COLOR ATLAS OF HUMAN POISONING AND ENVENOMING

JAMES H. DIAZ

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Preface

The field of medical toxicology can be simply divided into animal and human poisonings from animal, plant, or man-made sources. Even more precisely, toxinology is the study of poisoning and envenoming by biological organisms, and toxicology is the study of human poisoning from manmade sources. Living organisms, such as animals, plants, and fungi, produce biological toxins. Man-made toxins, or toxoids, are produced by controlled chemical reactions, often on an industrial scale, designed to produce novel pharmaceuticals, cosmetics, household cleansers, fertilizers, herbicides, pesticides, and other useful and necessary consumer and commercial products. Unfortunately, some biological toxins have already been developed, deployed, and used as bioterror weapons (e.g., ricin from the castor bean and Shiga toxin from Shigella bacteria). Other biological toxins, most notably Staphyloccal toxins A and B, botulinum toxins, and a variety of fungal mycotoxins, can be mass-produced by rogue nations for biological warfare and agricultural and antipersonnel terrorism. Many biological toxins, such as poison hemlock, pyrethrin, and red squill, and man-made toxoids, such as arsenic and thallium salts and pyrethroids, have long been used as pesticides, fungicides, and even as human poisons. Several types of poison gases, including both vesicant and neurotoxic agents, were intentionally released during World War I and in very recent wars (Iran-Iraq War) and terror attacks (Sarin nerve gas attacks in Japan).

This book will serve as a visual and written reminder of the ubiquitous sources of toxins and toxoids in the environment and the outcomes of accidental or intentional toxic exposures in humans. This book will not serve as a comprehensive, major reference source for all toxicologic emergencies; many such comprehensive and even subspecialized toxicology texts are now available. The key features and benefits of this book include serving as a handy atlas and review outline of human poisoning with photographs and diagrams of toxic plants and animals, their mechanisms of poisoning or envenoming, and the human lesions (anatomic, electrocardiographic, and radiographic) caused by toxic exposures. In addition, this text combines the four subspecialties of toxicology (Analytical, Medical, Environmental, and Industrial) into one comprehensive atlas with bulleted text, tables, and figure legends that treat toxic exposures in both children and adults. This book will be a useful study guide for emergency physicians, military physicians, pediatricians, public health physicians and veterinarians, and health science and medical students and graduates in training or practice, or preparing to take image-intense specialty or subspecialty board examinations. Finally, this text will serve as a ready reference for current health science students who seek immediate visual association of venomous species and toxicokinetics with the rapid identification of envenoming species, the clinical and diagnostic outcomes of envenoming or poisoning, and the recommended treatment strategies to limit toxic exposures and injuries.

This text is intentionally organized in a clinical encounter fashion, beginning with a discussion of general poisoning management and useful antidotes and later detailing specific management strategies and antidotes for separate poisonings and envenomings. The book concludes with chapters on biochemical warfare agent exposure and research design and analysis. Biological and chemical terrorism and warfare agents are timely subjects that are still evolving, particularly in the areas of early detection by biosurveillance monitoring systems and real-time polymerase chain reaction (PCR) analyses and personnel protection by preventive immunization, rapid decontamination, specific reversal agents, and personal protective equipment.

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About the Author

A native of New Orleans, Louisiana, Dr. James H. Diaz earned several degrees with distinction from Tulane University, including Bachelor of Science, Doctor of Medicine, Master of Health Administration, Master of Public Health and Tropical Medicine, Diploma in Clinical Tropical Medicine and Travel Health, and Doctor of Public Health. Dr. Diaz is board-certified in anesthesiology, critical care medicine, pain management, general preventive medicine and public heath, occupational and environmental medicine, and medical toxicology. He currently serves as Professor of Public Health and Program Head, Environmental and Occupational Health Sciences, at the Louisiana State University (LSU) Schools of Medicine and Public Health in New Orleans, Louisiana, and as Adjunct Professor of Pathobiological Sciences at the LSU School of Veterinary Medicine in Baton Rouge, Louisiana.

Dr. Diaz has published more than 100 original articles and chapters in scientific journals and textbooks and is the editor and primary contributing author of Perinatal Anesthesia and Critical Care, W.B. Saunders, Company, 1991. Dr. Diaz's current clinical interests include the practices of general preventive medicine and public health, occupational medicine, environmental and travel medicine, and medical toxicology. His current academic interests include: (1) occupational and environmental cancer and injury risk factors; (2) environmental and tropical diseases of travelers; (3) emerging environmentally associated infectious diseases, particularly food-borne, waterborne and vector-borne communicable diseases; (4) human envenomings; and (5) poisonings with natural, alternative, and over-the-counter pharmaceuticals. In 2001, Dr. Diaz was elected to lifetime membership in Delta Omega, the national public health honor society, for academic scholarship and contributions to population health promotion, disease and injury prevention, and preventive medical practice.

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Definitions

Xenobiotics: Foreign, natural, or man-made (synthetic) chemicals, including drugs, pesticides, environmental, and industrial agents.

Pharmacokinetics: The application of mathematical models to describe and predict the behavior of drugs during their absorption, distribution, metabolism, and elimination.

Pharmacodynamics: The relationships of drug concentrations to their observed clinical effects.

Toxicokinetics: The application of mathematical models to describe and predict the behavior of xenobiotics in toxic or excessive doses during their absorption, distribution, metabolism, and excretion.

Toxicodynamics: The relationships of toxic concentrations of xenobiotics to their observed clinical effects.

Absorption

Routes of Absorption

Enteral Administration

Oral: Variable absorption, yet most commonly used route; subjects all xenobiotics to first-pass hepatic metabolism; oral doses often diluted by foods; intestinal absorption delayed by enteric coatings, drug concretions and bezoars, anticholinergics, sedatives, and drug-induced pylorospasm.

Sublingual: Xenobiotics enter systemic circulation closer to the central nervous system (CNS) without first pass, avoiding gastric delays and inactivation. Example: nitroglycerin (NTG).

Rectal: Also avoids gastric delays and inactivation; useful during nausea and vomiting; provides shortcut to central circulation and reduces first pass by 50%.

Parenteral Administration

Intravascular: Intravenous route (iv) most commonly used; avoids both gastrointestinal tract and first-pass hepatic metabolism; useful for drugs poorly absorbed by or unstable in gastrointestinal tract. Example: insulin, lidocaine.

Intramuscular and subcutaneous: Good for slow, sustained delivery of depot preparations of drugs. Example: antibiotica.

Intrathecal and intraventricular: Used primarily for cancer drugs, local anesthetics, opioids, and antibiotics. Caution: use only sterile, preservative-free medications to avoid risks of chemical arachnoiditis. Example: preservative-free morphine and clonidine for chronic pain.

Delayed Gastrointestinal Absorption

Delayed gastric emptying: Often results from fatty meals, anticholinergics, antiserotoninergics (ondansetron), barbiturates, ethanol, glutethimide, methaqualone, and opioids.

Drug coatings, bezoars (undigested food or foreign [hair] proteinaceous materials), concretions: Will all require initial disintegration prior to absorption. Example: enteric-coated tablets, long-acting preparations, meprobamate (frequently forms concretions), foods (persimmons = form phytobezoars).

Gastric outlet pylorospasm: Most frequently caused by common gastric irritants. Example: iron, salicylates.

Routes vs. Rates of Absorption

Routes of Absorption

Enteral: Oral, rectal.

Parenteral: Intradermal, subcutaneous, intravascular (intravenous, intra-arterial), intramuscular.

Cutaneous: Topical and transdermal.

Miscellaneous: Inhalation, sublingual, transmucosal, intranasal, intrathecal, intraventricular.

Rates of Absorption

Fastest-to-slowest: Intravascular > inhalation > sublingual > intranasal > intramuscular > rectal > oral > subcutaneous > topical > transdermal.

Rate of absorption: Predicts the onset of action of xenobiotics.

Extent of absorption: Predicts the bioavailability of the xenobiotic or the extent of its pharmacologic effect. Example: digoxin has 50% bioavailability.

Rates vs. Bioavailabilities

Physiochemical Factors Influencing Absorption

Physical Factors

Molecular weight (MW): Low MW promotes rapid absorption by passive diffusion.

Blood flow: High blood flow favors high absorption. Example: intestinal > gastric absorption.

Surface area: High surface area favors high absorption. Example: intestinal > gastric absorption.

Contact time: Absorption is inversely proportional to gastrointestinal transit time. Example: cathartics speed transit time and limit absorption.

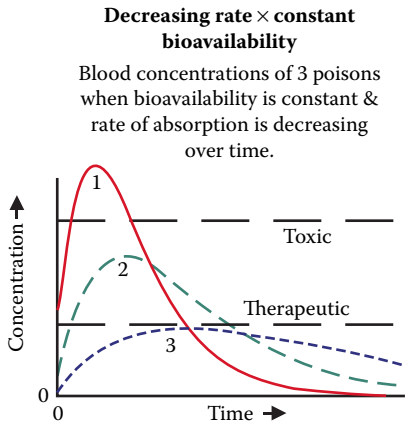

FIGURE 1.1a The blood concentrations of three poisons when bioavailability is constant and rate of absorption is decreasing over time.

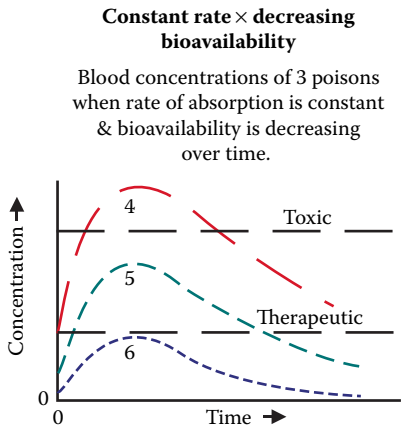

FIGURE 1.1b Constant rate x decreasing bioavailability. The blood concentrations of three poisons when rate of absorption is constant and bioavailability is decreasing over time.

Chelators of heavy metal toxins enhance the bioavailability of safer, complexed toxins, but have no impact on transit time or absorption, unless combined with cathartics. Example: deferoxamine and Fe, penicillamine and Cu, succimer and Pb.

Solubility, Polarity, pH

Water solubility: Water-soluble (hydrophilic) xenobiotics cannot cross lipoprotein membranes and must filter through aqueous channels.

Lipid solubility: Lipid-soluble (lipophilic) xenobiotics readily cross lipoprotein membranes for increased absorption and often enter enterohepatic cycles that decrease renal elimination. Example: Opioids: Fentanyls. From long-acting to short-acting; Carfentanil > fentanyl > sufentanil > alfentanil.

Polarity: Lack of polarity or charge favors enhanced absorption by passive diffusion.

pH: Acidic drugs (ASA) demonstrate increased absorption in the acidic stomach; basic drugs demonstrate increased absorption in the alkaline intestine (jejunum > ileum).

Toxin Transport Mechanisms

Passive Diffusion

Concentration gradient: The gradient between high-to-low concentrations that provides the driving force for passive diffusion.

Saturation potential: None; passive diffusion is not susceptible to saturation or zero-order kinetics.

Energy source: Concentration gradients alone.

Fick's Law of Diffusion: Governs the rate of passive diffusion = dQ/dT = DAK (C1 – C2)/h, where D = diffusion constant, A = surface area of membrane, and C1 – C2 = difference in poison concentrations on either side of membrane.

Active Transport

Carrier protein: Required for active transport against concentration gradients.

Saturation potential: High; protein carriers are often saturated in overdose, allowing toxins to accumulate in the central circulatory compartment.

Energy source: Energy is provided by the hydrolysis of ATP. Active transport is a highly energy-dependent process.

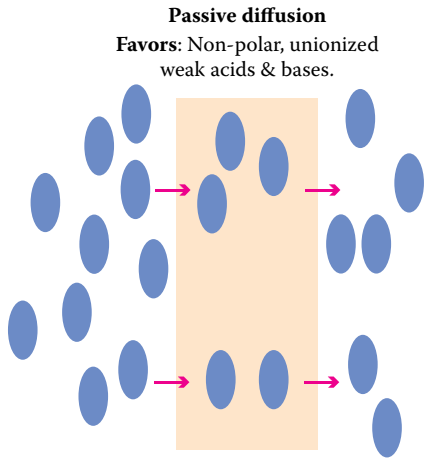

FIGURE 1.2a Passive diffusion favors nonpolar, unionized weak acids and bases.

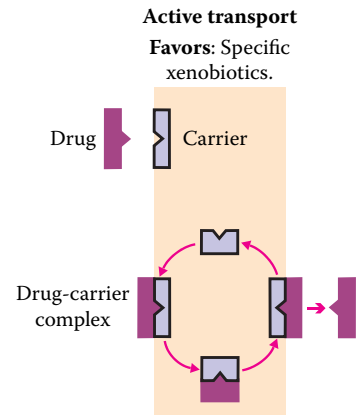

FIGURE 1.2b Active transport favors specific xenobiotics.

Distribution

Bound vs. Unbound Drugs

Bound Drugs

- Specialized proteins bind xenobiotics in plasma and tissue compartments, making toxins unavailable for distribution.
- **Albumin:** Binds acidic ("A") drugs with low V_d = aspirin, phenoxyacetic acid herbicides, anticonvulsants, anticoagulants (warfarin or coumadin).
- **α-1-acid glycoprotein:** Binds basic ("B") drugs with low V_d = β-blockers, amide local anesthetics, tricyclic antidepressants (TCAs).
- **Specialized carrier proteins:** Exist in the blood-transferrin (carries Fe); in the kidney-metallothionein (carries Cd, Pb, and Hg); and in the retina-melanin (carries chloroquine and chlorpromazine [CPZ]).

Unbound Drugs

- Only unbound drugs freely distribute through membranes to tissues.
- **Bioavailability:** Applies to unbound drugs only.
- **Saturation or zero-order kinetics:** Toxic overdoses often saturate protein binders and carriers (albumin-binder, transferrin-Fe carrier), making large concentrations of unbound drugs available for tissue distribution and organ toxicity. Example: ASA-CNS toxicity; Fe-hepatotoxic and cardiotoxic.
- **Lab serum concentrations:** Of limited value in determining serum concentrations of unbound drugs because labs measure both bound and unbound drugs to determine serum values that closely approximate plasma concentration.

Physiochemical Determinants of Xenobiotic Distribution

- **Blood flow:** Determined by the cardiac output and accounts for initial distribution of xenobiotics and preferentially perfuses brain, liver, kidneys > muscle > fat > bone.
- **Drug structure:** Uncharged, hydrophobic, and lipophilic drugs readily cross lipoprotein membranes.
- **Protein binding:** Plasma and specialized carrier proteins sequester xenobiotics in the central plasma compartment and often become saturated, resulting in high plasma concentrations of unbound toxins.
- **Physiologic barriers:** Protect downstream target organs from xenobiotic distribution and toxicity. Example: blood–brain barrier, placental barrier, blood–testis barrier.

Bioavailability, Concentration, and the Volume of Distribution (V_d)

Definitions and Relationships

- **V_d:** The theoretical volume into which a drug distributes.
- **V_d:** Determines how much of a drug remains inside or outside the central circulatory (plasma) compartment sampled by serum concentrations.
- **V_d:** Drugs with V_d < 1 L/kg remain inside the plasma compartment available for removal by hemodialysis (HD). Example: ASA V_d = 0.2; ethylene glycol (antifreeze) V_d = 0.6.
- **V_d:** Drugs with V_d > 1 L/kg distribute from plasma to tissues and are unavailable for removal by HD. Example: digoxin V_d = 5; TCA V_d = 10–15.

Determinants of the V_d

- Drug dose administered
- Drug bioavailability
- Peak plasma concentration
- Formula: V_d = dose in mg/kg × bioavailability (%)/plasma concentration. Alternatively, plasma concentration = dose in mg/kg/V_d × weight in kg

Classical Compartment Models of Distribution

One-Compartment Model

- **Definition:** Some xenobiotics rapidly enter the central circulatory compartment for rapid distribution to tissues; plasma concentrations mirror tissue concentrations.

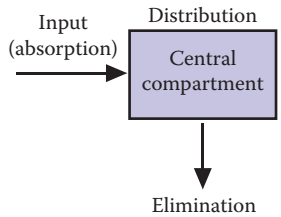

FIGURE 1.3a One-compartment distribution model. Some xenobiotics rapidly enter the central circulatory compartment for rapid distribution to tissues; plasma concentrations mirror tissue concentrations.

Two-Compartment Model

- **Definition:** Most xenobiotics do not instantaneously equilibrate with tissues, but are initially distributed to highly perfused organs, and subsequently distributed to less perfused peripheral tissues. Example: Digoxin, barbiturates, lidocaine.

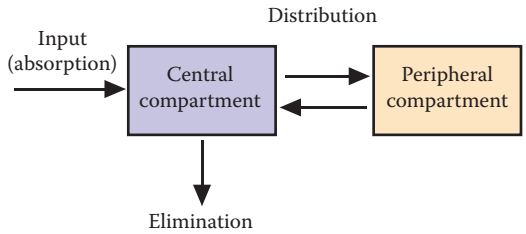

FIGURE 1.3b Two-compartment distribution model. Most xenobiotics do not instantaneously equilibrate with tissues, but are initially distributed to highly perfused organs, and subsequently distributed to less perfused peripheral tissues. Ex: barbiturates, digoxin, lidocaine.

Metabolism

Metabolic Reactions

Phase I Hepatic Reactions

- **Mechanisms:** Preparative or nonsynthetic reactions that often precede phase II reactions and either add oxygen and introduce polar groups to (by oxidation > reduction and hydrolysis) or expose polar groups on (by dealkylation) xenobiotics to increase their polarity and water solubility in preparation for further hepatic metabolism (by phase II) or renal elimination.
- **Enzymes:** All phase I enzymes are members of the hepatic microsomal (endoplasmic reticulum fraction) mixed function oxidase (oxygen-adding) enzyme system (Cytochrome [CY] P-450 family). All phase I hepatic reactions require the reducing agent nicotinamide adenine dinucleotide phosphate (NADP) to add O_2 to and increase the polarity of xenobiotics.

Phase II Hepatic Reactions

- **Mechanisms:** Synthetic reactions that often replace or follow, but rarely precede, phase I reactions, designed to conjugate polar groups, reduce electric charges, and assure water solubility for the ultimate renal elimination of xenobiotics. Conjugation occurs with glucuronide > sulfate, acetate, methyl groups, or amino acids (glycine > taurine and glutamic acid).
- **Enzymes:** Phase II hepatic enzymes may belong to either the liver's microsomal (CYP-450) or cytosolic fractions.

Common Members of the CYP-450 Hepatic Enzyme Family and Their Representative Enzyme Substrates

- CYP1A1 — Polycyclic aromatic hydrocarbons (PAHs)
- CYP1A2 — Acetaminophen
- CYP2A6 — Nicotine
- CYP2D6 — Debrisoquine
- CYP2F1 — Ethanol
- CYP3A4 — Many antiarrhythmics, oral contraceptive pills (OCPs), warfarin. The most important member of the CYP-450 family that metabolizes many drugs, including macrolide antibiotics (erythromycins), antifungal azoles, the nonsedating antihistamines (astemizole and terfenadine – Seldane®), and cisapride (Propulsid®). When two or more drugs metabolized by CYP-450 3A4 are prescribed, the toxicity of the slowest metabolized drug can be enhanced, producing adverse effects. Both terfenadine and cisapride caused QRS widening and, rarely, fatal torsades de pointes when prescribed with other 3A4-metabolized drugs and were withdrawn from the market by the U.S. Food and Drug Administration (FDA).

Drug Interactions

Hepatic Enzyme Inducers

- Increase substrate drug metabolism and thereby decrease therapeutic drug efficacy.
- **Anticonvulsants:** Barbiturates, carbamazepine, phenytoin, primidone.
- **Sedatives:** Ethanol, glutethimide.
- **Antibiotics:** Isoniazid (INH), rifampin (decreases efficacy of oral contraceptive pills [OCPs]), griseofulvin.
- **Miscellaneous:** Omeprazole, polycyclic aromatic hydrocarbons (PAHs), St. John's wort (can decrease efficacy of cycloserine, indinavir, and oral contraceptives (OCPs); interacts with selective serotonin reuptake inhibitors (SSRIs), and has been associated with suicides and deaths in depressed patients on SSRIs, possibly associated with central serotonin excess).

Hepatic Enzyme Inhibitors

- Decrease substrate drug metabolism, usually increasing toxicity of drug, but decreasing toxicity of metabolites. Example: cimetidine for mushroom poisoning to block the metabolism of the hepatotoxic poison, amanitin.

- **Antifungals:** All azoles.
- **Antibiotics:** All macrolides, chloramphenicol, primaquine, trimethoprim-sulfamethoxazole, ciprofloxacin.
- **Antiarrhythmics:** Amiodarone, β-blockers, quinidine, verapamil.
- **H_2-blockers and proton-pump inhibitors:** Cimetidine, ranitidine, omeprazole.
- Most antipsychotics and tricyclic antidepressants (TCAs).
- **Miscellaneous:** Allopurinol, OCPs, grapefruit juice.

Pharmacogenetics

Genetic Polymorphisms

- **Definition:** Inherited (autosomal recessive, often X-linked), inter-individual differences in the structure and function of specific hepatic microsomal or cytosolic enzymes that alter either phase I or phase II hepatic metabolic reactions to promote or, more rarely, to reduce the toxicity of xenobiotics, usually therapeutically administered drugs. Example: fast (decreased efficacy) vs. slow (increased toxicity) acetylators of the anti-tuberculosis drug isoniazid (INH).

Common Genetic Polymorphisms

- **Fast vs. slow INH acetylators:** 95% of Asians and Blacks are fast (rapid) acetylators of INH at lower risk of INH neurotoxicity; 50% of Americans and >70% of Scandinavians are slow acetylators at higher risk of INH toxicity.
- **Pseudocholinesterase deficiency:** 2% of Americans and most Alaskan and Canadian Inuits cannot metabolize ester local anesthetics (including cocaine) and succinylcholine with higher risks of toxicity, especially cocaine-induced myocardial infarction (MI) and CVA, and succinylcholine-prolonged paralysis.
- **Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency:** Common in Blacks (confers malaria protection) and renders red blood cells incapable of responding to oxidative structural stresses imposed by oxidant drugs (nitrites, sulfa), resulting in hemolysis or methemoglobinemia, often refractory to methylene blue reversal.

Pharmaceutical Excipients

What Are Excipients?

- **Definition:** Excipients are the chemical ingredients other than active drugs that are included in pharmaceutical preparations for a variety of reasons.
- **Uses:** Binders, coatings, colors, diluents, disintegrators, flavorings, preservatives, sweeteners, solvents.

Commonly Used Excipients

Colors: Dyes can cause allergic reactions. Example: FD&C Reds 40 and 19, carnine, quinolone yellow.

Flavorings: Licorice (glycyrrhizic acid) inhibits cortisol metabolism, causing or exacerbating hypertension and promoting hypokalemia.

Sweeteners: Aspartame is contraindicated in phenylketonurics.

Preservatives: Benzyl alcohol in IV flush solutions and multi-dose medication vials can cause acidosis and shock in preemies – "Gasping Baby" Syndrome.

Solvents: Polyethylene glycol in IV drugs irritates veins and has caused metabolic acidosis and acute renal failure after applying topical antimicrobial (sulfonamides) creams for extensive burn therapy.

Therapeutic Index (TI)

What Is the Therapeutic Index (TI)?

- **Definition:** The TI is the ratio of the dose of a drug that causes toxicity to the dose that produces the desired and intended effect. The TI can only be determined by administering increasing drug doses to volunteers and observing for toxic responses.

How Is Drug Safety Assessed? (by large vs. small TIs)

- **Large TI = a large therapeutic window:** Large doses of the drug are relatively safe to administer, unless drug allergy exists. Close patient monitoring is unnecessary due to drug's safety profile. Example: penicillin, OCPs.
- **Small TI = a small therapeutic window:** Drug toxicity is possible even at low drug doses. Drug

serum concentrations and early toxic effects must be closely monitored. Example: warfarin-monitor the INR or PTT, digoxin-monitor dig levels, serum K.

Dose-Response Relationships

Receptor Theory

- **Definition:** Many xenobiotics bind to specific protein receptors by ionic forces > hydrophobic or hydrophilic forces > Van der Waals forces to create a stable drug-receptor complex, the key to traversing lipoprotein membrane barriers and entering organ and tissue compartments.

Receptor States

Agonist: Xenobiotic that activates protein receptor and opens barriers to tissues.
Partial agonist: Xenobiotic that only partially activates protein receptor.
Antagonist: Xenobiotic that totally prevents the binding of an agonist to its specific protein receptor.
Partial antagonist: Xenobiotic that partially prevents the binding of an agonist to its specific protein receptor.
Mixed agonist/antagonist: Xenobiotic that both activates some receptors and paradoxically inhibits other receptors. Example: Butorphanol, nalbuphine, pentazocine.
Competitive antagonist: Xenobiotic that competes with agonist for its receptor.
Noncompetitive antagonist: Xenobiotic that interferes with agonist binding.

Efficacy vs. Potency (ED_{50})

How Effective Is the Drug?

- **Definition:** Efficacy is a measure of the maximal effective response produced by a drug. Efficacy depends on the number of drug-receptor complexes formed and the **efficiency** with which the activated complex produces a cellular response.

How Potent Is the Drug?

- **Definition:** Potency is a measure of how much of a drug is required to elicit a given response.
- Potency is expressed as the **effective dose 50** [ED_{50}] or the dose of a drug that elicits 50% of the maximal response.
- The lower the dose required for a given response, the more potent the drug.
- Potent drugs have steep dose-response curves (plasma concentration vs. time) demonstrating that small increases in drug dose will elicit large changes in response. Example: digoxin, warfarin.

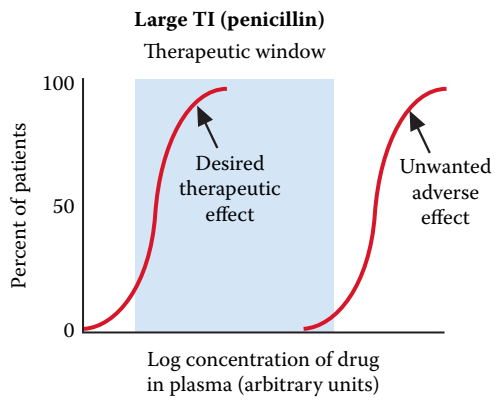

FIGURE 1.4a Large therapeutic index. A large therapeutic index reflects a large therapeutic window in which large doses of a drug are relatively safe to administer, unless drug allergy exists. Ex.: penicillin.

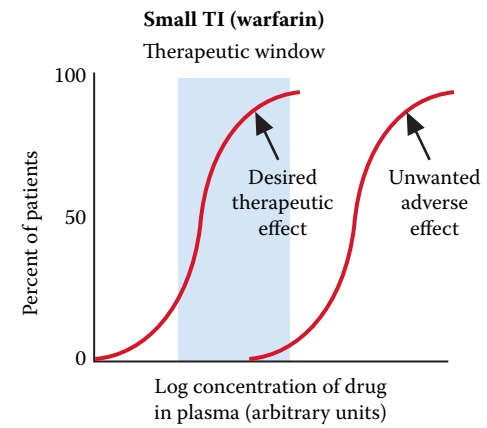

FIGURE 1.4b Small therapeutic Index. A small therapeutic index reflects a small therapeutic window in which drug toxicity is possible even at low doses. Ex.: digoxin, warfarin.

Excretion

Drug Elimination Kinetics

First-Order Kinetics

- The rate of a drug's elimination is directly proportional to its plasma concentration. The higher the concentration, the more rapid the drug elimination. Drug decay curve is curvilinear. Example: 90% of all drugs.

Zero-Order Kinetics

The rate of a drug's elimination is independent of its concentration because (1) the drug's hepatic metabolizing enzyme system quickly becomes saturated to capacity, and (2) a constant, predictable amount of drug is eliminated per unit of time. Drug decay curve is linear. Example: ethanol.

Combined Elimination or Michaelis-Menten Kinetics

The rate of a drug's elimination is initially first order, and then switches to zero order when the drug's hepatic metabolizing enzyme system becomes saturated to capacity. Combined elimination kinetics is also known as **Michaelis-Menten** kinetics. Drug decay curve is initially curvilinear and then becomes linear.

Plasma Clearance of Xenobiotics

Definition: Clearance (Cl) is measured as the volume of plasma cleared of a xenobiotic per unit of time.

Cl = Rate of elimination/Plasma concentration × Time
= Rate of elimination × V_d
= IV dose administered/Area Under the Curve (AUC) of C × t
Where C = concentration and t = time.

Renal Elimination of Xenobiotics

1. Glomerular filtration (GF): Physical filtering that depends on cardiac output and renal perfusion, and is independent of a drug's pH or lipid solubility; measured as the glomerular filtration rate (GFR), normally 20% of renal plasma flow (600 mL/minute) or 125 mL/minute.
2. Proximal tubular secretion: Xenobiotics that are not eliminated from the blood in the glomerular filtrate can be removed later by active transport using specific carrier proteins within the proximal tubules.
3. Distal tubular reabsorption: As high concentrations of uncharged, water-soluble (hydrophilic) phase I drug metabolites reach the distal convoluted tubules (DCTs), concentration gradients are created between the DCTs and the central circulatory compartment, allowing drug metabolites to be reabsorbed into plasma. Conversely, phase II hepatically metabolized drugs remain highly ionized, become trapped in the urine, and are unable to back-diffuse into the central circulation. Example: alkalinization of the urine with sodium bicarbonate and forced diuresis with IV fluids will ion-trap acidic ASA and phenoxyacetic acid herbicide metabolites in the urine and augment GFR for enhanced elimination of toxic metabolites.

Enhanced *In Vivo* Elimination of Xenobiotics

Corporeal Enhanced Elimination

Alkaline diuresis: Traps weak acids and their metabolites (barbiturates, phenoxyacetic acid herbicides, salicylates-ASA) in the DCTs and enhances their renal excretion.

Gut dialysis: Multiple doses of oral activated charcoal (AC) use reverse diffusion gradients to back diffuse xenobiotics with low V_d values (<1 L/kg) from the plasma compartment and back into the gut for fecal excretion. Example: multiple doses of AC are often indicated for theophylline poisoning.

Extracorporeal Enhanced Elimination

Hemodialysis (HD): Most effective means of extracorporeal elimination of xenobiotics.

Hemoperfusion (HP): Only effective for drugs that are absorbed to AC. Example: theophylline.

Hemofiltration (HF): Effective for the slow and prolonged removal of high-molecular-weight (4,500–40,000 Daltons) compounds, not amenable to hemodialysis (<500 Daltons).

Peritoneal dialysis: Ineffective for the enhanced elimination of xenobiotics and not recommended for poisonings.

Enhanced Extracorporeal Elimination of Xenobiotics

Extracorporeal Enhanced Elimination

Indications for Enhanced Elimination

- Poisoned patients not responding to supportive care.
- Poisoned patients with impaired hepatic or renal elimination systems.
- Severely poisoned patients with high drug concentrations associated with high morbidity and mortality. Example: ethylene glycol.
- Poisoned patients at high risks due to advanced age, pregnancy, or concurrent diseases.
- Poisoned patients with co-existing and non-responsive volume or electrolyte disturbances. Example: fluid overload, acidosis, hyperkalemia.

Drug Factors Favoring the Use of Enhanced Elimination

- Low V_d < 1 L/kg; Example: ASA, ethylene glycol
- Low molecular weight (MW): <500 Daltons
- Water-soluble compounds
- Non-protein-bound compounds
- Low endogenous renal clearance
- One-compartment model kinetics

Enhanced Elimination Techniques

Hemodialysis: Success requires that the toxin be of low MW and low V_d, water soluble, and not protein bound. Complications include bleeding, thrombosed access sites, and the elimination of therapeutic drugs, antidotes (folic acid), and water-soluble vitamins (vitamin K). Example: bromides, ethanol, methanol, ethylene glycol, chloral hydrate, lithium, and ASA are easily dialyzed.

Hemoperfusion: Success requires that the toxin be adsorbed to AC. Preferred for poisoning with theophylline and anticonvulsants (carbamazepine, phenobarbital, and phenytoin).

Hemofiltration: Not as effective as HD or HF, but can be continued for days with fewer complications. Advantages include ability to eliminate high MW (4500–40,000 Daltons) and protein-bound toxins. Preferred for toxins slowly eliminated from tissue binding sites. Example: aminoglycosides, lithium, and procainamide.

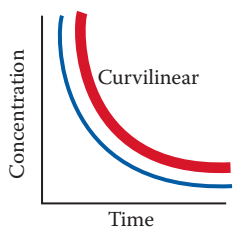

FIGURE 1.5a First-order kinetics. The rate of a drug's elimination is directly proportional to its plasma concentration. Thus, the higher the drug concentration, the more rapid is the drug's elimination. Ex.: most drugs.

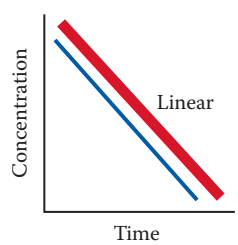

FIGURE 1.5b Zero-order kinetics. The rate of the drug's elimination is independent of its concentration, and a constant amount of drug is eliminated per unit time. Ex.: ethanol.

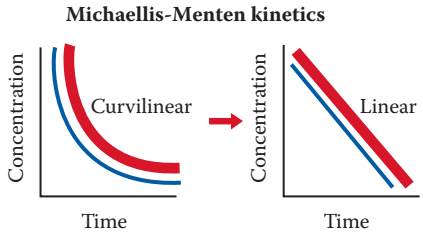

FIGURE 1.6 Michaelis-Menten Kinetics. The rate of a drug's elimination is initially by first-order kinetics, and then switches to zero-order kinetics when the drug's hepatic metabolizing enzyme system becomes saturated to capacity.

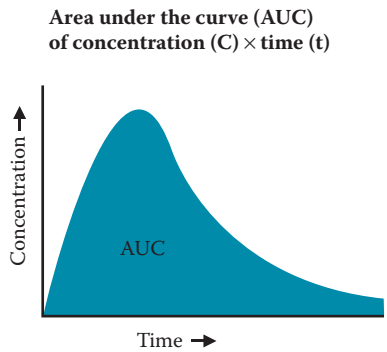

FIGURE 1.7 Plasma clearance. Plasma clearance is reflected by the area under the curve of a drug's plasma concentration over time, or clearance = the rate of elimination/plasma concentration x time.

Poisoning in the Elderly

Behavioral and Physical Considerations

- **Reduced muscle mass and increased body fat:** Promotes increased Vd of lipophilic toxins.
- **High total body water:** Promotes increased Vd of water-soluble toxins.
- Compliance problems.
- **Age-related CNS problems:** Confusion, depression, disorientation, dementia.
- **Dosing problems:** Multiple medications, drug tolerance.

Pharmacokinetic Considerations

- **Absorption:** Decreased gastric acid secretion and decreased gut motility may increase drug toxicity.
- **Distribution:** Decreased albumin binding and increased α1-acid glycoprotein binding, coupled with decreased gut and hepatic perfusion, may increase drug toxicity.
- **Metabolism:** Decreased phase I hepatic metabolism; phase II hepatic metabolism remains unchanged.
- **Excretion:** Decreased renal plasma flow (RPF) = decreased glomerular filtration rate (GFR) = decreased excretion by filtration.

Poisoning in Children

Epidemiology

- 67% of annual poisonings occur in children ≤19 years old. Ingestion is the route of exposure in 76% of cases.
- Children <5 years old have the highest rate of poisoning visits to emergency departments.

Ingested Agents

- Most commonly ingested agents include cosmetics and personal care products.
- 52% are medications.
- 48% are non-medications.
- Most lethal agents: cocaine, anticonvulsants, antidepressants, cleaning products, hydrocarbons.

Most Commonly Ingested Agents

Cosmetics and personal care products
Cleaning products
Analgesics
Plants
Cough and cold preparations
Foreign bodies
Topical agents
Pesticides
Vitamins
Hydrocarbons

General Management

Ipecac: Use at home within 1 hour of ingestion if directed. Avoid with coma, convulsions, corrosives, hydrocarbons, coagulants, and in children under the age of 6 years.

Position: Left lateral decubitus, Trendelnberg (left side down, head down).

Lavage: Only with airway protection and life-threatening (TCA) overdose within 1 hour.

AC: Administer 1g/kg within first hour; ineffective for alcohols, corrosives, hydrocarbons, metals, and minerals.

MDAC: Consider for carbamazepine, phenobarbital, theophylline.

Cathartics (indicated with MDAC): Mg citrate > sorbitol, whole-bowel irrigation for slow-release drugs, iron and lithium, body packers and stuffers (cocaine and heroin).

Chapter 2

The General Management of the Poisoned Patient

Chapter Outline

Preventing gastrointestinal absorption of the toxin

Gastric emptying
Emesis vs. lavage
Activated charcoal (AC) and multi-dose activated charcoal (MDAC)
Cathartics
Whole-bowel irrigation (WBI)
Alternative methods of gastrointestinal emptying

Enhancing elimination of the toxin

Methods

Preventing Gastrointestinal Absorption of the Toxin

Gastric Emptying

Indications for Gastric Emptying

- High-risk, potentially lethal ingestions: Aspirin, calcium channel blockers (CCBs) (especially verapamil), chloroquine, colchicine, cyanide, tricyclic antidepressants (TCAs).
- Recent ingestions, less than 1 to 2 hours, especially for slow-release drugs.
- Consequential toxicity: Seizures, hypotension, arrhythmias.
- Ineffective or nonexistent antidotes: CCBs, iron, colchicine, paraquat, selenious acid.
- Enteric-coated or slow, sustained-release tablets: Aspirin, theophylline, verapamil.
- Poisonings with agents that reduce gastrointestinal motility: Anticholinergics, opioids, sedative/hypnotics.
- Poisonings with agents that cause pylorospasm and gastric outlet obstruction: Aspirin, meprobamate, iron.
- Poisonings with agents that form gastric concretions or masses: Aspirin, enteric-coated and sustained-release tablets, iron, meprobamate, phenobarbital.

Contraindications to Gastric Emptying

- Caustic acid/alkali ingestions
- Hydrocarbon ingestions
- Sharp and pointed material ingestions
- Drug packet ingestions
- Bleeding diathesis, coagulopathies
- Esophageal varices and Mallory-Weiss tears of the esophagus
- Significant vomiting
- Nontoxic ingestions

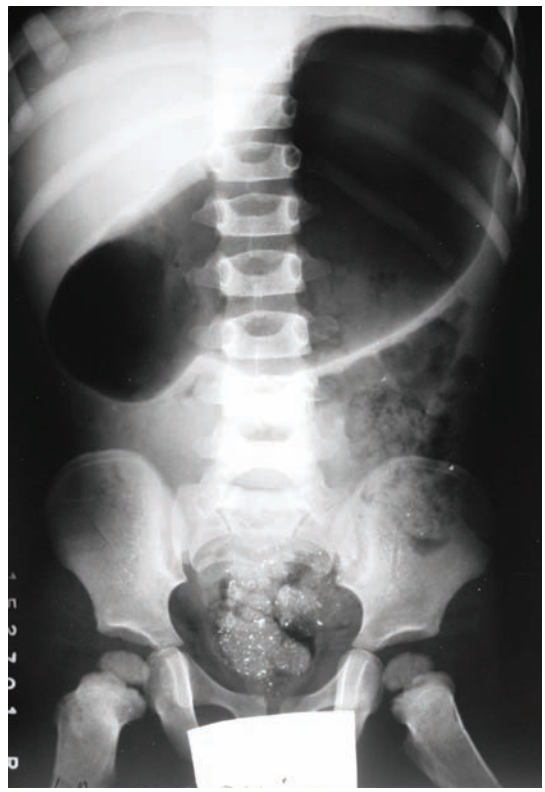

FIGURE 2.1 Non-dissolving radiopacities in the gastrointestinal tract. Abdominal radiograph of a 3-year-old boy with a history of ingesting leaded paint chips peeling off doors and windows. Note radiopaque leaded paint chips in colon and rectum. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Ipecac Emesis

Indications

- Witnessed ingestions, usually at home
- Home use; contraindicated in the emergency department (ED)
- Ingestions of objects too large for lavage tubes
- Ingestions by infants older than 6 months and small children

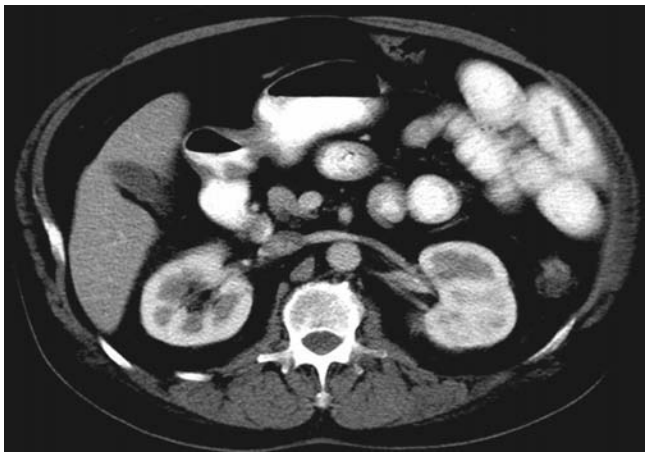

FIGURE 2.2 Body stuffer: heroin. Axial abdominal oral and intravenous contrast-enhanced computerized tomogram (CT) at the level of the renal veins that demonstrated a rectangular container of heroin in a jejunal loop. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Contraindications

- Potential or compromised airway protective reflexes
- Imminent seizure or coma: Isoniazid, camphor, meperidine
- Imminent deterioration: tricyclic antidepressants, meperidinepropoxyphene, propranolol, tramadol
- Caustic acid/alkali ingestions
- Hydrocarbon ingestions
- Sharp material ingestions
- Increased risks of bleeding
- Significant vomiting
- Nontoxic ingestions

Dose

- Adults and children older than 5 years old: 30 ml (2 Tbsp.); may repeat one time
- Children 1 to 5 years: 15 mL (1 Tbsp.)
- Infants 6 to 12 months: 10 mL (2 tsp.)

Complications

- Intractable vomiting (rare), delayed emesis while unconscious
- Mallory-Weiss esophageal tears
- Pneumomediastinum
- Aspiration pneumonitis
- Delaying activated charcoal administration
- Electrolyte abnormalities
- Substance abuse = bulimia

Emesis vs. Lavage

Orogastric Lavage

Indications

- High-risk ingestions when a drug or toxin is still accessible in the stomach (<1 hour)
- Ingestions that delay gastric emptying, cause gastric outlet obstruction, or form gastric concretions
- Ingestions of enteric-coated or sustained-release preparations

Contraindications

- Compromised or unprotected airway
- Caustic acid or alkali ingestions
- Sharp material ingestions
- Drug packet ingestions
- Bleeding diathesis or increased risks of gastrointestinal hemorrhage
- Prior significant emesis
- Nontoxic ingestions

Procedure

- Adults: 36–40 French orogastric tube
- Children: 22–28 French orogastric tube
- Endotracheal tube if airway is compromised
- Left lateral decubitus position
- Confirm proper orogastric tube placement by x-ray
- Lavage in aliquots: Adults 250 mL/kg and children 10 mL/kg of normal saline until clear; maximum 1 L for children.
- Instill activated charcoal (AC) via orogastric tube

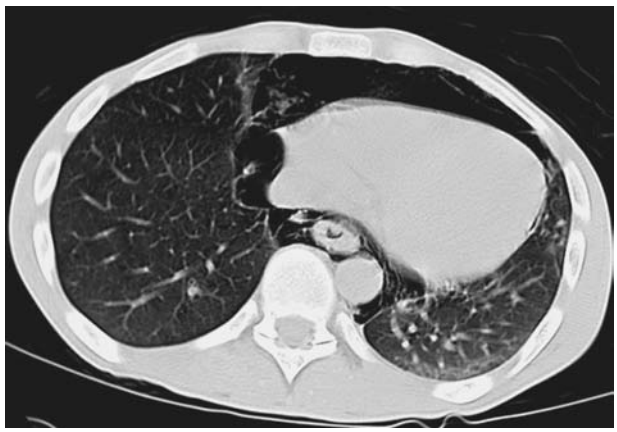

FIGURE 2.3 Orogastric tube-induced gastric perforation with pneumomediastinum. Computerized axial tomogram (CT) of the chest that demonstrates a huge pneumomediastinum surrounding the distal esophagus, heart, and descending thoracic aorta following the insertion of an orogastric tube for gastric lavage and activated charcoal (AC) administration. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Complications

- Inadvertent tracheal intubation or airway trauma
- Esophageal/gastric perforation with pneumomediastinum, mediastinitis, or hemorrhage
- Emesis
- Aspiration pneumonitis

Activated Charcoal (AC) and Multi-Dose Activated Charcoal (MDAC)

Indications

- **Activated Charcoal (AC):** Any substance known to bind to AC, especially highly toxic substances
- **Multi-Dose Activated Charcoal (MDAC):** All drugs and toxins known to bind with small volumes of distribution (less than 1 L/kg), low renal clearance, little protein binding, and enterohepatic recirculation of toxic metabolites
- Drugs that reduce gastrointestinal motility, form gastric concretions, and enteric-coated or sustained-release preparations

Contraindications

- Patients at risk for aspiration with unprotected airways
- Caustic acid and alkali ingestions
- Ileus or small bowel obstruction
- Most hydrocarbon (need endoscopy) and heavy metal ingestions: Hydrocarbons and metals do not bind to AC
- Most large-volume (dose usually in grams/kilogram) ingestions: Iron, lithium, ethanol
- Single-substance ingestions of iron, lithium, ethanol

Dose/Procedure

- Initial: 1 g/kg for both adults and children; add sorbitol for initial AC dose only
- **MDAC:** 0.5–1.0 g/kg every 1 to 4 hours, with no additional cathartics
- Consider nasogastric tube and antiemetics to control vomiting
- Allow AC to leave stomach before emptying stomach

Complications

- Aspiration
- Emesis
- Obscuring gastrointestinal mucosa and limiting visibility during endoscopy
- Constipation
- Small bowel obstruction

Cathartics

Indications

- To speed gastrointestinal transit of drugs or toxins that remain in the gastrointestinal tract and may continue to be adsorbed to or desorbed from AC
- Combine only with the initial dose of AC or MDAC and do not repeat

Contraindications

- Abdominal trauma

- Intestinal ileus or small bowel obstruction
- Preexisting diarrhea
- Hypovolemia and dehydration
- Renal failure (Mg citrate and Mg sulfate could cause further neurologic and respiratory depression from hypermagnesemia)
- Routine use in children
- Prior cathartic dose

Dose of Cathartics

- Sorbitol 70% is preferred: Adults 1 g/kg and children 0.5 g/kg
- 10% Mg citrate: 4 mL/kg for children and adults, maximum 300 mL
- Mg sulfate: Adults 1 g/kg and children 0.5 g/kg

Complications

- Excessive diarrhea
- Emesis
- Electrolyte abnormalities
- Hypermagnesemia (Mg citrate and Mg sulfate)
- Hypokalemia
- Hyponatremia or hypernatremia (sorbitol)
- Volume depletion and dehydration
- Hypernatremic dehydration (sorbitol)

Whole-Bowel Irrigation (WBI)

Indications

- **Sustained-release drugs:** Theophylline, calcium channel blockers, especially verapamil
- **Enteric-coated drugs:** Aspirin, verapamil
- **Drugs or toxins not adsorbed by AC:** Iron, heavy metals, lithium, potassium
- **Slowly dissolving substances:** Iron tablets, lead paint chips, bezoars, and concretions
- **Crack vials:** body stuffers, cocaine and heroin
- **Drug packets:** Body packers, cocaine and heroin

Contraindications

- Paralytic ileus or small bowel obstruction
- Abdominal trauma
- Rapidly absorbed drugs and toxins: alcohols
- All liquid ingestions
- Hydrocarbon ingestions
- Caustic acid and alkali ingestions
- Parenterally administered drugs

Dose

- Adults: 2 L/hour
- Children: 0.5 L/hour

Complications

- Vomiting, especially with rapid administration
- Bloating
- Decreased efficiency of activated charcoal
- Rectal itching

Alternative Methods of Gastrointestinal emptying

Other Miscellaneous Binding Agents

- Cholestyramine and colestipol: For methotrexate and organochlorine pesticides — lindane (Kwell®) and chlordecone (Kepone®)
- Sodium polystyrene sulfonate (Kayexalate®): For lithium and potassium

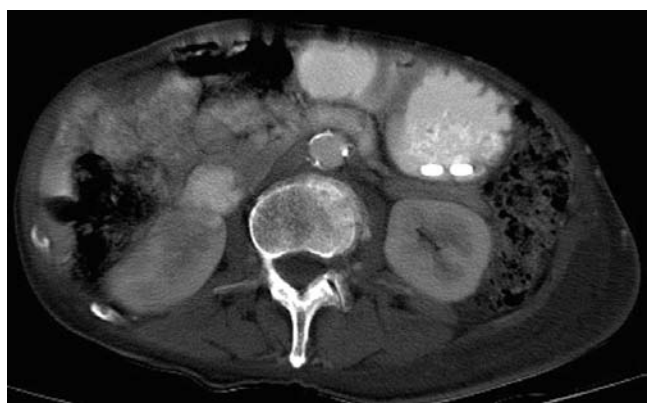

FIGURE 2.4 Slowly dissolving substances: enteric-coated phenothiazine tablets in stomach. Axial oral and contrast-enhanced computerized tomogram (CT) at the stomach level that demonstrates two slowly dissolving radiopaque substances (enteric-coated phenothiazine tablets). (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

- Potassium ferricyanoferrate (Prussian blue): For thallium and cesium
- Fuller's earth (diatomaceous earth): For paraquat and diquat

Surgical Emptying

- Rupture of cocaine drug packets
- Mechanical bowel obstruction by cocaine drug packets, vials, or pipes
- Bezoars: Aspirin, bromide, meprobamate

Enhancing Elimination of the Toxin

Methods

Indications

- Poisons with small volumes of distribution: poison remains in the blood compartment
- Poison with low endogenous renal clearance rates: alcohols, beta-blockers, lithium, phenytoin, paraquat, salicylates, theophylline
- Poisons that are not lipid-soluble or highly protein-bound

Urinary Alkalinization

- **Mechanism:** To trap weak acids in renal tubular fluid to prevent tubular absorption and promote urinary excretion.
- **Indications:** Consider urinary alkalinization for all weak acids, such as salicylates, phenobarbital, chlorpropamide; formic acid (methanol), chlorphenoxyacetic acid herbicides; for methotrexate; and to protect the kidneys during myoglobinuria from rhabdomyolysis.
- **Complications:** Volume overload, metabolic alkalosis.
- **Urine acidification** is not recommended.

Forced Diuresis

- **Mechanism:** To produce diuresis by volume expansion with Na-containing solutions, normal saline, or lactated Ringer's solution; often combined with diuretics.
- **Indications:** Not recommended except to protect the kidneys from myoglobinuria during extensive rhabdomyolysis. Exception: forced Cl diuresis with NaCl and mannitol for platinoid (cisplatin) overdose.
- **Complications:** Volume overload and electrolyte disturbances.

Peritoneal Dialysis

- **Mechanism:** To enhance the elimination of water-soluble, low-molecular-weight, poorly protein-bound substances with low volumes of distribution.
- **Indications:** Too slow to be useful and not recommended.

Hemodialysis

- **Mechanism:** To enhance the elimination of water-soluble, very low-molecular-weight (less than 500 Daltons), non-protein-bound compounds with low volumes of distribution (less than 1 L/kg) and low endogenous renal clearance rates (less than 4 mL/kg/min).
- **Indications:** Bromide, lithium, potassium, salicylates, all alcohols (ethylene glycol, methanol, isopropanol), and chloral hydrate and its primary metabolite, trichloroethanol.
- **Complications:** Bleeding, access related complications, air embolism, nosocomial infections.

Charcoal Hemoperfusion

- **Mechanism:** To enhance the elimination of compounds adsorbed by AC in an extracorporeal fashion; can be used in series with hemodialysis.
- **Indications:** Anticonvulsants: carbamazepine, phenobarbital, and phenytoin; theophylline; thallium (exception: thallium is the only heavy metal adsorbed to AC). In series with hemodialysis: carbamazepine, theophylline, procainamide, thallium.
- **Complications:** Same as dialysis + charcoal embolization, leukopenia, thrombocytopenia, hypocalcemia.

Continuous Hemofiltration

- **Mechanism: To enha**nce the elimination of very high-molecular-weight (10,000 to 40,000 Da) compounds using the patient's own arterial pressure (continuous arteriovenous hemofiltration [CAVH]) or a blood pump (continuous venovenous hemofiltration [CVVH]) to continuously perfuse a large pore size dialysis membrane.
- **Indications:** To clear very large molecules, such as methotrexate, heparin, protamine, insulin, myoglobin, and antibiotics, especially vancomycin.
- **Complications:** Same as hemodialysis and secondary to anticoagulation; removal of beneficial therapeutic drugs = antibiotics, antidotes, vitamins.

Plasmapheresis

- **Mechanism:** To enhance elimination of large-molecular-weight compounds (greater than 15,000 Da) that are not dialyzable and have limited endogenous metabolism. Fresh frozen plasma (FFP) and albumin are used to replace removed plasma.
- **Indications:** To remove large protein-bound molecules, such as Ag/Ab complexes, especially digoxin-Fab complexes.
- **Complications:** Transfusion-related anaphylaxis or allergic manifest**ations.**

Exchange Transfusion

- **Mechanism:** Same as plasmapheresis, but the replacement of removed blood is with packed red blood cells (PRBCs).
- **Indications:** Usually reserved for neonates.
- **Complications:** All transfusion related.

Chapter 3

Physical, Diagnostic, and Laboratory Evaluation of the Poisoned Patient

Chapter Outline

Physical assessment of the poisoned patient

Primary survey and treatment
Secondary survey and treatment
The unknown overdose
Overdose in pregnancy
Caustic cutaneous and ocular exposures

Pharmacokinetics

Drug compartment models
Drug elimination kinetics

Laboratory assessment of the poisoned patient

Types of lab tests
Testing methods (and degree of sensitivity and specificity, + to +++)
Blood/serum levels
Routine serum toxicology

Radiographic evaluation

Visualizing toxins
Toxin-induced skeletal changes
Chest x-rays: Lungs
Chest x-rays: Pleura, mediastinum, heart
Abdominal x-rays
Head computerized tomographic (CT) scan

Electrocardiographic (ECG) assessment

Electrolyte and temperature disturbances
Digitalis and tricyclic antidepressants (TCAs)
Tachyarrhythmias and common causes
Drug-induced tachycardias
Drug-induced bradyarrhythmias

Nontoxic exposures

Epidemiology of nontoxic exposures
Categorizing nontoxic exposures
Common nontoxic household exposures

Physical Assessment of the Poisoned Patient

Primary Survey and Treatment

Primary Survey

- Clear the airway.
- Assess and protect cervical spine.
- Intubate comatose patients for ventilation, lavage, and activated charcoal (AC) administration.
- Order arterial blood gas analysis and carboxyhemoglobin (COHb) level.
- Initiate electrocardiographic, temperature, oxygenation ($S_{TC}O_2$), and central and peripheral perfusion monitoring.
- Start IV, fluid load-normal saline or lactated Ringer's solution; draw complete blood count (CBC), glucose, electrolytes, BUN, creatinine, toxicology screen.
- Manage three seizure types: (1) benzodiazepine (BZ) responsive seizures — suspect ethanol withdrawal; (2) special antidote-required seizures — suspect pyridoxine or isoniazid (INH); (3) tonoclonic seizures and/or persistent seizure activity on the electroencephalogram (EEG) — suspect carbon monoxide (CO).

Nonspecific Treatments = Coma Cocktail and Oxygen

- Dextrose: 0.5–1.0 g/kg; use $D_{50}W$ ($D_{10}W$ for children) to manage or exclude hypoglycemia.
- Thiamine: 100 mg IV to manage or prevent Wernicke-Korsakoff syndrome in alcohol abusers (unnecessary in children).
- Naloxone: 2 mg IV for both children and adults with opioid toxidromes.
- Oxygen at high flow rates, 8–10 L/min.

Secondary Survey and Treatment

Secondary Survey

- Exclude heart murmurs = suspect subacute bacterial endocartitis, common in intravenous drug users (cocaine and heroin).
- Exclude bradydysrhythmias and tachydysrhythmias = suspect digitalis, β-blockers, calcium channel blockers, tricyclic antidepressants.
- Exclude silent abdomen = suspect anticholinergics, opioids.
- Examine extremities for needle tracks (intravenous drug abusers) and evidence of heavy metal poisoning = Mees lines — arsenic, thallium; arsenical keratoses on hands and feet, arsenic-induced black foot's disease.

Secondary Treatment

- Gastric emptying: No emesis, orogastric lavage and initial AC with cathartic.
- Consider enhanced elimination beginning with MDAC.
- Consider other modalities of enhanced elimination.

The Unknown Overdose

Contraindicated Treatments

- No analeptics
- No flumazenil
- No forced diuresis
- No urinary acidification
- No Class IA or Class IC antiarrhythmics = all are sodium channel blockers that could prolong QRS duration and precipitate ventricular tachyarrhythmias, including torsades de pontes
- No long-acting opioid antagonists (only naloxone)

- Choose appropriate vasopressor support to avoid myocardial sensitization and arrhythmogenesis.

Alcohol and Drug Overdose

- Give coma cocktail.
- Monitor central venous pressure (CVP) and/or pulmonary artery pressure (PAP) prior to fluid loading and inotropic treatment.
- Suspect concomitant trauma. Head CT scan? Cervical spine films?
- Secure intensive care unit bed.
- Alcohol-smelling breath does not indicate intoxication; suspect combined etiologies. Patients with sole ethanol overdoses will awaken in 3 to 4 hours.

Overdose in Pregnancy

- Manage hypotension aggressively.
- Maintain left lateral decubitus position.
- Anticipate respiratory acidosis.
- Avoid unusual antidotes, except naloxone.
- Maintain high index of suspicion for carbon monoxide poisoning; measure carboxyhemoglobin (COHb) levels by co-oximetry; order hyperbaric oxygenation (HBO) for COHb levels greater than 15%.
- Normal pulse oximetry may be misleading: tissue hypoxia may be present with carbon monoxide (CO), cyanide (CN), and hydrogen sulfide (H_2S) poisoning despite normal pulse oximetry. Co-oximetry is indicated to exclude tissue hypoxia and cytotoxicity.

Caustic Cutaneous and Ocular Exposures

- **Skin:** (1) Personal protective equipment (PPE) for Emergency Medical Services (EMS) personnel — to prevent contamination and poisoning of EMS; (2) identify, remove, and bag all clothing and other personal items; (3) bathe patient with soap and water two times; (4) never try to neutralize acid or alkali burns; (5) do not apply topical creams or greases, as this may lead to prolonged contact with toxin with increased absorption and greater risk of burn injury.
- **Eye:** (1) Use topical anesthetic and lid retractor; (2) irrigate with 1 to 2 L sterile balanced salt solution (BSS) preferred over normal saline, lactated Ringer's solution, water irrigation; (3) apply pH strip to fornix to monitor and maintain pH 6.5 to 7.6. Alkalis cause liquefaction necrosis of lipoproteins and result in more severe conjunctival and mucosal burns than acids, which produce coagulation necrosis that blocks further tissue penetration.

Pharmacokinetics

Drug Compartment Models

- **One-compartment model:** Simple instantaneous equilibration model in which drug or toxin enters central circulatory compartment and is rapidly distributed to tissues, with plasma concentrations determining proportional changes in tissue concentrations. Example: ethanol.
- **Two-compartment model:** Most common model in which drug or toxin instantaneously distributes to two compartments — the more highly perfused central compartment and its viscera (brain, lungs, heart, liver, kidneys) and the less perfused tissue compartments (muscle, fat, skin). Example: barbiturates, volatile anesthetics.
- **Three- to five-compartment model:** Most complex model in which drug or toxin (especially heavy metals) distributes first to a central circulatory compartment, then to a highly perfused visceral compartment, and finally to the least perfused third compartment (bone, teeth, nails, hair). The soft tissue and bone compartments are often subdivided into labile and stable equilibrating subcompartments in a five-compartment model. Example: lead, cadmium.

Drug Elimination Kinetics

- **First-order:** The rate of a drug's elimination is directly proportional to its plasma concentration; a constant percentage of drug is eliminated per unit time. A plot of concentration vs. time is curvilinear. Example: most drugs.
- **Zero-order:** A constant amount of drug is eliminated per unit time, reflecting a saturation of the drug's metabolizing enzyme systems. Plot of concentration vs. time is linear. Example: alcohol.
- **Michaelis-Menten:** Drug elimination pattern changes from first-order to zero-order kinetics as drug concentration increases, reflecting gradual saturation of metabolizing pathways. Both plots of concentration vs. time are curvilinear.

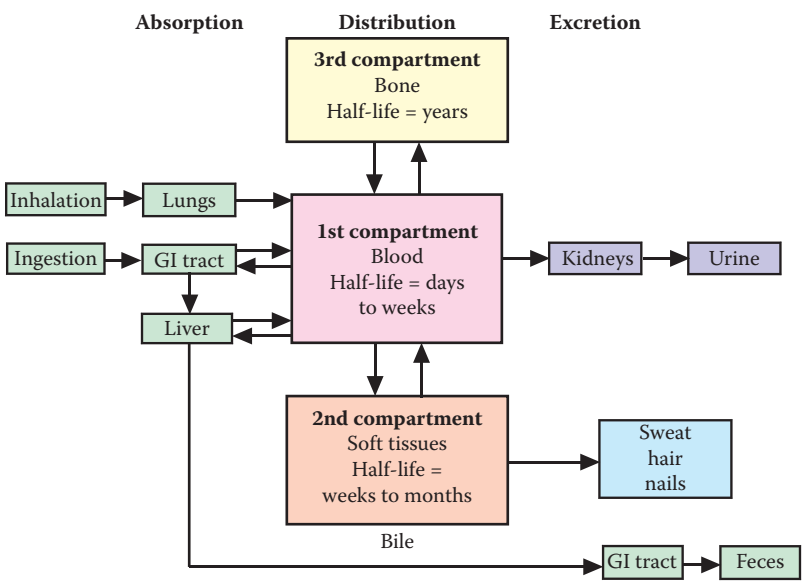

FIGURE 3.1 Ingested lead distributes in a three-compartment model. Ingested lead is distributed in a three-compartment model in which the heavy metal is initially distributed to a central circulatory compartment; then to a highly perfused visceral organ compartment; and finally to the least perfused third compartment composed of bone, teeth, nails, and hair.