
Clinical Toxicology of Drugs:

Principles and Practice

VASILIOS A. SKOUTAKIS, PHARM.D.

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Foreword

During the past two decades, the practice of pharmacy has emerged into patient services, and clinical aspects of drug therapy and management have become a part of the student's background. A knowledge of the toxicologic problems that drugs and other agents can pose must go hand in hand with the study of the proper and appropriate therapeutic approaches to the treatment of the ill, diseased, or injured patient. At times, only a delicate line separates a clinically desired event from a harmful or toxic manifestation of the drug. Students of pharmacy and the pharmacy practitioner are offered a unique opportunity to become actively involved in the provision of patient-oriented services in clinical toxicology.

The discipline of toxicology, which dates back to ancient times, has currently advanced to an extremely important position in contemporary society. Acute intoxications of children and deliberate suicidal and homicidal overdoses by adults constitute a continuing source of morbidity in the United States and around the world. Similarly, drug abuse, drug addiction, adverse drug effects, chronic drug intoxications, and hazards related to environmental and industrial chemicals all contribute, not only to a number of serious health problems, but to the total cost of national health care. Prevention of toxic events and

proper treatment of poisonings can help reduce the tragic consequences of death and suffering while reducing the economic cost to the families of the patients involved.

At the present time, many disciplines are involved in instruction, research, training, and services in toxicology. Physicians, nurses, pharmacologists, dentists, veterinarians, chemists and biochemists, public health scientists, and pharmacists are all contributing to the rapid development of different specialty areas of toxicology. However, there are relatively few trained scientists, educators, and practitioners available to provide patient-oriented services and public health education in the area of clinical toxicology.

The pharmacist, with his or her background in the basic sciences of pharmacology, physiology, biochemistry, and chemistry, as well as clinically oriented courses in drug therapy and adverse drug reactions, is in a unique position to act in the field of clinical toxicology. In fact, in many communities in this nation, the pharmacy may be the only public health center, and thus the pharmacist may become the first person contacted in the event of an intoxication. Through these pharmacies, both in the community and in certain hospital settings, the practicing

pharmacist is often called to provide poison information, drug abuse programs, and programs that deal with public health problems.

Presently, most of the colleges of pharmacy in this country can offer one or more courses in toxicology, including clinical toxicology, with rotations of students in poison centers, and even in hospital emergency wards. Through these educational programs and experiences, the emerging pharmacist can become a key figure in all aspects of clinical toxicology.

A number of valuable texts on toxicology have been written to train pharmacists and other health care professionals in the mastery of the cognitive concepts in toxicology. For the most part, these texts have dealt with basic aspects of toxicology. A few texts in the past have dealt with clinical aspects of toxicology; a more modern approach to the subject, however, emphasizing not only principles of toxicology, but dealing also with intoxicated patients and the toxicology laboratory, has not been available.

The textbook, *Clinical Toxicology of Drugs: Principles and Practice*, provides the student, educator, and practitioner with the information needed to pursue and practice patient-oriented toxicology. Dr. Skoutakis has masterfully produced a book of clarity and thoughtful organization, dealing with commonly seen drug-related intoxications. This book will become a valuable addition to the reference library of the pharmacist, whether he or she practices in a community setting or in an institution. The text should also take a prominent position in various other resource centers, such as poison control centers, hospital emergency rooms, public health offices, and centers and institutions dealing with health care. Finally, the text will be an excellent supplement to courses dealing in clinical toxicology.

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The physician in almost any branch of medicine today faces the eventuality of being confronted with the drug-intoxicated patient. Such situations frequently are medical emergencies with life-threatening potential, requiring prompt therapeutic measures. In an age when hundreds of new drugs are marketed annually, it has become virtually impossible for the physician to be familiar with the pharmacodynamics of more than a few of these agents.

In addition, clinical toxicology has become a complex subject, involving not only a myriad of drugs with a variety of actions, but also taking into consideration the effects of drug interactions, routes of excretion, and alterations in drug metabolism by such variables as kidney or liver disease. The best approach to the problem for the physician would appear to be the development of fundamental

knowledge of the principles of management of the intoxicated patient, coupled with a readily available reference of the more commonly seen overdoses.

To this extent, *Clinical Toxicology of Drugs: Principles and Practice* succeeds admirably. Dr. Skoutakis is to be commended for not attempting to provide an exhaustive review of all possible agents, better left to the reference library or poison center. Instead, the approach taken here provides the student and physician alike with a clinically oriented and practical text that should prove invaluable to some and useful to all.

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Preface

Accidental drug ingestions by children and deliberate suicidal and homicidal drug intoxications and overdosages by adults are numerous in this era of drug-oriented society, and such incidents constitute a continuing source of morbidity and mortality. In 1977 in the United States alone, 12,866 people died from accidental, suicidal, and homicidal intoxications.

The management of these patients places a considerable burden on the physician, both inside and outside the hospital, because (1) little time in the medical school curriculum is devoted to clinical toxicology, (2) the number and variety of new chemicals and drugs to which patients can be exposed is unlimited, and frequently the names, characteristics, and toxic effects of these new agents are unfamiliar to physicians, and (3) specific information concerning formulations, toxicity, symptoms, and treatment of intoxicated patients may not be available from the chemical and pharmaceutical industries. Therefore, one of the challenges facing medicine and other health care professions today is to keep up to date with new information regarding current trends and promising developments in the prevention, detection, diagnosis, and treatment of intoxicated patients.

The primary concern of the clinical toxicologist is the rational management of the intoxicated patient. It is from this viewpoint that *Clinical Toxicology of Drugs: Principles and Practice* was written. Portions of the material and/or topics appearing in this textbook were initially published in the *Clinical Toxicology Consultant*, a journal of which I am editor and publisher. The textbook, as its title implies, is clinically oriented and deals with both the general considerations and principles of management of the intoxicated patient (Section I), as well as with the management of specific drug overdosages (Section II). It is designed for students and practitioners of all areas of health care.

For the students, its goal is to assist them (1) to acquire a thorough knowledge and understanding of clinical toxicology through an integrated study of physiology, pathology, pharmacology, and pharmacokinetics, (2) to establish a knowledge base with regard to problem solving; that is, the ability to use data obtained from the patient or laboratory to formulate a reasonable interpretation of the patient's clinical condition, and (3) to develop a rational therapeutic plan for the management and monitoring of intoxicated patients.

As for the practitioners, its goals are (1) to assist them in dealing quickly and effectively with the rational management of intoxicated patients, and (2) to serve them as a reference source in their daily practice.

This book is personal in many ways and carries with it a permanent sense of deep gratitude to many people: To my wife, to whom this book is dedicated, for her patience, love, support, and understanding throughout the years; to my parents, brothers, and sisters for their love, encouragement, and constant support; to those teachers who along the way had the desire, motivation, and skill to urge me to set high academic standards in the pursuit of excellence; to Drs. Sergio R. Acchiardo, Sidney A. Rosenbluth, Domingo R. Martinez, and Gary W. Cripps for their friendship, counsel, wisdom, knowledge, and skill, as well for the educational opportunities they provided for me while I was a student; to the late Dr. James A. Leventis, a true friend, whose memory and influence will always remain with me; to the late Dean of The College of Pharmacy, Dr. Sheldon D. Feurt, for the counsel, educational opportunities, and support he provided for me, both as a student and a faculty member; and last, but not least, to all of my students, residents, and fellows who allowed me the great privilege of teaching them and learning together with them.

In preparation for this book, I imposed on the friendship of many of my colleagues, both for their contributions to specific chapters in their areas of expertise and for their review and criticism of each chapter: Drs. S.R. Acchiardo, G.E. Bass, Jr., J. Bell, G.J. Burckart, P.A. Czajka, B.R. Ekins, J.I. Escobar, R.L. Kingston, W. Klein-Schwartz, A.S. Manoguerra, D.R. Martinez, J.B. Mowry, G.M. Oderda, K. Saxena, L.J. Sioris, I.S. Sketris, S. Ternullo, M.I.B. Thompson, J.C. Veltri, B.D. White, and N. Wojciechowski; their assistance, skill, and willingness to participate are greatly appreciated. My special appreciation also goes to Dr. John Autian, Dean of the College of Pharmacy; Dr. George C. Wood, Chairman, Department of Drug and Material Toxicology; and Dr. Fred E. Hatch, Jr., Professor of Medicine and Nephrology, and Chief, Division of Nephrology, for their support and encouragement in the preparation of this textbook.

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Section I

The Intoxicated Patient

Toxic Emergencies: Principles of Treatment

Vasilios A. Skoutakis

Accidental intoxications by children and deliberate suicidal and homicidal overdoses by adults constitute continuing sources of morbidity and mortality in the United States. Recent national statistics attest to this problem. Data from the National Center for Health Statistics, Mortality Statistic Branch, reveal that 12,866 people died in 1977 due to accidental, suicidal, and homicidal intoxications. The deaths of all ages from accidental, suicidal, and homicidal intoxications and from undetermined intent in 1977 are summarized in Table 1-1.¹

From the reported findings, it is clear that increased efforts must be made to prevent the incidents of accidental overdoses and reduce the morbidity and mortality due to suicidal and homicidal overdoses. However, despite all precautions, accidental, suicidal, and homicidal intoxications/overdoses will continue to remain an important problem in our society, one which every clinician must be prepared to treat promptly and effectively. Furthermore, there are few areas in pediatric and adult medicine in which a patient's survival is more directly correlated with proper management than in cases of intoxication.

When the intoxicated pediatric or adult patient is presented to a clinic or a hospital facility for treatment, he may be asymptomatic, symptomatic but awake, semicomatose, or comatose. The first priority for the clinician in the management of the patient is to assess and treat the patient according to his clinical status and not the intoxicant ingested. Furthermore, the management of pediatric and adult intoxicated patients is similar, except that volumes of fluid or medications administered to

Table 1-1. Deaths Due to Ingestions in 1977.

TYPES OF INGESTION	SUBSTANCES INVOLVED	NUMBER OF DEATHS
Accidental in children under 5 years of age	Solid and liquid substances (including drugs)	94
	Gases and vapors	35
Accidental for all ages	Solid and liquid substances (including drugs)	3,374
	Gases and vapors	1,596
Suicidal	Barbiturates	847
	Salicylates and congeners	73
	Antidepressants, tranquilizers, other psychotherapeutic agents	520
	Other drugs	1,685
	Non-drug solid and liquid substances	754
	Gases and vapors	2,608
	Barbiturates	118
	Salicylates	31
	Antidepressants, tranquilizers, other psychotherapeutic agents	85
	Other drugs	577
Undetermined intent for all ages	Total non-drug solid and liquid substances	277
	Total gases and vapors	295
	Drugs, other solids, liquids, and gases	46
Total number of deaths in 1977		12,866

pediatric patients must be adjusted to be appropriate to body size and/or weight.

THE ASYMPTOMATIC OR SYMPTOMATIC BUT AWAKE PATIENT

In some cases, when brought to a clinic or an emergency room (ER), the intoxicated patient may be asymptomatic because a sufficient dose or quantity of the intoxicant has not been ingested, or because not enough of the intoxicant has been absorbed to produce significant signs and symptoms. In other cases, the intoxicated patient may have a variety of signs and symptoms but will be awake. The variability of signs and symptoms in such a patient can be attributed to the intoxicant ingested, the time elapsed since ingestion, the amount ingested, the method by which the intoxicant was taken (e.g., orally, intravenously, or through inhalation), and the patient's prior medical history (e.g., diabetes, hepatitis, asthma, heart disease, renal disease, or traumatic experience, particularly to the head).

Therefore, when such an intoxicated pa-

tient is presented to a clinic or an ER, and prior to the initiation of any therapeutic measures, the vital signs (e.g., respiration, blood pressure, pulse rate, and temperature) must be checked and recorded, and a quick physical examination of the head, lungs, heart, abdomen, and central nervous system (CNS) should be performed and evaluated. In addition, pertinent information should be obtained from the patient, if possible, or from the person(s) who brought the patient in for treatment, regarding the patient's past medical history, therapeutic drug history, and intoxicant(s) ingested. Unfortunately, sometimes even when a friend or family member accompanies the intoxicated patient, the history obtained may be unreliable or unknown, or the patient may be uncooperative. In such cases, prior hospital admissions or the use of toxicology laboratory can be of valuable assistance.

EMESIS OR GASTRIC LAVAGE

Once the clinical condition of the intoxicated but alert and awake patient has been

assessed and stabilized, the next step should be to remove the toxic ingestant from the patient's stomach before significant absorption can occur. Evacuation of the stomach can be accomplished by the induction of emesis or by gastric lavage. It is now clear that gastric lavage, although more predictable and immediately active, is less effective than emesis in removing the toxic ingestant from a patient's stomach, because the stomach normally traps large quantities of the toxic ingestant in several pouches inaccessible to the lavage tube.^{2,3}

Syrup of ipecac. The most effective way to induce emesis is by the administration of syrup of ipecac (not the fluid extract, 14 times more concentrated).⁴ The recommended dose of syrup of ipecac is 10 ml orally for children 1 year of age, 15 ml orally for children 1 to 5 years old, and 15 to 30 ml for children over 5 years old. The recommended dose for adults is 30 ml

orally. It should be followed by one or two glasses of water, because ipecac only works effectively on a full stomach (administering ipecac on an empty stomach is like squeezing an empty balloon). The emetic action of syrup of ipecac has an average latent period of 20 to 30 minutes and depends in part on gastrointestinal (GI) absorption.^{4,5} Therefore, ipecac cannot be used in conjunction with other therapeutic measures intended to minimize absorption of the ingestant. A second dose of ipecac should be administered if no vomiting occurs after 20 to 30 minutes. The initial emesis should be placed in a disposable container and sent to the toxicology laboratory for confirmation of the intoxicant ingested when warranted. Vomiting should be induced even if several hours (4 to 6) have elapsed after ingestion, since many substances when ingested in large quantities not only can remain for a long period in the stomach in

Table 1-2. Commonly Ingested Corrosives and Petroleum Distillates.

CLASSIFICATION	COMMON PRODUCTS		TREATMENT
Corrosives/caustics	Acids	Automobile battery acid	Immediately irrigate all exposed areas or contaminated tissues. Do not induce emesis. Administer orally milk or water or both.
		Hydrochloric acid	
		Phenol	
		Toilet bowl cleaners	
	Bases	Ammonia	Immediately irrigate all contaminated tissue, or administer orally water or milk or both. Do not give acids (e.g., vinegar) to neutralize alkali products or bicarbonate (baking soda) to neutralize acidic products. This method produces heat and more tissue damage. Do not induce emesis. Do not administer activated charcoal. Do not perform gastric lavage. Discourage oral administration of large amounts of fluids, since this may induce emesis.
		Ammonium hydroxide	
		Chemical drain openers	
		Chemical oven cleaners	
		Copper sulfate, sodium hydroxide (Clinitest tablets)	
		Electric dishwasher detergent granules	
Petroleum distillates (Hydrocarbons)		Lye	Do not induce emesis if ingested dose is not greater than 1 ml/kg of body weight. Avoid oral administration of large volumes of fluid. This may cause emesis. Avoid administration of oils. Obtain chest roentgenogram. Implement supportive and symptomatic care as indicated.
		Potassium hydroxide	
		Sodium hypochlorite (active ingredient in household bleach)	
		Furniture polish	Do not induce emesis if ingested dose is not greater than 1 ml/kg of body weight. Avoid oral administration of large volumes of fluid. This may cause emesis. Avoid administration of oils. Obtain chest roentgenogram. Implement supportive and symptomatic care as indicated.
		Gasoline	
		Kerosene	
		Mineral seal oil	
		Lighter fluid	

the form of mass concentrations but can also decrease GI transit time, resulting in a prolongation of the toxicologic manifestations and increasing the risk of possible complications.

Administration of syrup of ipecac is contraindicated if loss of the gag reflex has occurred and in severely depressed or convulsing patients, because of the danger of tracheal aspiration of vomitus. Syrup of ipecac is also contraindicated in patients who have ingested corrosives, because of tissue damage,⁶ or liquid hydrocarbons if the amount ingested is *not* greater than 1 ml/kg of body weight, because they are potent lung irritants.⁷ The commonly available and frequently ingested corrosives and petroleum distillate products and their treatment are summarized in Table 1-2. If significant CNS depression intervenes between the administration of syrup of ipecac and the occurrence of vomiting, the airway must be protected by insertion of a cuffed endotracheal tube to avoid aspiration pneumonia. In such cases, the patient should be admitted and treated as in the comatose situation discussed later in the chapter.

Other emetics. Other methods and/or agents that have been used for the induction of emesis are mechanical gagging and administration of apomorphine, copper sulfate, sodium chloride, mustard powder, raw eggs, and soapy water.⁸⁻¹⁰ Mechanical induction of vomiting by gagging is not the method of first choice because it is so often ineffective.⁸ The administration of apomorphine, 0.06 mg/kg intramuscularly (IM), tends to produce vomiting within 5 minutes, and administration of 0.01 mg/kg intravenously (IV) results in immediate action.^{5,9} However, it is not recommended as the agent of choice because of its CNS and respiratory-depressant effects and because it is not readily available. Emetics such as copper sulfate, sodium chloride, mustard powder, raw eggs, and soapy water, are ineffective, potentially dangerous, and should not be

used.¹⁰ Again, syrup of ipecac is the drug of choice; it is safe enough for home use and can be purchased without a prescription.

PREVENTION OF ABSORPTION

Since neither emesis nor gastric lavage empties the stomach completely, prevention of absorption by trapping of the ingested intoxicant should be initiated in all intoxicated patients after the induction of emesis.

Activated charcoal. Because it absorbs most intoxicants in the GI tract and prevents their absorption into the blood stream, activated charcoal is the drug of choice.¹¹⁻¹³ The theoretical dose is 5 to 10 times the estimated toxic weight of the ingested intoxicant. However, since in the clinical setting the ingested dose of the intoxicant is usually not known, the activated charcoal dose is 30 to 50 g for adults and 30 g for children, and is administered orally in a slurry with water. The administration of activated charcoal should be carried out slowly over a period of 15 minutes, in order to minimize possible gastric distention and resultant emesis, which can cause the patient to aspirate some of the charcoal contents. Activated charcoal also can serve as a marker of intestinal transit time, and when it appears in the stool, it indicates that further absorption of the intoxicant from the intestinal tract will not occur. There are no known contraindications to the use of activated charcoal. However, substances such as corrosives, petroleum distillates, alcohols, lead, and iron do not adsorb to activated charcoal. Its administration therefore is not recommended in patients who have been intoxicated by any of these substances either alone or in combination with other intoxicants.

Catharsis. Another useful way to prevent further absorption of the ingested intoxicant is to administer a saline cathartic. Saline cathartics promote intestinal