

Fatal Drug Reactions Among Medical Inpatients

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In a series of 6,199 consecutively monitored medical patients, deaths due to drugs administered in hospitals was recorded in 27 cases (0.44%). Most of the fatalities were attributed to commonly used drugs. Hyperkalemia and pulmonary edema, attributed, respectively, to potassium supplements and parenterally administered fluid therapy, were particularly prominent. Other drug-attributed mechanisms which resulted in death were depression of the central nervous system, superinfection, hemorrhage, cardiorespiratory complications, dehydration and electrolyte depletion, hypoglycemia, anaphylaxis, liver failure, perforated duodenal ulcer, and hypercalcemia.

It is widely recognized that the administration of drugs may result in serious consequences and even death. The extent and nature of this problem have not in the past been carefully quantitated, since this requires intensive surveillance of large numbers of patients with careful attention given to the apparent effects of each drug administered.

The present communication reports on the drug-attributed death rate in a series of 6,199 consecutive medical inpatients intensively monitored for drug effects. The nature of this monitoring program is such that the potential role of each drug received in the subsequent course of the patient's illness is considered.

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Methods

The methods employed by the comprehensive drug-surveillance program have been described in detail elsewhere.¹⁻⁴ For the present study, it is necessary to emphasize pertinent aspects of these methods and to describe some special procedures which were adopted.

Trained nurse-monitors are responsible for recording, in a standardized manner, a large quantity of information on consecutive patients admitted to monitored medical wards. Included for each patient is a record of all drugs ordered, which includes dosage, routes of administration, and starting and stopping dates. Suspected adverse reactions (defined as any undesired or unintended effect of a drug) are detected in two ways. First, whenever a drug is discontinued, the attending physician is promptly interviewed by the nurse-monitor and asked why he stopped the drug. An adverse reaction is one of the

reasons which he may give. Second, even if he gives some reason other than a drug reaction, he is, nevertheless, asked whether any suspected reaction occurred while the drug was being administered.

All suspected reactions are promptly reported to the Clinical Pharmacology Unit and then investigated. On the basis of the juvenile evidence, the investigating clinical pharmacologist makes a judgment on whether any drug, or group of drugs, in fact caused the alleged reaction.

In those cases in which death follows shortly after a drug-attributed adverse event, an additional

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detailed investigation is made to evaluate the relationship of drug therapy to death. The attending physician is interviewed again, and the patient's record is reviewed to obtain the best available clinical information. No case is included as a "drug death" unless both the attending physician and the Clinical Pharmacology Unit agree that the drug or drugs implicated are the most important or sole factors responsible for death.

This survey has been confined to those drugs that were administered while the patients were under surveillance. Deaths due to drugs taken prior to admission have been excluded, unless the same drugs were also taken while the patients were monitored.

For the most part, a decision on whether to accept or reject a case has not proved to be difficult, but there have been occasions when a final decision was difficult, even after careful review of all the available data. The decision to include or exclude a case was then a matter of judgment. The following reports of cases illustrate a straightforward, an intermediate, and a difficult decision.

Report of Cases

CASE 24.—A 48-year-old man with carcinoma of the bronchus received asparaginase intravenously, 80,000 units in 150 ml of normal saline solution. A second treatment with the same dose of asparaginase was commenced one week later. After a few milliliters had been given, the patient became agitated. Asparaginase was immediately discontinued. (Subsequently, the reason given to the nurse-monitor was adverse reaction—"anaphylaxis.") The patient rapidly lapsed into deep coma, developed irreversible shock, and died a short time later, despite resuscitative measures.

Death was attributed to anaphylaxis following the intravenous administration of asparaginase.

CASE 4.—A 55-year-old man with cirrhosis of the liver was transferred for further treatment after recovery from hepatic coma. On admission, he was fully conscious and had massive ascites. The serum bilirubin level was 22.1 mg/100 ml (direct, 12.0 mg/100 ml; the blood urea nitrogen level was 15 mg/100 ml. On the first and third days, he received furosemide, 80 mg by mouth; potassium chloride, 15 mEq three times a day, was started at the same time. After the second dose of furosemide, he became drowsy. The drug was stopped for that reason. Potassium chloride was continued in unaltered dosage. During the last three days of his life, oliguria developed. Quite suddenly, he became severely hypotensive and went into shock. An electrocardiogram showed first degree atrioventricular heart block and tall, symmetrical, peaked T waves. The serum potassium level was 7.7 mEq/liter. Potassium chloride was discontinued because of "hyperkalemia." In spite of treatment, the ECG evolved into a sine-wave pattern, and he died in cardiac arrest.

The patient was critically ill. However, it was believed that the proximate cause of death was hyperkalemia, induced by potassium chloride and potentiated by terminal oliguria.

CASE A.—A 78-year-old man with acute inferior myocardial infarction suddenly lost consciousness six days after onset of the heart attack. Immediately, epinephrine (1 part in 1,000 parts of water), 1 ml in 9 ml of normal saline solution, was injected into the heart, and the cardiac resuscitation team arrived as the injection was completed. Treatment included intravenously administered sodium bicarbonate, ventilation, and external cardiac massage. External direct-current shock resulted in conversion of ventricular fibrillation to ventricular tachycardia, which promptly reverted back to ventricular fibrillation. Two further attempts resulted in the same succession of events, and direct-current shock was thereafter ineffective.

It was claimed by the resuscitation team that epinephrine prevented successful conversion. However, the clinical pharmacologist felt that there was reasonable doubt. The case was *not* accepted as a drug-related death.

Results

This series included 6,199 patients representing six hospitals: one hospital for the treatment of chronic diseases, and five general medical hospitals.¹⁻⁴ The mean age of the patients was 58 years, and 61% were men. There were 744 patients who died in hospital (12%), and of these, 27 were judged to have died as a result of drug treatment. Thus, drug deaths accounted for 0.44% of the total series, or 3.6% of the hospital deaths.

The drug deaths are detailed in the Table. The major mechanisms were hyperkalemia (five cases), fluid overload (four cases), depression of the central nervous system (three cases), superinfection (three cases), hemorrhage (two cases), cardiac or respiratory arrest or both (two cases), dehydration and

electrolyte depletion (two cases), hypoglycemia (two cases), anaphylaxis (one case), liver failure (one case), perforated duodenal ulcer (one case), and hypercalcemia (one case).

Drug categories implicated in the fatalities were as follows:

1. Potassium supplements (five deaths out of 1,949 patients exposed).
2. Intravenously administered fluids (four deaths out of 2,048 patients exposed).
3. Narcotic and sedative drugs (three deaths).
4. Antibiotics (three deaths out of 2,548 patients exposed).
5. Parenterally administered anticoagulants (two deaths out of 361 patients exposed).
6. Digitalis glycosides (one death out of 1,254 patients exposed).
7. Diuretics (two deaths out of 1,254 patients exposed).
8. Insulin preparations (two deaths out of 353 patients exposed).
9. Single deaths were attributed to neostigmine, asparaginase, cyproterone acetate, adrenal steroids, and diethylstilbestrol.

Five of the patients were considered terminally ill immediately prior to the onset of their reactions, and though drug therapy was judged responsible for their death, life was probably not appreciably shortened as a result. The majority, 15 patients, were severely ill, but it was believed that their lives, at the time of their reactions, were not otherwise in immediate danger. The remaining seven patients were moderately ill.

Comment

Most of the information on fatal drug reactions has in the past been accumulated either as a result of sporadic reports of cases in the medical literature or through adverse-reaction reporting systems, such as that operated by the US Food and Drug Administration or that operated by the British Committee on Safety of Drugs. Such information is incomplete and provides no quantitation of fatal ef-

Deaths Due to Administration of Drugs*			
Cause of Death	Case No.	Drug(s)	Comments
Hyperkalemia	1	Potassium chloride	Woman, age 52. Diagnosis: Cirrhosis. Developed cardiac arrest while receiving potassium chloride 90 mEq/day. Serum potassium prior to death was 8.8 mEq/liter.
	2	Potassium chloride	Woman, age 58. Diagnosis: Metastatic carcinoma of breast. Receiving diuretics and potassium chloride, 60 mEq/day. Developed BUN of 53 mg/100 ml and serum potassium of 7.2 mEq/liter. ECG "consistent with hyperkalemia." Died suddenly shortly thereafter.
	3	Potassium chloride, spironolactone	Woman, age 55. Diagnosis: Mitral stenosis. Receiving diuretics, including spironolactone, and potassium chloride, 45 mEq/day. Death followed multiple bouts of ventricular tachycardia. Serum potassium on day prior to death was 7.1 mEq/liter.
	4	Potassium chloride	Man, age 55. Diagnosis: Cirrhosis. Receiving diuretics and potassium chloride, 45 mEq/day. Developed sudden hypotension. ECG revealed grade 1 atrioventricular block followed by sine-wave pattern. Serum potassium, 7.7 mEq/liter. Died in cardiac arrest.
	5	Potassium chloride	Woman, age 84. Diagnosis: Congestive heart failure. Receiving diuretics and potassium chloride 90 mEq/day. Admission BUN, 110 mg/100 ml. Suddenly developed severe arrhythmia and cardiac arrest. Serum potassium on day of death, 8.0 mEq/liter.
Fluid overload	6	5% dextrose in water, normal saline	Woman, age 60. Diagnosis: Metastatic carcinoma of breast. While receiving 3 liters of intravenously administered fluids with phosphate buffer and hydrocortisone for hypercalcemia, developed irreversible pulmonary edema.
	7	5% dextrose in water	Man, age 73. Diagnosis: Congestive heart failure. While receiving 2 liters of fluid for intractable vomiting, developed irreversible pulmonary edema.
	8	5% dextrose in water, normal saline, lactated Ringer's solution, blood	Man, age 48. Diagnosis: Cirrhosis. Received 8 liters of fluid, including blood transfusion of 2 liters, over 12-hr period for bleeding varices. Developed irreversible pulmonary edema during 8th liter.
	9	5% dextrose in water	Man, age 72. Diagnosis: Congestive heart failure. Receiving 4 liters of fluid over 60-hr period for dehydration. Oliguria was present. During 4th liter, developed irreversible pulmonary edema.
Depression of central nervous system	10	Morphine sulfate	Man, age 63. Diagnosis: Bronchopneumonia, obstructive lung disease. Received morphine sulfate, 5 mg, by intramuscular injection. Found dead 1 hr later.
	11	Chlorpromazine	Woman, age 55. Diagnosis: Severe chronic obstructive lung disease. Received chlorpromazine, 50 mg by intramuscular injection, for agitation. Within 30 min, developed coma and cardiac arrest during attempted intubation.
	12	Chlordiazepoxide	Man, age 48. Diagnosis: Chronic alcoholism. Received chlordiazepoxide, 200 mg/day for 3 days, to prevent delirium tremens. On day 4, developed severe drowsiness, vomited, aspirated, and developed cardiac arrest. Despite resuscitation, died in coma with aspiration pneumonia 2 days later.
Superinfection	13	Cephalothin sodium, oxacillin, ampicillin, kanamycin, Coly-mycin, adrenal steroids	Man, age 48. Diagnosis: Fever of unknown origin. Treated with multiple antibiotics and steroids for 6 weeks. Developed fulminating pneumonia and died. Autopsy revealed necrotizing pneumonitis, due to <i>Candida albicans</i> , and Waldenström's macroglobulinemia.

Deaths Due to Administration of Drugs			
Cause of Death	Case No.	Drug(s)	Comments
Superinfection	14	Chloramphenicol, penicillin	Man, age 50. Diagnosis: Chronic alcoholism. Admitted with fever of unknown origin. Received aqueous penicillin for 2 days and chloramphenicol, 2 gm/day by intramuscular injection, for 5 days, with improvement. Suddenly developed high fever, with gram-negative septicemia, and irreversible shock, followed by death 3 days later.
	15	Chloramphenicol, methylprednisolone	Man, age 55. Metastatic bronchogenic carcinoma. Treated for bronchopneumonia with chloramphenicol, 2 gm/day by intramuscular injection, and methylprednisolone, 240 mg/day, with initial improvement. On day 4, developed high fever and irreversible shock. Blood culture prior to death revealed <i>Escherichia coli</i> resistant to chloramphenicol.
Hemorrhage	16	Heparin sodium	Woman, age 67. Diagnosis: Pulmonary embolism. After heparin sodium therapy, 5,000 units by intravenous injection every 6 hr for 1 day, developed massive hemoptysis, followed by asphyxia and death. Autopsy revealed massive intrapulmonary hemorrhage.
	17	Heparin sodium	Woman, age 47. Diagnosis: Thrombophlebitis. Received heparin sodium, 10,000 units by intravenous injection, every 6 hr. On day 2, suddenly developed irreversible shock and died. Autopsy revealed massive retroperitoneal hemorrhage.
Arrhythmia	18	Digoxin	Man, age 79. Diagnosis: Cor pulmonale. Given digoxin on admission for heart failure. On day 7, developed complete heart block with intermittent sinus tachycardia. Died in ventricular fibrillation 1 hr later.
	19	Neostigmine	Woman, age 54. Diagnosis: Diabetes mellitus and pneumonia. Developed tachycardia shortly after admission. Received neostigmine, 0.5 mg, by intravenous injection to slow heart rate in order to identify arrhythmia. Administration of drug was followed immediately by multiple arrhythmias and cardiorespiratory arrest. Resuscitation was successful in achieving sinus rhythm, but patient remained in coma and died hours later.
Dehydration and electrolyte depletion	20	Spironolactone, acetazolamide, chlorothiazide, furosemide	Man, age 71. Diagnosis: Malignant ascites. Received combinations of diuretics for 8 days. On day 9, became severely dehydrated and febrile; this was followed by irreversible shock and death. Prior to death, serum sodium, 111 mEq/liter; serum chloride, 80 mEq/liter.
	21	Hydrochlorothiazide, furosemide	Woman, age 86. Diagnosis: Congestive heart failure. Received diuretics for 10 days. On day 10, there was severe dehydration. Serum sodium, 115 mEq/liter, and serum chloride, 72 mEq/liter. Death following shock and coma occurred the same day.
Hypoglycemia	22	Protamine zinc insulin suspension, isophane insulin suspension, chlorthalidone, diazepam, diphenhydramine hydrochloride, atropine sulfate, phenobarbital	Man, age 69. Diagnosis: Diabetes mellitus. Developed insulin coma corrected by intravenous administered glucose. Recurrent severe insulin coma 2 days later. No recovery following intravenously administered glucose, and death occurred shortly thereafter. Blood glucose prior to death and after administration of glucose was 60 mg/100 ml (Somogyi). In the hours prior to death, received chlorthalidone, diazepam, atropine, diphenhydramine and phenobarbital for agitation and sweating.
	23	Soluble insulin	Man, age 64. Diagnosis: Diabetic ketoacidosis. Admitted in diabetic coma and received 680 units of soluble insulin. Rapid clinical improvement occurred. However, hypoglycemia developed (blood glucose, 27 mg/100 ml) followed, on recovery after intravenously administered glucose, by acute myocardial infarction, pulmonary edema, and death.

Deaths Due to Administration of Drugs			
Cause of Death	Case No.	Drug(s)	Comments
Anaphylaxis	24	Asparaginase	Man, age 48. Diagnosis: Metastatic bronchogenic carcinoma. Received 80,000 units of asparaginase in 50 ml of saline without complication. One week later, this treatment was repeated. After 5 ml of infusion, patient developed acute severe anaphylactic reaction and died.
Liver failure	25	Cyproterone acetate	Man, age 62. Diagnosis: Carcinoma of prostate. Receiving long-term therapy with cyproterone acetate. Admitted, while still receiving therapy, with jaundice which progressed to death in liver failure. Autopsy revealed cholestatic jaundice with eosinophilic inclusion bodies in parenchymal cells. Histologic diagnosis was drug-induced liver disease.
Perforated duodenal ulcer	26	Prednisolone, hydrocortisone	Man, age 61. Diagnosis: Metastatic bronchogenic carcinoma. Treated with steroids for 12 days. Suddenly developed fever, coma, and death on day 13. Autopsy revealed multiple duodenal ulcers, one of which had perforated.
Hypercalcemia	27	Diethylstilbestrol	Woman, age 64. Diagnosis: Metastatic carcinoma of breast. Received diethylstilbestrol, 5 mg/day, for 8 days. Serum calcium rose from 11 mg/100 ml to more than 20 mg/100 ml. Coma followed by death on 8th day of treatment.

*Drug-prescribing information is obtained by nurse-monitors directly from order written by attending physician. It is often not customary for physician to prescribe the form (or brand name) of drug to be given. For example, if an order is written for ampicillin, 500 mg every six hours by mouth, the hospital pharmacy may provide either the anhydrous or trihydrate form of drug. Furthermore, since stocks

change and sometimes more than one form is in stock, there may be no consistency in the form provided from time to time, even for the same patient. Thus, in instances in which the precise form of drug was unknown, a drug such as ampicillin has been designated simply by that term without reference to specific form used.

fects, either for drugs in general or for specific drugs.⁵

Two limited series of consecutive patients monitored for drug-attributed deaths have been published. In 1966, Seidl et al⁶ reported on a series of 714 consecutive medical inpatients. Seven were judged to have died of adverse drug reactions in the hospital (1.0%). Respiratory depression due to sedative and narcotic drugs accounted for two deaths, and other causes were superinfection (antibiotics), nodal tachycardia (digoxin), hypotension (methyldopa), and leukopenia (mercaptopyrine). In another series involving 731 medical inpatients, Ogilvie and Ruedy reported 17 drug-attributed deaths (2.3%).⁷ Twelve of these were ascribed to digitalis glycosides and four to superinfection, and one patient with obstructive airway disease died after receiving morphine.

The current communication concerns the first extensive series, to our knowledge, of consecutive medi-

cal inpatients carefully monitored for toxic effects of drugs, and it covers a broad range of hospitals, diseases, and drugs.

Drug-attributed deaths were relatively infrequent, occurring in 27 of 6,199 medical inpatients (0.44%), but they accounted for an appreciable proportion of hospital deaths (3.6%). In contrast to other reports, the present study points to fluid and electrolyte therapy as a major source of drug deaths. The data indicate that potassium chloride may be especially dangerous in the presence of complicating factors, such as renal failure, but that it can be lethal even when they are absent. Furthermore, this drug cannot be considered wholly safe when given by mouth or when given together with diuretic drugs which tend to produce potassium loss. In the total monitored series, a surprisingly high proportion of patients (31%) have received potassium chloride, but usage has varied widely among the monitored hospitals from 8% to 52%. This sug-

gests that potassium chloride may be administered in some institutions more often than is necessary and that more stringent indications might result in a decreased mortality.

Much the same considerations apply to parenterally administered fluids. The administration of 5% dextrose in water, for example, has also varied between hospitals (range, 10% to 42%; mean, 27%). The rapid administration of large volumes of fluid in the presence of heart failure is particularly dangerous, but the risk of pulmonary edema is a real one, even in the absence of apparent predisposing factors.

Two of the three patients who died after sedative or narcotic treatment had obstructed airways. The hazards involved in giving such treatment to patients with respiratory tract disease, especially if they tend to retain carbon dioxide, are well known.

A relationship between antibiotics, adrenal steroids, and super-

infection was found in this study. The death rate due to this complication, while encouragingly low, nevertheless supports the principle that antimicrobial treatment should be reserved for specific indications and confined to necessary drugs. Concomitant adrenal steroid treatment should, if possible, be avoided.

Heparin sodium has been responsible for death in two out of the 361 patients exposed. Both were women, and one was 67 years old. In a previous study, it has been shown that bleeding due to heparin is most common among elderly women.⁸

Digoxin and neostigmine were each responsible for one death of a patient in cardiac arrest. It is reassuring to note the low recorded mortality with digoxin (one out of 1,254 patients). Elsewhere, it has been pointed out that the doses of digoxin used in the monitored hospitals appear to be appreciably lower than those given in studies in which a higher mortality has been reported.⁹

Diuretic drugs, especially the more potent ones such as furosemide, are not innocuous. The two deaths in this series emphasize the need for sound indications and for moderation and care in the use of these powerful agents.

Similar considerations apply to insulin. Hypoglycemia may prove fatal and is a medical emergency calling for prompt and vigorous treatment. Symptomatic treatment before the onset of coma with sedatives and other drugs is obviously contraindicated.

Anaphylaxis, liver failure, perforated ulcer, and hypercalcemia are all recognized as potentially fatal adverse drug effects, but in this series, they have been encountered infrequently. Drug deaths due to other mechanisms, such as renal damage or bone marrow depression, have not yet been observed.

It must be emphasized that all the drug deaths in this study con-

cern cases in which cause and effect relationships were suspected by the attending physicians. There remains the problem of deaths in which drugs may have been responsible, but were not suspected. Techniques of event analysis¹⁰ can provide for a preliminary approach to such problems and are feasible within a comprehensive monitoring system.^{11,12}

Finally, the deaths reported here concern drugs administered in hospitals to medical patients. Consequently, this series does not reflect other drug deaths, such as those related to long-term drug usage (eg, analgesic nephropathy) or to delayed adverse reactions (eg, bone marrow aplasia due to chloramphenicol), which may be more common among outpatients.

Participating hospitals include Lemuel Shattuck Hospital, Peter Bent Brigham Hospital, Boston City Hospital (Tufts Service), and Boston Veterans Administration Hospital, Boston; Roger Williams General Hospital, Providence, RI; St. Joseph's and Westminster Hospitals, London, Ontario; and Hadassah Hebrew University Hospital, Jerusalem, Israel.

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Nonproprietary and Trade Names of Drugs

Cephalothin sodium—*Keflin*.
Furosemide—*Lasix*.
Methyldopa—*Aldomet*.

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