Potential risks and prevention, part 1: Fatal adverse drug events

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Abstract: Potential risk factors for and the preventability of fatal adverse drug events (ADEs) were studied.

Case reports of ADEs published in *Clin-Alert* during 1976–95 were the source of information on fatal ADEs. Patient, drug, and event variables were identified, and the causality, predictability, and preventability of each case were assessed. Data were entered into a relational database for analysis.

The data indicated 447 cases involving a fatal ADE. Ten percent of the fatal ADEs were assessed as definite, 46% as probable, and 44% as possible. Fatal-ADE frequency increased with age. Forty-five percent of the patients were 40–69 years of age, and 40% were healthy. Central-nervous-system agents, antineoplastics, antimicrobials, and cardiovascular agents accounted for 69% of the deaths. Only 33% of patients received more than the usual dosage. Many of the suspected drugs could have been monitored with blood level tests but were not, and baseline testing of critical blood count and liver and renal function was often not performed. The most common causes of death were hepatitis, hepatic failure, cardiopulmonary arrest, overdose, and agranulocytosis. ADE types were distributed as adverse drug reactions (58%), allergic reactions (19%), medication errors (17%), and drug interactions (6%). Sixty-eight percent of the fatal ADEs were judged to have been preventable; of these, a pharmacist could have prevented 57%. Litigation was reported for 14% of the fatal-ADE cases; judgments and settlements averaged $1.1 million.

A review of published case reports of ADEs for 1976–95 yielded information on possible risk factors for fatal ADEs and on which events may have been preventable.

Index terms: Allergies; Anti-infective agents; Antineoplastic agents; Blood levels; Cardiac drugs; Central nervous system drugs; Death; Dosage; Drug interactions; Drugs, adverse reactions; Errors, medication; Pharmacists; Tests, laboratory; Toxicity

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The use of medication usually benefits the patient. Often, however, there are bothersome adverse effects; much less commonly, a patient will have an adverse reaction that necessitates medical attention. Very rarely, a patient dies as a result of taking medication.

This report is the first in a series of four describing significant adverse drug events (ADEs). An ADE, for the purpose of these reports, includes adverse drug reactions (ADRs), drug interactions, allergic drug reactions, and medication errors that harm the patient. This study was conducted to generate hypotheses on what may contribute to fatal ADEs and whether these tragic events can be prevented. The second report will discuss drug-induced permanent disabilities,[1] the third will look at drug-induced threats to life,[2] and the fourth provides a summary analysis of the first three.[3] Such events are of concern to the patient, the patient's family, the health care system, and the pharmacy profession as it becomes more patient focused.

The frequency of fatal ADEs in the U.S. population is still unclear. Estimates range from 7,000 to 140,000 per year.[4,5] The occurrence of fatal ADEs in hospitals varies with the type of patient. The frequency of fatal ADEs in medical inpatients has been found to range from 0% to 2.3%.[6-14] Armstrong et al.[15] reported the prevalence of fatal ADEs to be 0.019% in surgical inpatients. Four inpatient studies found a prevalence range for

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fatal ADEs of 0–0.9% in mixed (medical, surgical, gynecological, and psychiatric) patient populations.[16-19] Two cross-sectional studies involving large governmental databases on spontaneously reported ADRs found that 2.5–3% of all ADEs were fatal.[20,21]

In a postmortem study by Gotti,[22] 8.3% of autopsies of hospitalized patients were drug associated. In another postmortem study, Irey[23] reported that 52% of drug-associated autopsies involved a drug overdose; 27%, a true ADR; 6%, a malignant condition treated with cytotoxic drugs; and 3%, a diagnostic or therapeutic error. The mean prevalence of fatal ADEs for these hospitalized patients was 0.254%. However, both studies may have included cases of suicide and drug abuse.

A study of death certificates for the period from 1983 to 1993 revealed an increase in the number of medication error-related deaths in the United States from 2876 to 7000 a year.[24] The limitations of studies relying on death certificates are well-known, however, and include misclassifications and underreporting.[25]

The public is starting to become aware of the problem of fatal ADEs, as evidenced by recent national news reports.[26,27] The 1999 report on medication errors from the Institute of Medicine was well publicized.[4]

The objectives of this study were to (1) identify case reports of fatal ADEs, (2) develop a relational database of these events, (3) analyze the database for trends, (4) identify potential risk factors, and (5) identify ADEs that may have been preventable, including those that may have been prevented by a pharmacist.

Methods

Case reports of ADEs published in *Clin-Alert* (Technomic Publishing Company, Lancaster, PA), an abstracting service, during 1976–1995 were the source of information on fatal ADEs. (Because of publication lag time, some of these ADEs occurred earlier than 1976.) *Clin-Alert* was selected because of its long history and its reputation for publishing high-quality reports of ADEs. However, to ensure the validity of using abstracts, 30 randomly selected *Clin-Alert* abstracts were compared with the full published reports.

Reports of ADEs associated with suicide, drug abuse, and pregnancy were excluded from analysis. The case reporter usually suspected a drug as the cause of the fatality. The investigator also reviewed each case for causality. A fatal ADE was defined as an adverse event in which a drug, in all likelihood, substantially contributed to the patient's death. Causality was estimated by using global introspection—the investigator's thoughtful self-analysis. Specific laboratory test values (when reported), the progression of the event, and the opinion of the case reporter were considered in deciding the drug's contribution to the reported death.

Each reported ADE was placed into one of three categories: definite, probable, and possible ADEs. A definite ADE was defined as an event that followed a reasonable temporal sequence after administration of the drug (or relative to established drug levels in the body fluids or tissues), that followed a known response pattern, that was confirmed by improvement on stopping the drug (dechallenge), and that reappeared on repeated exposure (rechallenge). A probable ADE was defined as an event that followed a reasonable temporal sequence, that followed a known response pattern, that was confirmed by dechallenge, and that could not be reasonably explained by the known characteristics of the patient's clinical state. A possible ADE was an event that followed a reasonable temporal sequence, that followed a known response pattern, and that could have been produced by the patient's clinical state or other therapy administered.[28] Cases not meeting one of these three sets of criteria were not regarded as involving drugs and were not used.

Each ADE was carefully reviewed for various patient, drug, and event variables, some of which may be potential risk factors for a fatal ADE. Patient variables included age; sex; weight; race; primary and secondary diagnoses; liver function; renal function; complete blood count; allergy history; history of alcohol, tobacco, and drug abuse; severity of illness during therapy with the suspected drug; number of comorbidities; and a comorbidity rating.[29] Drug variables included therapeutic class, indication for the drug, route of administration, dosage, setting where the drug was started, duration of therapy, whether plasma drug levels were determined, and number of drugs used concurrently. Event variables included the fatal ADE, the organ system affected by the threat to life, when the event occurred after initial therapy, where the patient died, and the stated or most probable drug-related mechanism for the life-threatening event (ADR, drug allergy, medication error, or drug interaction).

When the fatal ADE involved any of the mechanisms listed above, additional information was recorded. For interacting drugs, the severity of the interaction was classified by using the scheme of Hansten and Horn.[30] Other drug interaction variables included dosages, routes of administration, blood levels of the object and participant drugs, and how long the drugs were used concomitantly. Blood levels were labeled high if they were twice the normal range and very high if they were more than twice the normal range.

The predictability of each fatal ADE was estimated. Type A ADRs were defined as unwanted, harmful events that were associated with the pharmacology of the drug or were dose related. Type B ADRs were defined as unwanted, harmful events that were bizarre and unrelated to the drug's pharmacology or dosage.

Allergic reactions were classified as anaphylactic, cytotoxic, immune complex related, cell mediated, or "other." The latter category included angioedema, pneumonitis, drug fever, acute pulmonary infiltration, chronic pulmonary fibrosis, drug-induced asthma, and skin-related reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

A medication error was defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.[31] Medication error variables included the kind of error, what happened, the principal cause of the error, the type of error, where the error occurred, what part of the institution the medication was used in, and whether the medication was retrieved from areas traditionally holding floor stock. The error type was categorized as a slip (an attention rather than knowledge deficit) or a mistake (a conscious error usually due to lack of training, education, or understanding).[32] If a lawsuit was mentioned, the information gathered included the basis of the suit, the defendant, any verdicts or settlements, and any financial judgment.

With all these variables taken into consideration, each fatal ADE was closely examined to determine if it could have been prevented. The following questions were asked; answering yes to one or more made the event considered preventable[33]:

1. Was the drug involved in the problem considered inappropriate for the patient's clinical condition?
2. Were the dose, route, and frequency of administration inappropriate for the patient's age, weight, and disease?
3. Was required therapeutic drug monitoring or other necessary laboratory testing not performed?
4. Was there a history of allergy to the drug?
5. Was a drug–drug interaction involved in the reaction?
6. Was a toxic serum drug level (or laboratory monitoring test result) documented?
7. Was poor compliance involved in the reaction?
8. Was there an error?

If the ADE was considered preventable, a strategy that would most effectively prevent it was assigned.

If the error was preventable, the circumstances of the error were considered in terms of a pharmacist practicing under the pharmaceutical care model and the likelihood of a pharmacist preventing the error, either in the hospital or community pharmacy setting. For this exercise, the following assumptions were made for the hospital setting: (1) there is a unit dose system, (2) there is a centralized i.v. admixture system, (3) the pharmacist is practicing in the patient care area, (4) all new orders are discussed or reviewed with the pharmacist before the patient receives the drug, (5) there is daily monitoring of therapy and drug administration, and (6) there is a pharmacy computer system with access to laboratory results. The assumptions for the community pharmacy setting were as follows: (1) there are a sufficient number of certified pharmacy technicians who do the dispensing, (2) there is a computer system supportive of pharmaceutical services, (3) the pharmacist discusses each drug regimen with the patient, and (4) the pharmacist performs patient counseling.

A list of mechanisms for preventing medication errors was developed after the literature was reviewed. For each medication error, the investigators selected (by agreement) the most effective prevention for that error. To avoid bias, preventive mechanisms were not decided a priori; rather, they became obvious when reviewing each error. As the study unfolded, a complete list of preventive mechanisms was developed.

The same person coded the data collection sheets for all variables. The sheets were double-checked by a second person (the same person each time) for accuracy and completeness. Machine-readable data sheets (Teleform 6.0, Cardiff Software, Inc., Vista, CA) were scanned into a relational database (Microsoft Access 2, Microsoft Corp., Redmond, WA). Data entry was then checked for accuracy and completeness. The data were sorted, and frequency distributions and cross-tabulations were performed.

Results

Reports. The ADE reports ranged over a 20-year period from 1976 to 1995. The pretested, randomly selected *Clin-Alert* abstracts were found to be 97% accurate and 98% complete when compared with the full case reports. The frequency of fatal ADEs in *Clin-Alert* was 8%. The prepared data reflected 447 cases involving a fatal ADE. The main source of the reports was medical journals (85%), and most of the reports were from North America (53%) and Europe (31%).

Causality. Ten percent of the fatal ADEs were assessed as definite, 46% as probable, and 44% as possible. With respect to predictability, 34% of the ADR reports represented type A events and 66% type B events.

Patients. The mean ± S.D. age of the patients was 44 ± 24 years (range, <1 to 92 years). Except for patients less than 10 years old, the number of ADE reports increased with patient age (Table 1). Forty-five percent of the patients were 40–69 years of age. A majority (53%) were female. No primary diagnoses were prominent. In cases in which the severity of illness was known, 40% of patients were healthy, 36% were moderately

ill, 20% were severely ill, and 4% were terminally ill.

Drugs. Almost all drugs (87%) were used in accordance with the indications listed in *AHFS Drug Information*.[34] Central-nervous-system agents, antineoplastics, antimicrobial agents, and cardiovascular agents accounted for 69% of the deaths. The drugs suspected of inducing a fatal ADE varied with the mechanism involved (Table 2).

Most patients (67%) who had a fatal ADE received usual or below-usual dosages (Table 3). Autonomic agents, smooth-muscle relaxants, and electrolyte, caloric, and water-balancing agents accounted for most of the cases in which a dosage exceeded the usual dosage. The parenteral (46%) and oral (42%) routes of administration were used most often. However, other routes were the ones most often associated with more-than-usual dosages.

Drug levels could have been monitored in 177 cases of fatal ADEs (40%). However, such monitoring occurred in only 18 of the cases (10%). In 13 (72%) of the 18 cases, the drug level was found to have been high or very high.

When the location where the drug was started was known, most patients (56%) received the drug while in a hospital; 41% were outpatients, and 3% were in other locations. Most of the fatal ADEs took place within 31 days of the start of therapy, with 25% occurring during the first 24 hours (Table 4).

Events. Table 5 lists the most common fatal ADEs identified. Over 23% of all fatal ADEs involved the liver and biliary systems. The most common events were drug-induced hepatitis and hepatic failure. An autopsy was reported to have taken place in 27% of cases; a drug level was reported in only 5% of these.

Mechanisms. The mechanisms of fatal ADEs were ADRs (58%), drug allergies (19%), medication errors (17%), and drug interactions (6%). The frequency of allergic reactions increased with age. Patients less than 1 year of age had 13% of the fatal allergic events, while those over 69 had 30%. Of errors, 45% occurred in children less than 1 year of age, while 11% occurred in those over 39.

Twenty-one percent of the ADEs were associated with antineoplastic agents. Twenty-six percent of the medication allergies were associated with antimicrobial agents. Forty percent of the drug interactions and 33% of the errors were associated with central-nervous-system agents. Of allergic drug reactions, 22% were classified as anaphylactic, 35% as cytotoxic, 19% as immune complex related, 2% as cell mediated, and 22% as other.

Drug interactions. There were 26 fatal drug interactions, ranging in severity from category 1 to unclassified; about 42% of the interactions were unclassified events, while about 39% were category 3 events (Table 6). In 55% of the cases, the duration of exposure to the interacting drugs was one to seven days. In 27% of the cases, the interacting drugs were used for less than 24 hours.

Table 1.
Age of Patients with Fatal Adverse Drug Events (ADEs) (*n* = 401)

Age (yr)[a]	No. (%) Fatal ADEs
<10	51 (12.7)
10–19	27 (6.7)
20–29	28 (7.0)
30–39	47 (11.7)
40–49	53 (13.2)
50–59	64 (16.0)
60–69	65 (16.2)
>69	66 (16.5)

[a]Mean ± S.D. age, 44.4 ± 24.1 years.

Table 2.
Drugs and Mechanisms Most Commonly Suspected of Inducing Fatal Adverse Drug Events[a]

Adverse Drug Reaction	Allergy	Error	Interaction	All[b]
Amiodarone	Antineoplastics	Chlorpromazine	Bleomycin	Valproic acid
Bleomycin	Carbamazepine	Halothane	Clozapine	Cyclophosphamide
Carbamazepine	Ciprofloxacin	Lidocaine	Filgrastim	Bleomycin
Cyclophosphamide	Diatrizoate	Meperidine	Hydralazine	Trimethoprim–sulfamethoxazole
Diatrizoate	Diphtheria and tetanus toxoids and pertussis vaccines	Morphine	Hydrochlorothiazide	Diatrizoate
Doxorubicin	Gold salts	Phenylbutazone	Lithium	Halothane
Methotrexate	Lidocaine	Propranolol	Phenytoin	Sulfasalazine
Mitomycin	Methyldopa	0.9% sodium chloride injection	Warfarin	Amiodarone
Propofol	Methylprednisolone	Theophylline		Antineoplastics
Sulfasalazine	Nomifensine	Valproic acid		Methotrexate
Trimethoprim–sulfamethoxazole	Penicillamine			Ciprofloxacin
Valproic acid	Phenobarbital			Carbamazepine
	Quinine			Penicillamine
	Sulfasalazine			Methylprednisolone
	Trimethoprim–sulfamethoxazole			Methyldopa

[a]Listed in order of decreasing frequency.
[b]All drugs causing fatal adverse drug events by all mechanisms. Listed in order of frequency.

Medication errors. Of the medication errors identified in this study, 67% were prescribing errors. In 41% of the errors, patients had been prescribed the wrong dosage, and in 23% the drug was considered a poor choice. Mistakes accounted for 66% of the errors, while 34% were due to slips.

Lawsuits. Lawsuits with financial judgments were reported in 14% of the fatal-ADE cases. In 44% of the cases, the physician was the defendant. The most common complaint was poor monitoring of the drug therapy. A jury decided 57% of the cases. Judgments and settlements ranged from $35,000 to $9,000,000 (mean, $1,061,318).

Prevention. Sixty-seven percent of the fatal ADEs could have been prevented, and, of these, 57% could have been prevented by a pharmacist (Table 8). Preventability did not vary with length of therapy or patient age. Better patient monitoring may have prevented many of the fatal ADEs (Table 9). Better patient monitoring and review of orders before the drug was administered to the patient were the major mechanisms for preventing fatal ADEs.

Table 3.
Dosages Used in Cases of Fatal Adverse Drug Events (ADEs) (*n* = 289)

Dosage	No. (%) Fatal ADEs
Below usual	7 (2.4)
Usual[a]	186 (64.4)
Two to three times usual	75 (26.0)
More than three times usual	21 (7.3)

[a]As listed in reference 34.

Table 4.
Onset of Fatal Adverse Drug Events (ADEs) after Initiation of Suspected Drug (*n* = 368)

Time of Onset (Days)	No. (%) Fatal ADEs
<1	92 (25.0)
1–7	74 (20.1)
8–31	82 (22.3)
32–365	82 (22.3)
>365	38 (10.3)

Table 5.
Fatal Adverse Drug Events (*n* = 447)

Type of Fatal Event	No. (%)
Hepatitis	18 (4.0)
Hepatic failure	18 (4.0)
Cardiopulmonary arrest	17 (3.8)
Overdose	15 (3.4)
Agranulocytosis	11 (2.5)
Fulminant hepatic failure	9 (2.0)
Pulmonary fibrosis	9 (2.0)
Aplastic anemia	9 (2.0)
Toxic epidermal necrolysis	8 (1.8)
Hepatic necrosis	8 (1.8)
Hepatotoxicity	8 (1.8)
Pseudomembranous colitis	8 (1.8)
Thrombocytopenia	7 (1.6)
Leukemia	6 (1.3)
Vasculitis	6 (1.3)
Renal failure	6 (1.3)
Other	284 (63.5)

Discussion

Most of the patients in this study who died of an ADE were middle aged, were fairly healthy, and had received moderately toxic drugs at usual dosages. Thus, host factors like renal and liver function and genetic predisposition may have been involved. Central-nervous-system agents, antineoplastics, antimicrobials, and cardiovascular agents accounted for most of the deaths. Many of the patients were poorly monitored. Baseline testing was infrequent, and patients were rarely monitored while taking the suspected drugs. The toxic effects came about through adverse reactions, drug interactions, drug allergies, and errors, and the hepatic and biliary systems were affected the most.

The drugs most commonly associated with a fatal ADE varied by type of ADE. Drugs suspected of inducing all of the types of fatal ADEs are listed in the "All" column in Table 2. Warfarin, heparin, digoxin, and potassium chloride did not make it into this column. Most physicians, nurses, and pharmacists know that these drugs are potentially dangerous and are therefore likely to be especially vigilant regarding their use. Alternatively, perhaps the editors of *Clin-Alert* chose not to publish abstracts concerning these events.

Manual and computer programs can be designed to screen for patients receiving risky drugs. Other options may include screening for routes other than oral or by injection, as these less frequently used routes were often found to be associated with overdoses.

The data reflect the importance of a pharmacist being available when medication is prescribed. Most errors involved prescribing. Most prescribing problems involved selecting an inferior drug or a wrong dosage. In addition, many patients were be-

Table 6.
Drug Interactions Suspected of Contributing to Fatal Adverse Drug Events (ADEs) (*n* = 26)

Severity Level[a]	No. (%) Fatal ADEs	Definition	Object Drug	Participant Drug
Category 1	1 (3.8)	Avoid combination. Risk always outweighs benefit.	Phenelzine	Phenylpropanolamine
Category 2	2 (7.7)	Usually avoid combination. Use combination only under special circumstances.	Apazone Methotrexate	Warfarin Naproxen
Category 3	10 (38.5)	Minimize risk. Take action as necessary to reduce risk.	Acetaminophen Clozapine Cyclosporine Diazoxide Gentamicin Lithium Phenytoin Phenytoin Tarazone	Alcohol Carbamazepine Ketoconazole Hydralazine Amphotericin B Haloperidol Warfarin Isoniazid Trifluperazine
Category 4	2 (7.7)	No action needed. Risk of adverse outcomes appears small.	Lorazepam Streplase	Clozapine Heparin
Category 5	0 (0)	Evidence suggests no interaction.		
Unclassified	11(42.3)	Not listed.	Amiodarone Bleomycin Bleomycin Cyclophosphamide Hydrochlorothiazide Lithium Magnesium sulfate Medroxyprogesterone Succinylcholine Tolazoline Zinc sulfate	Contrast media Cisplatin Filgrastim Filgrastim Methyldopa Hydrochlorothiazide Hydralazine Radiation therapy Thiopental Dopamine Penicillamine

[a]Defined in reference 30.

ing prescribed relatively toxic drugs without proper baseline monitoring, such as a complete blood count and liver and renal function tests. Such tests can be recommended or ordered by a pharmacist.

Once a drug is prescribed, the pharmacist should make sure that the drug prescribed is the drug being administered and then monitor the effects while it is being taken. So many of the drugs involved in the ADEs could have been monitored with blood tests but were not. Twenty-five percent of the fatal ADEs in this study occurred within the first 24 hours of therapy. Pharmacists should order serum drug testing (if available) and closely monitor the patient during this critical time period.

Fatal allergic drug reactions increased in frequency with age—possibly a new finding.[35] Also, 45% of the fatal medication errors involved children less than one year of age. Special precautions and vigilant monitoring are indicated.

Only 6% of the fatal ADEs were associated with a drug interaction, and there were only one category 1 and two category 2 interactions. Most of the drug interactions were unclassified. *Hansten and Horn's Drug Interactions Analysis and Management* does not generally include interactions involving drugs used in anesthesia or radiology. There also may not be enough unclassified interactions reported.

Two thirds of the medication errors resulted from mistakes rather than slips, and many of the mistakes were in prescribing. One solution is having a pharmacist nearby to consult.

Many of the fatal ADEs could have been prevented, including by pharmacists. It appears that most preventive effort should be put into designing better computer systems to screen for potential medication-use problems and into having more pharmacists in patient care areas. Most computer systems in hospitals and community pharmacies are designed for administrative rather than clinical and safety purposes.

It is not known why an autopsy was performed for only a small proportion of the fatal ADEs and why only a few autopsy reports included a blood level for the suspect drug. This needs further investigation.

Several potential risk factors (age, severity of illness, inherent drug toxicity, duration of therapy, and plasma drug levels) should be studied by using more rigorous epidemiologic methods to determine their contribution to fatal ADEs.

The most recent controlled study of risk factors for ADEs in hospitalized patients found that ADEs occurred more often in sicker patients who stayed in the hospital longer.[36] However, after adjusting for level of

Table 8.
Preventability of Fatal Adverse Drug Events (ADEs) by Severity of Illness (*n* = 376)

Patient Status	No. Patients (%)	No. (%) Fatal ADEs	
		Preventable	Preventable by Pharmacist
Relatively healthy	150 (39.9)	101 (67.3)	58 (57.4)
Moderately healthy	136 (36.2)	101 (74.3)	54 (53.5)
Severely ill	74 (19.7)	44 (59.5)	27 (61.4)
Terminally ill	16 (4.3)	7 (43.8)	6 (85.7)

Table 9.
Possible Mechanisms for Preventing Fatal Adverse Drug Events (ADEs) (*n* = 271)

Mechanism	No. (%) Fatal ADEs
Better patient monitoring	73 (26.9)
Prospective review of orders	55 (20.3)
Computer screening	48 (17.7)
Patient risk assessment	23 (8.5)
Concurrent regimen review	22 (8.1)
Patient education	11 (4.1)
Physician education	9 (3.3)
Other	30 (11.1)

care and length of stay, few risk factors emerged. The study looked at ADEs in general, not just fatal ADEs. In addition, only a few risk variables were analyzed.

The limitations of this study are consistent with those of most spontaneous ADE-reporting systems: the amount and quality of clinical data, underreporting, and reporting poorly defined clinical syndromes. The most significant shortcoming is the inability to discover for sure whether a drug caused the reported event. There also may have been bias on the part of editors concerning what case reports to publish in their journals.

Few case reports gave information on renal function, complete blood count, or liver function before the drug was started. Secondary diagnoses were rarely stated, and the recovery status of the patient was missing in many case reports. Thus, comorbidity and a comorbidity index could not be used. Information about race or ethnicity, body weight, use of tobacco and alcohol, substance abuse, and ADE history was almost always missing. Most reports did not clearly state the location of the ADE. In an institutional setting, it was often unclear whether the medication came from floor stock, a unit dose system, an i.v. admixture system, or an automated device.

The study was also limited by the absence of a control group for making comparisons and calculating odds ratios for each variable, and estimates of the overall prevalence of different ADE-related factors are not possible. Thus, most of the results are useful only for generating hypotheses. However, until further study is undertaken, the results can be used by pharmacists to help screen for patients who may be at risk for a fatal ADE.

Some of the drug interactions may have not been known and listed in drug interaction texts at the time of an event.

Further study with more rigorous epidemiologic methods is needed to quantify risk factors for fatal ADEs. The fatal drug interactions reviewed in this study also need closer scrutiny. There is also a need for better guidelines on how to prepare a case report on a fatal ADE.

Conclusion

A review of published case reports of ADEs from 1976 to 1995 yielded information on possible risk factors for fatal ADEs and on which events may have been preventable.

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