Potential risks and prevention, part 3: Drug-induced threats to life

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Abstract: Potential risk factors for and the preventability of drug-induced threats to life were studied.

Case reports of adverse drug events (ADEs) published in *Clin-Alert* during 1977–97 were the source of information on drug-induced life threats. 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 846 drug-induced life threats. Seventy-four percent of the cases were assessed as definite or probable. Patients received usual or below-usual dosages in 89% of the cases. Patients tended to be middle-aged and only moderately ill. The drug categories most frequently associated with life threats were antimicrobials and central-nervous-system agents. Plasma drug level monitoring should have been performed in 127 cases but occurred only in 31 cases (24%). Event types were distributed as adverse drug reactions (50%), allergic reactions (35%), drug interactions (11%), and medication errors (4%). A commercial reference classified almost half of the drug interactions associated with a life threat as posing minimal or no potential risk to the patient. Half of the life-threatening events were judged to have been preventable; about half of these could have been prevented by a pharmacist. Litigation was reported for only 1% of the cases of drug-induced threats to life; judgments and settlements averaged $1.2 million.

A review of published case reports of ADEs for 1977-97 yielded information on possible risk factors for drug-induced life threats and on which events may have been preventable.

Index terms: Age; Allergies; Anti-infective agents; Blood levels; Central nervous system drugs; Dosage; Drug interactions; Drugs, adverse reactions; Errors, medication; Pharmacists; Prescribing; Reports; Toxicity

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This report is the third in a series of four describing significant adverse drug events (ADEs), including adverse drug reactions (ADRs), allergic drug reactions, drug interactions, and medication errors.[1-3] The present study was conducted to generate hypotheses about what may contribute to drug-induced threats to life and to discover what mechanisms or guidelines are needed to prevent these events.

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

Methods

The methods used in this study were the same as for the study described in part 1.[1] A drug-induced life threat was defined as an event which, given no medical intervention, would have led to the patient's demise, and it is more than likely that a drug was the predominant precipitating factor for the event. Since a literature search failed to reveal any references listing or exploring such events, life threats were based on information provided in emergency medicine texts and a list of critical laboratory test values (Appendix A) from a large metropolitan teaching hospital. In addition, the list of possible drug-induced life threats and

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symptoms was provided to an internal medicine physician for his opinion. The final list of diagnoses used when screening cases is shown in Appendix B. Specific laboratory test values in the cases, when available, allowed the investigators to decide whether a case fit the criteria of a life threat for that patient.

Results

Reports. The reports ranged over a 20-year period from 1977 to 1997 (reports for 1982 were not available). The prepared data reflected 846 cases involving a drug-induced life threat. Drug-induced life threats accounted for 15% of all *Clin-Alert* reports during this period.

The reporting of drug-induced life threats in *Clin-Alert* increased during each five-year period between 1977 and 1997. From 1977 to 1981, 20% of *Clin-Alert* reports involved drug-induced life threats; from 1993 to 1997, 29%. The main source of the reports was medical journals (91%), and most of the reports were from North America (56%) and Europe (34%).

Causality. Eleven percent of the life threats were assessed as definite, 63% as probable, and 26% as possible. Seven percent of the ADRs were type A reactions, and 93% were type B reactions.

Patients. The mean ± S.D. age of the patients was 45.1 ± 22.3 years (range, <1 to 94 years) (Table 1). The number of reports generally rose with patient age. A majority of the patients (54%) were female. No primary diagnoses were prominent. In cases in which a secondary diagnosis was known, 7% of the patients had renal impairment as a secondary diagnosis. In cases in which the severity of illness was known, 9% of the patients were relatively healthy, 76% were moderately ill, 15% were severely ill, and none were terminally ill.

Drugs. Almost all of the drugs (97%) were used for indications listed in *AHFS Drug Information*.[4] Approximately 45% of the reports described the use of a central-nervous-system or antimicrobial agent. The drugs listed in Table 2 represent 21% of the drug-induced life threats. Two of the top drugs suspected of causing a drug-induced life threat were nonprescription medications.

Most patients (89%) who had a life threat received usual or lower-than-usual dosages (Table 3). Autonomic agents accounted for the most cases in which a dosage exceeded the usual dosage. The routes of administration used most often were oral (46%) and administration by injection (46%). Oral administration was the route used in most cases in which the usual dosage was exceeded.

Drug levels could have been monitored in 127 cases (15%) but were monitored in only 31 (24%) of these cases. In 29 (94%) of these 31 cases, the drug level was either high or very high.

Most patients (89%) received their drug while in a hospital. Most of the drug-induced life threats occurred between 1 and 31 days of the start of drug therapy, with 12% occurring during the first 24 hours (Table 4). Most often (96% of the time), the patient was still taking the drug when the life threat occurred.

Central-nervous-system agents accounted for the greatest number of the ADRs (28%) and allergic reactions (23%), followed by antimicrobials. Central-nervous-system and cardiovascular agents accounted for 48% of the drug interactions.

Events. Half of the events were ADRs, 35% were allergic drug reactions, 11% were drug interactions, and 4% were medication errors. Table 5 lists the most common drug-induced life-threatening events identified. These 15 events constitute a majority of the cases analyzed. Anaphylactic reactions were the most common type of event. Sixty-two percent of the events affected the respiratory, hematopoietic, or cardiovascular system.

Mechanisms. Patients older than 49 years had 64% of all drug interactions, 48% of all ADRs, and 41% of all allergic reactions. Sixty-eight percent of the ADRs occurred after therapy with a drug given at its usual dosage. Of allergic reactions, 52% were classified as anaphylactic, 29% as cytotoxic, 4% as immune complex related, and 16% as other.

Table 1.
Age of Patients with Drug-Induced Life Threats (LTs) (*n* = 830)

Age (yr)[a]	No. (%) LTs
<10	65 (7.8)
10–19	65 (7.8)
20–29	90 (10.8)
30–39	111 (13.4)
40–49	108 (13.0)
50–59	131 (15.8)
60–69	147 (17.7)
>69	113 (13.6)

[a] Mean ± S.D. age, 45.1 ± 22.3 years.

Drug interactions. There were 89 life-threatening drug interactions, ranging in severity from category 1 to unclassified (Table 6).[5] As shown in the table, most interactions were category 3 events. In 54 (78%) of the drug interactions, usual dosages were used for the object and participant drugs. In addition, both drugs were administered orally in 59% of the interactions. In 44% of the cases, exposure to the interacting drugs lasted one to seven days. In 35% of the cases, the interacting drugs were used for less than 24 hours.

Medication errors. Of the medication errors identified, 42% were prescribing errors. In 48% of the errors, patients had been given the wrong dosage. Slips accounted for 71% of the errors. The principal cause of the errors was inattentiveness (68%).

Lawsuits. Lawsuits were reported in 1% of all cases. The defendants varied, and most cases were settled out of court. The range of settlements was $32,000 to $8 million, with a mean of $1,152,182.

Prevention. Nearly 50% of the drug-induced life threats could have been prevented. A pharmacist could have prevented half of the prevent-

able events. Preventability increased with the length of therapy and with patient age. A majority of the moderately ill or severely ill patients may have had their life threat prevented. For more than one third of these patients, the event might have been prevented by a pharmacist (Table 7).

Active, concurrent monitoring by a pharmacist may have prevented many of the drug-induced life threats (Table 8). Computer screening and an earlier discontinuation of the therapy were also major preventive mechanisms. All dispensing errors should have been prevented. Also, most (67%) of the medication errors associated with self-administration may have been avoided. Drug categories with a high potential for prevention were diagnostic agents (69%) and antineoplastic agents (65%). A pharmacist might have prevented half of these events. Also, 45% of ADRs and all drug interactions could have been prevented.

Discussion

The patients in this study affected by drug-induced threats to life were mostly middle-aged and only moderately ill. Plasma levels were available for most of the drugs that might have been associated with a life threat. However, drug levels were not measured very often. When blood was collected for testing, most patients had either high or very high levels of the offending drug in their blood. Furthermore, there was a need for more monitoring for overdoses and drug interactions. The study suggested that life-threatening combinations of drugs may be being prescribed that are not yet classified as posing a risk to the patient.

Middle-aged patients had a majority of the ADRs (with a usual dosage received in a majority of cases) and a large number of the allergic reactions. This age group had a majority of the life threats (almost three quarters involving normal dosages) caused by drug interactions and a

Table 2.
Drugs Most Commonly Suspected of Inducing Life Threats (LTs) (*n* = 846)

Drug	No. (%) LTs
Heparin	19 (2.2)
Methotrexate	15 (1.8)
Vancomycin	15 (1.8)
Phenytoin	13 (1.5)
Cyclosporine	11 (1.3)
Trimethoprim–sulfamethoxazole	11 (1.3)
Sulfasalazine	9 (1.1)
Carbamazepine	9 (1.1)
Dextran	9 (1.1)
Ibuprofen	8 (0.9)
Ritodrine	8 (0.9)
Lithium	8 (0.9)
Immune serum globulin	8 (0.9)
Valproic acid	8 (0.9)
Verapamil	8 (0.9)
Streptokinase	8 (0.9)
Aspirin	8 (0.9)
Other	671 (79.3)

Table 3.
Dosages Used in Cases of Drug-Induced Life Threats (LTs) (*n* = 654)

Dosage	No. (%) LTs
Below usual	47 (7.2)
Usual[a]	536 (82.0)
Two to three times usual	36 (5.5)
More than three times usual	35 (5.4)

[a]As listed in reference 4.

Table 4.
Onset of Drug-Induced Life Threats (LTs) after Initiation of Suspected Drug (*n* = 564)

Time of Onset (Days)	No. (%) LTs
<1	70 (12.4)
1–7	161 (28.5)
8–31	156 (27.7)
32–365	133 (23.6)
>365	44 (7.8)

Table 5.
Drug-Induced Life Threats (*n* = 846)

Life Threat	No. (%)
Anaphylaxis	101 (11.9)
Thrombocytopenia	61 (7.2)
Renal failure	58 (6.9)
Hemorrhage	27 (3.2)
Hypotension	25 (3.0)
Neutropenia	25 (3.0)
Pulmonary edema	25 (3.0)
Anaphylactoid reaction	23 (2.7)
Agranulocytosis	23 (2.7)
Toxic epidermal necrolysis	22 (2.6)
Stevens-Johnson syndrome	19 (2.2)
Cardiac arrest	18 (2.1)
Pseudomembranous colitis	17 (2.0)
Erythema multiforme	17 (2.0)
Respiratory failure	16 (1.9)
Other	369 (43.6)

Table 6.
Drug Interactions Suspected of Contributing to Life Threats (LTs) (*n* = 89)[a]

Severity Level, No. (%) LTs[5]	Definition	Object Drug	Participant Drug or Food
Category 1, 2 (2.2)	Avoid combination. Risk always outweighs benefit.	Disulfiram	Ethanol
		Itraconazole	Terfenadine
Category 2, 9 (10.0)	Usually avoid combination. Use combination only under special circumstances.	Carbamazepine	Diltiazem
		Clarithromycin	Ergotamine
		Cyclophosphamide	Indomethacin
		Enalapril	Allopurinol
		Levastatin	Gemfibrozil
		Methotrexate	Probenecid
		Methotrexate	Naproxen
		Selegiline	Meperidine
		Warfarin	Metronidazole
Category 3, 42 (47.2)	Minimize risk. Take action as necessary to reduce risk.	Acetaminophen	Warfarin
		Amiodarone	Digoxin
		Carbamazepine	Erythromycin
		Chlorpropamide	Trimethoprim–sulfamethoxazole
		Cimetidine	Methadone
		Ciprofloxacin	Warfarin
		Clarithromycin	Disopyramide
		Clonidine	Chlorpromazine
		Clonidine	Haloperidol
		Colchicine	Erythromycin
		Cyclosporine	Diltiazem
		Digoxin	Alprazolam
		Digoxin	Erythromycin
		Digoxin	Itraconazole
		Digoxin	Quinidine
		Diltiazem	Digoxin
		Dipyridamole	Adenosine
		Disopyramide	Erythromycin
		Ibuprofen	Lithium
		Isoniazid	Cheese
		Indomethacin	Bumetanide
		Methotrexate	Trimethoprim
		Methotrexate	Trimethoprim–sulfamethoxazole
		Metoprolol	Fluoxetine
		Metoprolol	Verapamil
		Midazolam	Sufentanil
		Nifedipine	Magnesium
		Norfloxacin	Theophylline
		Phenytoin	Amiodarone
		Phenytoin	Chloramphenicol
		Phenytoin	Cimetidine
		Propranolol	Fluoxetine
		Roxithromycin	Digoxin
		Sotalol	Diltiazem
		Streptomycin	Pancuronium
		Terfenadine	Itraconazole
		Valproic acid	Erythromycin
		Warfarin	Ciprofloxacin
		Warfarin	Erythromycin
Category 4, 7 (7.9)	No action needed. Risk of adverse outcomes appears small.	Aspirin	Ibuprofen
		Cimetidine	Morphine
		Clonazepam	Phenobarbital
		Haloperidol	Propranolol
		Phenytoin	Ibuprofen
		Phenelzine	Propoxyphene
		Verapamil	Dantrolene
			Ibuprofen
			Dantrolene
Category 5, 4 (4.5)	Evidence suggests no interaction.	Ciprofloxacin	Theophylline
		Nifedipine	Ranitidine
		Ranitidine	Kava
		Warfarin	Bendroflumethiazide

Continued on next page

Table 6 (*continued*)

Severity Level, No. (%) LTs[5]	Definition	Object Drug	Participant Drug or Food
Unclassified, 25 (28.1)	Not listed.	Alprazolam	Magnesium
		Aminoglutethimide	Tolbutamide
		Aminoglycoside	Metoclopramide
		Apozone	Buspirone
		Chlorpromazine	Pancuronium
		Clozapine	Thiotepa
		Colistin	Pancuronium
		Cyclophosphamide	Vecuronium
		Cyclosporine	Phenylephrine
		Cyclosporine	Levopromazine
		Halothane	Amiloride
		Haloperidol	Trimethoprim–sulfamethoxazole
		Hydochlorothiazide	Ethanol
		Ibuprofen	Cancer drugs
		Ibuprofen	Fentanyl
		Levamisole	Clozapine
		Lidocaine	Bupivacaine
		Methimazole	Glycopyrrolate
		Ritodrine	Halothane
		Ritodrine	Local anesthetic
		Theophylline	Acarbose
		Verapamil	
		Warfarin	

[a]There was one life threat per drug or food pair, except for methotrexate and trimethoprim (two life threats), methotrexate and trimethoprim–sulfamethoxazole (three), and levamisole and cancer drugs (three).

third of all medication errors. This age group may differ in specific ways, such as in the chemical makeup of liver enzymes participating in drug metabolism.

The finding that most of the drug-induced life threats were associated with usual dosages seems particularly striking. Perhaps some critical variable may have been overlooked in this group of patients, such as renal function, liver function, or complete blood count. These tests should be performed at baseline before any potentially toxic drug is initiated.

The observation that many events involved the oral route is also intriguing. In fact, more orally administrated drugs caused life threats at normal dosages than drugs administered by injection. A higher proportion of drugs may be administered orally. A controlled study is needed to examine this finding.

In several cases in which a plasma drug level was monitored and reported, the level was found to be either high or very high compared with the therapeutic range. This would lead one to believe that there was something wrong with the patient's metabolic or elimination system or that the drug was administered in a larger than normal amount. A majority of the most commonly reported drugs are inherently toxic and can be monitored by plasma levels. Plasma drug monitoring was available for most of the top offending drugs (vancomycin, methotrexate, phenytoin, carbamazepine, lithium, and valproic acid), but only 24% of drugs associated with a life threat were monitored by plasma levels.

Many of the life threats that occurred could have been prevented. For example, thrombocytopenia might have been prevented by continual blood-count monitoring. Other life threats, such as agranulocytosis and neutropenia, could have been identified at baseline or early during therapy. Blood pressure could have been monitored to avoid severe hypotension, prothrombin time checked more often to prevent hemorrhaging, and renal tests carried out, especially in patients with underlying renal impairment.

Half of the life threats involved ADRs; this was expected. However, there were more allergic reactions and fewer errors than expected. The proportion of drug interactions was consistent with what was expected. The finding of fewer medication errors than expected could have resulted from a lack of reporting.

Central-nervous-system agents were responsible for almost a third of all ADRs and, together with anti-infectives, accounted for close to half of all allergic reactions. These two categories of agents should be monitored more closely.

Since cardiovascular and central-nervous-system agents were used together in a majority of interactions causing a life threat, these two therapeutic classes must also be considered high priority for monitoring.

Many drug interactions were unclassified, probably because drugs used in anesthesia and radiology are not covered by *Hansten and Horn's*

Table 7.
Preventability of Drug-Induced Life Threats (LTs) (*n* = 816)

Patient Status[a]	No. Patients (%)	No. (%) LTs	
		Preventable	Preventable by Pharmacist
Healthy	74 (9.1)	21 (28.4)	5 (23.8)
Moderately ill	619 (75.9)	325 (52.5)	170 (52.3)
Severely ill	123 (15.1)	64 (52.0)	30 (46.9)

[a]There were no terminally ill patients.

Table 8.
Possible Mechanisms for Preventing Drug-Induced Life Threats (LTs) (*n* = 424)

Mechanism	No. (%) LTs
Improved patient monitoring	94 (22.2)
Computer screening	77 (18.2)
Earlier discontinuation of therapy	55 (13.0)
Improved laboratory test monitoring	37 (8.7)
Patient risk assessment	35 (8.3)
Patient counseling	23 (5.4)
Use of more appropriate drug	20 (4.7)
Other	83 (19.6)

Drug Interactions Analysis and Management.[5] Pharmacists and other health care professionals may not be able to limit these life threats if such interactions are not listed. Further study of the unclassified interactions found to be associated with a life threat is needed.

Most of the interactions were in category 3 (and involved usual dosages, in most cases). Such interactions are supposed to have minimal risk, yet they caused a life threat. Pharmacists should seriously consider category 3 interactions when monitoring patients, since slight risk is applicable to overall populations, not individuals. Since most of the drug interactions involved an exposure time of 1.1 to 7 days, early subjective and objective monitoring may have been effective in reducing the risk of an ADE.

Most of the errors were in the area of prescribing. Almost all errors were slips, in which the clinician knew better but for some reason was inattentive. Thus, a second person, such as a pharmacist, could help avoid these errors.

Litigation was associated with the drug-induced life threat in only 1% of cases. Litigation may be underreported because of the nature of settlements and the need to avoid negative publicity.

A pharmacist could have prevented the life-threatening event for a significant number of the patients in this study, including patients who were healthy before receiving the offending drug. This finding represents a profound opportunity for pharmacists. For example, a type A reaction was recorded for many ADRs. This means that the life threat was dose related and thus could have been prevented by computerized screening or a pharmacist.

Some patients received overdoses, some were victims of errors, some had drug interactions, and some received drugs to which they were allergic. However, what is the explanation for the numerous middle-aged, relatively healthy patients with normal renal function who received normal dosages and still had a life threat? Similar results were reported for fatal ADEs and drug-induced permanent disabilities.[1,2] One explanation is that these seemingly normal patients had abnormalities in the enzymes responsible for metabolizing the drug or drugs suspected of causing the life threat.

Further study with more rigorous epidemiologic methods (case–control or cohort study) is needed to investigate the true risk factors for drug-induced life threats, and there is a need for standardized reporting methods. A controlled study of risk factors for ADEs in general has been reported, but it was limited and did not specifically address drug-induced life threats.[6]

The limitations of this study are similar to those listed for the study described in part 1.[1] Notwithstanding the limitations, there is considerable information here that can be used by pharmacists to help screen for patients who may be at risk for drug-induced threats to life.

Conclusion

A review of published case reports of ADEs for 1977-97 yielded information on possible risk factors for drug-induced life threats and on which events may have been preventable.

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Appendix A—Critical laboratory test values

Life Threat	Value
Anemia (severe)	Hemoglobin conc., <7 g/dL
Apnea	Carbon dioxide partial pressure, >50 mm Hg
Atrial fibrillation	160–200 beats/min or evidence of complications
Bradycardia (severe)	Heart rate, <40 beats/min
Hypercalcemia	>14 mg/dL
Hypocalcemia	<7.0 mg/dL
Hyperkalemia	>6.5 mg/dL
Hypokalemia	<2.5 mg/dL
Hypernatremia	>150 mg/dL
Hypertensive crisis	>120 mm Hg (diastolic)
Hypoglycemia	<50 mg/dL
Hyperglycemia	>500 mg/dL
Hypermagnesemia	>6 meq/L
Hyperuricemia	>15 mg/dL
Hyponatremia	<125 mg/dL
Hypotension	<80 mm Hg (systolic)
Hypothermia	<95 °F (core temperature)
Leukopenia	<2500
Neutropenia	<500
Renal failure	Blood urea nitrogen conc., >150 mg/dL
Thrombocytopenia	<20,000 cells/mL

Appendix B—Screening diagnoses for possible drug-induced life threats

Agranulocytosis
Anaphylactoid reaction
Anaphylaxis
Angioedema
Aplastic anemia
Apnea
Arrhythmia
Asphyxia
Asthma
Asthmatic reaction
Asystole
Ataxia
Atrial fibrillation
Azotemia
Bowel perforation
Bradycardia
Bronchospasm
Cardiac arrest
Cardiac collapse
Cardiac depression
Cardiomyopathy
Cardiopulmonary complications
Cardiorespiratory disturbance
Cardiovascular shock
Cerebral edema
Cerebral infarction
Coma
Cyanosis
Cytopenia
Diabetes insipidus
Encephalopathy
Epiglottitis
Erythema multiforme
Fulminant colitis
Glomerulonephritis
Heart block
Heart failure
Hemolysis
Hemolytic anemia
Hemolytic uremic syndrome
Hemorrhage
Hepatitis
Hepatomegaly
Hepatotoxicity
Hyperammonemia
Hypercalcemia
Hyperglycemia
Hyperkalemia
Hyperpyrexia
Hypertension
Hypertensive crisis
Hypoglycemia
Hypoglycemic coma
Hyponatremia
Hypotension
Hypoxia
Lactic acidosis
Liver damage
Liver failure
Lupus erythematosus
Lupus-like syndrome
Malignant hyperthermia
Manic syndrome
Meckel's diverticulum
Megaloblastic anemia
Meningitis
Methemoglobinemia
Myocardial infarction
Myopathy
Myxedema coma
Nephritis
Nephrotic syndrome
Nephrotoxicity
Neuroleptic malignant syndrome
Neuromuscular blockade
Neuropathy
Neutropenia
Nystagmus
Oliguria
Pancytopenia
Paralysis
Paralytic ileus
Perforated colon
Peritonitis
Platelet dysfunction
Pneumonitis
Porphyria
Pseudomembranous colitis
Pulmonary damage
Pulmonary disease
Pulmonary edema
Pulmonary infiltration
Red-blood-cell aplasia
Renal failure
Renal impairment
Respiratory depression
Respiratory failure
Seizure
Shock
Sinus arrest
Status epilepticus
Stevens-Johnson syndrome
Stupor
Syncope
Tachycardia
Thrombocytopenia
Thrombosis
Torsades de pointes
Toxic epidermal necrolysis
Toxic shock syndrome
Ulcer
Urticaria
Vasculitis
Ventricular fibrillation