

Adverse Drug Reactions and Death

A Review of 827 Cases

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• A study of 827 cases of adverse drug reactions (ADRs) in which autopsies were done was carried out to determine the relative frequency of drugs that caused adverse reactions, their sites of action, and the variety of pathologic processes induced by them. Because a variety of nondrug factors played critical roles in generating many of the ADRs, these 827 cases were divided into seven groups. Only one of these groups (25% of the total) met the criteria of ADRs in the usual definitional sense and were also lethal. The validity of the diagnoses of both the ADRs and the basic diseases being treated was strengthened by the addition of morphologic findings to the data base and by the use of an analytic algorithm that was specifically developed for and directed to the evaluation of ADRs.

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SEVERE and lethal adverse drug reactions (ADRs) are relatively rare occurrences in any one geographic location. By collecting data from many medical facilities located in 37 states during the past ten years, the Registry of Tissue Reactions to Drugs has studied more than 3,000 alleged ADR cases that were of sufficiently serious nature to have either biopsy or autopsy material available. This report analyzes the findings in those cases that were autopsied.

MATERIALS AND METHODS

The cases reported in this study were submitted to the registry as alleged ADRs. It became evident in the early stages of this study that there was need for standardization of criteria for the evaluation and diagnosis of ADR cases. There was developed within the Registry a methodology or algorithm that outlined procedures for selection of the causative drug and for linking the drug and the markers of the adverse reaction as empiric correlates.

Further, because of the usual complexity of many ADRs and their failure in many instances to fall neatly into unequivocal

"yes" or "no" categories as to drug causation, three intermediate degrees of certainty were interposed between the "causative" and the "negative" groups: "probable," "possible," and "coincidental."

After the available clinical, laboratory, and morphologic findings on each of the 1,932 patients in whom autopsies were done had been integrated, and the validation criteria developed in the previously mentioned methodology had been applied in each case, there were 827 cases that were placed in either the "causative" or the "probable" (consistent with) categories, indicating with reasonable certainty that the original allegation of the presence of an ADR was confirmed by the registry studies.

The total breakdown for all five "degrees of certainty" in these 1,932 cases is the following:

Category of Certainty	No. (%) of Cases
Causative and probable	827(43)
Possible	679(35)
Coincidental	311(16)
Negative	115(6)
Total	1,932(100)

Thus, in this large group of originally alleged ADRs, less than half of the cases met the criteria for validation of the presence of an ADR. In slightly more than one third, the allegation could be neither confirmed or denied; and in about one fifth, the allegation was denied. The utilization of this analytic methodology on these 1,932 cases removes them from the merely anecdotal category.

A description of this methodology and the operational definitions of the categories of certainty are detailed in a num-

ber of previous publications.¹⁻⁴

The material on these 1,932 cases included a clinical summary (including the history, physical findings, and the results of laboratory findings), a copy of the autopsy protocol, and tissue slides for morphologic examination. Hematoxylin-eosin-stained slides were available on all cases, and these were examined by light microscopy. Special stains, when indicated, identified the following: connective tissue (Masson trichrome), fat (oil red O), reticulum (Snook), elastic fibers and muscle (Movat), fungi (Gomori methenamine-silver), acid-fast bacteria (Ziehl-Neelsen), bile (Hall), and iron (Mallory). Additional special procedures on selected cases included x-ray diffraction and infrared and ultraviolet spectrophotometry.

RESULTS

Validated ADRs were judged to be present in 827 (43%) of the 1,932 cases. Although they had two common denominators (death and the presence of a validated ADR), further study disclosed the necessity for subdividing them into seven distinct groups. This became apparent when it was noted that there were also many "uncommon" denominators in these 827 cases: some were not related to the "medicinal" use of a drug; some were avoidable; some were predictable; some had very high risk-to-benefit ratios; some were relatively minor and nonlethal (though occurring in association with death from other causes); some were related to errors of the medical team or patient; and in some, the coexistence of a potentially lethal ADR and a potentially lethal basic disease or concomitant morbid state made it impossible to determine which was responsible for the death.

There were, then, many instances in this series of 827 cases that did not fit into the definition of an ADR as laid down by the World Health Organization⁵: "An adverse reaction is defined . . . as one which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis, or therapy."

Furthermore, some of these cases did not fit into the usual connotation of an ADR because there were circumstances and factors other than the drug itself that played a role in producing the ADR.

Consequently, these 827 cases were divided into seven groups (Table). For overall and initial orientation, these may be consolidated into three major

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Categories of Adverse Drug Reactions in 827 Cases			
Group		No. of Cases	% of Total
1	Overdose, accidental and suicidal	428	51.8
2	Malignant conditions treated with cytostatics	48	5.7
3	Adverse reactions to occupational chemicals	19	2.3
4	ADR present but relatively minor and nonlethal	65	7.9
5	Coexistence of serious or lethal ADR with serious or lethal basic disease or concomitant morbid state	22	2.6
6	Lethal ADR associated with diagnostic or therapeutic errors	25	3.0
7	ADRs in the strict definitional sense	220	26.6
Total		827	99.9

categories: (1) One half were cases of drug overdose (accidental and suicidal) (group 1). (2) One fifth of the 827 cases (groups 2 to 6) did not meet the usual criteria of an ADR for a variety of reasons evident from their titles in the Table and from the definitions that follow. (3) Only one fourth (group 7) met the criteria of an ADR in the usual definitional sense.

Group 1.—There were 428 cases of drug overdose (accidental and suicidal), and these constituted 51.8% of the total. They failed to meet the definition of an ADR because drug dosages were above therapeutic amounts, and the consequences were neither unexpected nor unpredictable. The majority of these have been reported previously.^{9,7}

Group 2.—Patients in this group suffered from life-threatening illnesses (malignant disease) and sustained ADRs following treatment with cytostatic and immunosuppressive agents. There were 48 patients in this category (5.7% of the total). These cases have been reported elsewhere.⁸

Group 3.—This group included adverse reactions to chemical agents contracted in the setting of occupational and industrial exposure. They are included in recognition of the increasing incidence and importance of adverse reactions to environmental chemicals in our modern technologic society. There were 19 such cases (2.3%), including these combinations: vinyl chloride and hepatic angiosarcoma; exposures to industrial solvents with subsequent adverse hepatic or hematopoietic reactions; exposure to a variety of herbicides and insecticides with adverse reactions in the lungs, liver, or central nervous system; asbestos-related mesotheliomas;

and beryllium exposure causing pulmonary granulomas.

Group 4.—There were 65 cases (7.9%) in which ADRs were validated as being present, but they were of a relatively minor nature and were not the cause of death.

Group 5.—This group includes those cases in which the ADR was of a serious and potentially lethal nature but in which the concurrent basic disease or concomitant morbid state was also potentially lethal, and the cause of death could not be singled out. There were 22 cases of this type (2.6%).

Group 6.—This group includes instances of lethal ADRs involving diagnostic or therapeutic errors on the part of members of the medical team, the patient, or the patient's family or friends. There were 25 cases in this group (3%). Further characterization of this group might include such terms as "preventable" and "unjustifiable."

While the deaths in the 25 cases in the group 6 category were judged to be due to ADRs, they were conditioned by circumstances that set them apart from the other six groups. The therapeutic misadventures in these instances were related variously to these factors: (1) failure to heed warning signs furnished by prior history or by clinical laboratory tests, (2) failure of physician-patient or physician-physician communication regarding the prevention of future ADRs after one has already occurred, (3) the use of a potentially dangerous drug when it was not indicated or when the risk-to-benefit ratio was high, (4) failure to appreciate the possibility of dangerous drug-drug interactions, (5) gross overprescribing of a series of drugs with additive or cumulative effects, (6) im-

proper formulation or labeling of drugs, (7) the use of potent drugs by laymen without the supervision of the medical team, and (8) ignorance on the part of the lay public regarding the danger of the long-term use of some of the drugs available without prescription.

Group 7.—This group of 220 validated cases included those that appear to fit the ADR definition previously cited and that were unexpected and unpredictable in our present state of knowledge. This group made up 26.6% of the 827 cases reported in this series. The remainder of this report, then, will be devoted to these 220 cases of group 7.

"TRUE" CASES OF ADR

Age.—There was a wide range in the age distribution of these 220 cases, with all decades from the first to the tenth represented. The largest number occurred in the third decade, with a dominant plateau in the third through fifth decades, in which about 50% of the cases were found.

Age Group, yr	No. of Cases
0-10	28
11-20	16
21-30	38
31-40	35
41-50	35
51-60	25
61-70	27
71-80	14
81-90	1
91-100	1

Sex.—There was a slight predominance of cases among males; 113 (51%). There were 107 cases in females (49%).

Race.—Black patients made up 12% of the 220 cases, which corresponds closely to their percentage in the population of the United States. The entire racial distribution was white, 175; black, 26; Oriental, 7; Malayan, 2; American Indian, 2; and unknown, 8.

Sources of Cases.—The ADR cases were submitted to the registry by practicing pathologists located in 37 states during the ten-year period of its operation. These sources are tabulated as follows:

Source (%)	No. of Cases
Armed Forces hospitals (47.0)	104
Teaching centers	38
Station or regional	66
Civilian hospitals (38.6)	84
Medical centers	19

Community hospitals	65
Veterans Administration (11.7)	26
Miscellaneous (2.7)	6

It is evident that the sampling of cases represented not only teaching and university centers but also community hospitals in both the military and civilian categories. The "miscellaneous" category included a few cases occurring in physicians' and dentists' offices, outpatient clinics, and homes.

Treating Physician's Specialty.—Although eight areas of medical specialty are represented, general medicine dominated the picture. Medicine and surgery combined made up nearly two thirds of the cases.

Specialty	No. of Cases (%)
General medicine	93(42.0)
Surgery	41(19.0)
Pediatrics	31(14.0)
Genitourology	25(11.4)
Psychiatry	10 (4.6)
Obstetrics-gynecology	8 (3.7)
Orthopedics	6 (2.7)
Dentistry	3 (1.3)
Miscellaneous	3 (1.3)

Categories of Drugs.—Thirty-two categories of agents were involved in the ADRs of group 7. Drug categories that were related to five or more cases are listed; nine categories accounted for about 90% of the 220 cases. Note that antiinfectives were dominant, with anesthetic agents a not-very-close second.

Category	No. of Cases
Antiinfectives	76
Anesthetics	42
Tranquilizers	18
Steroids	14
Analgesics	14
Diagnostic agents	11
Cytostatics	11
Anticoagulants	6
Anticonvulsants	5
Total	197

Specific Drugs.—There were 75 drugs associated with ADRs in this group. The ten most frequently involved drugs and their order of frequency is listed.

Drug (Year Introduced)	No. of Cases
Halothane (c 1956)	28
Penicillin (c 1947)	28
Tetracycline (c 1948)	12
Chlorpromazine (c 1954)	9
Chloramphenicol (c 1949)	7
Isoniazid (c 1952)	6
Hexachlorophene (c 1948)	5
Aspirin (c 1899)	5

Methotrexate (c 1948)	4
Methoxyflurane (c 1962)	4

About half (108) of the cases in this group were associated with these ten drugs. The remaining drugs occurred with a frequency of less than four cases per drug. Of the ten agents, the drug with the longest usage in the practice of medicine was the salicylate (aspirin) group (introduced in 1899). The most recent drug was methoxyflurane (introduced in 1962). Omitting the salicylates, the remaining nine drugs averaged 24 years of usage to 1975. In the overall picture, 85% of the cases in group 7 involved drugs that averaged 20 years of usage to 1975, indicating that the great majority of agents responsible for ADRs were not new.

Twelve cases in group 7 (5.4%) were considered to be in the category of combined-drug reactions. Illustrative examples include renal failure associated with the combination of methoxyflurane and tetracycline; steroids combined with cytostatic agents, resulting in opportunistic infection; succinylcholine chloride and an anesthetic agent, with subsequent malignant hyperpyrexia; and the combination of a monoamine oxidase inhibitor and an antidepressant, followed by hypertension and hyperthermia.

Routes of Administration.—In the 220 cases in group 7, there were 14 different routes of drug administration. The oral route was the most frequent (43%); intramuscular, intravenous, or subcutaneous routes were used in 32% of the cases. Few routes were spared in this group.

Route or Means	No. of Cases
Oral	95
Intramuscular	38
Inhalation	37
Intravenous	28
Topical	7
Transplacental	3
Subcutaneous	3
Skin (absorption)	2
Rectal	2
Intraurethral	1
Submucosal	1
Irrigation (of wound)	1
Epidural	1
Intraureteral	1

Sites of Adverse Drug Reactions.—Sixteen target organs, organ systems, or tissue sites were involved in ADRs in this group. The more common of these were the liver, 60 cases; bone marrow, 40; cardiovascular sys-

tem, 12; kidney, 11; central nervous system, 11; and gastrointestinal system, 7. The largest single group—"body as a whole"—is not included. There were 71 instances of this "site," which included anaphylactic, acute drug intoxication, hyperthermic, and idiosyncratic cases. In these, localized anatomic ADR lesions were not demonstrable; most of the morphologic lesions consisted of nonspecific congestion of the lungs and viscera.

While in the great majority of cases there was one target organ in which the ADR occurred, there were ten instances of multiple ADR sites in the same case. These included several instances of disseminated candidiasis with fungal lesions in brain, heart, lung, kidney, spleen, and liver in opportunistic infections following steroid therapy (secondary effects of an ADR); several cases of hemorrhagic foci in multiple viscera associated with anticoagulant therapy (heparin sodium, warfarin sodium); a number of instances of hypersensitivity-type vasculitis involving vessels in the kidney, spleen, lungs, and liver (colchicine, indomethacin); focal granulomatoid lesions in both the myocardium and liver associated with chlorpropamide therapy; one instance of chlorpromazine-related concurrent pancytopenia and hepatic cholestasis; and one example of reticulum cell sarcoma in both the lungs and the brain related to immunosuppressive therapy following renal transplant (azathioprine and prednisone).

The Drug-Induced Diseases.—The following diagnoses accounted for 86% of the ADRs in this group:

Diagnosis	No. of Cases
Anaphylaxis	50
Hepatocellular injury	46
Blood dyscrasias	40
Pancytopenia	17
Agranulocytosis	16
Leukopenia	4
Thrombocytopenia	2
Agranulocytosis and thrombocytopenia	1
Acute drug toxicity	15
Nephrosis	11
Hepatic steatosis	9
Hemorrhagic diathesis	6
Cerebral spongiosis	5
Gastrointestinal ulcers	4
Hyperthermia	3

The remaining diagnoses occurred with a frequency of three times or

less. These included three fatal skin reactions (toxic epidermal necrolysis associated with methylphenidate hydrochloride, exfoliative dermatitis with sulfisoxazole, erythema multiforme with phenytoin), angiosarcoma of the liver (thorium dioxide), and reticulum cell sarcoma of brain and lungs (immunosuppressives in a kidney-transplant case).

Basic Diseases Being Treated.—These 18 diagnoses account for 50% (110) of the conditions for which these patients were receiving drug therapy.

Basic Diseases	No. of Cases
Upper-respiratory tract infection	12
Psychiatric illness	11
Cholecystitis	9
Multiple sclerosis	8
Urethritis	7
Pyelonephritis	7
Arthritis	7
Diabetes mellitus	6
Prostatic hypertrophy	5
Tonsillitis	5
Psoriasis	5
Skin burns	5
Appendicitis	4
Pneumonia	4
Peptic ulcer	4
Pharyngitis	4
Tuberculosis	4
Pregnancy	3

The remainder of the diagnoses occurred with a frequency of less than three times.

COMMENT

The preceding detailed analysis of the findings in these 220 validated cases of ADRs indicates a moderately broad sampling of ADR problems. All age decades were represented; there was essentially equal sex distribution; the white-black ratio was that of the country at large; cases came from both medical centers and community hospitals; there was a wide representation of drugs, drug categories, and routes of administration; there were 16 anatomic sites involved in the ADRs; there was a broad spectrum of both ADRs and basic diseases; cases came from eight of the medical specialties; and the broad geographic distribution included cases from 37 states.

It has been estimated that about 70% of reported ADRs are relatively minor.⁹ The cases reported in this series are a sampling from the remaining 30% that were more serious. What portion of the ADRs in this 30%

are lethal is not known.

Not only is the percentage of deaths that occur in ADRs not accurately known, but the actual number of nationwide deaths from ADRs is also unknown. The latter is the subject of considerable current debate; estimates range from 3,000 to 140,000 per year. This problem of the estimated number of lethal ADRs has been discussed and summarized by Koch-Weser.¹⁰

CONCLUSIONS

Summarization of the 827 cases reported in this series reveals that 50% were instances of drug overdose; 20% consisted of five groups that, for a variety of previously cited reasons, failed to meet the definitional criteria of an ADR; and only 25% could be considered "true" ADRs.

While these seven groups of ADRs associated with death appear to be a broad sampling of the adverse drug-reaction problem, there is no reason to presume that it is a representative sampling. In addition, there is no reason to assume that the respective percentages of the seven groups into which these 827 cases were divided represent a formula that can be applied to the national drug experience.

This study, within its confines and limitations, contains seven subdivisions or groups that likely are representative qualitatively of most of the variants of ADRs that can occur, ie, they represent most of the variety of factors (from drug manufacture to patient usage) that may play a role in producing ADRs.

In addition, this series of cases included only those on which necropsy findings were available. As a consequence, the data base for evaluating them was broadened to include not only the clinical and the laboratory information, but also the morphologic findings. Thus, their validation as to the presence of an ADR was on a reasonably solid basis. Also, the nature of the basic diseases and concomitant morbid states present in these patients was determined or confirmed on a combined clinicopathologic basis.

While this particular study cannot be said to be representative of the overall ADR situation, it is probably equally true that no other single study from a local area could be taken as nationally representative. If multiple and geographically separate

studies of this type were carried out, however, and the results were to be combined, a more adequate and representative sampling of the national situation regarding lethal ADRs could be accomplished and would come closer to giving an accurate ADR picture than is presently available.

If accurate and valid results were to be derived from such multiple and aggregated studies, they would have to have a common plan, use a common methodology, have similar operational definitions, be similarly broad-based, preferably include morphologic data, and use a commonly agreed-on grouping or subdivision of cases.

The relatively "hard" data that could emerge from such collaborative efforts might then be used to identify correctable factors in the genesis of ADRs, in turn leading to rational measures for the control or the reduction of ADRs in the future.

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Nonproprietary Names and Trademarks of Drugs

Azathioprine—*Imuran*.
Chlorpromazine—*Thorazine*, *CHLOR-PZ*, *Cromedazine*, *Promachel*.

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