may occur from everything that is prescribed or sold over the counter. Nevertheless, the dangers of some drugs, particularly the analgesics, should be more widely known.

As yet there is no way of producing precise evidence of the extent of the danger of death occurring from almost any drug. The exact amount of each preparation used annually in the United Kingdom is not known, and probably only a fraction of adverse reactions are reported to the Committee on Safety of Medicines. More widespread reporting would add to the value of the register of adverse reactions.

I am grateful to the Members of the Committee on Safety of Medicines and its Subcommittee on Adverse Reactions for permitting me to quote from the register, which is now available in most large hospitals in the United Kingdom. Particular gratitude is expressed to those who undertook the immense task of compiling the register.

Any views expressed are entirely personal ones.

References

- ¹ Inman, W. H. W., *British Medical Bulletin*, 1970, 26, 248.
- ² Girdwood, R. H., in *The Adverse Effects of Drugs*, ed. G. C. Hanson, p. 70. London, Beecham Research Laboratories, 1970.