Stoelting's

Pharmacology & Physiology in Anesthetic Practice

Sixth Edition

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DEDICATION

My coauthors and I dedicate this sixth edition of *Stoelting's Pharmacology & Physiology in Anesthetic Practice* to our dear colleague, coauthor, and friend, Dr. Mohamed A. Naguib, who passed away in 2020 at the age of 68 years.

Mohamed was a clinical anesthesiologist, a National Institutes of Health–funded basic scientist, and an entrepreneur who founded a company to develop new therapies for neuropathic pain based on his research. He was the mentor of record to many, including some of his coauthors in this edition. He was an unofficial mentor to countless others, including nearly the entire community of clinical pharmacologists in anesthesia.

You have likely read at least some of his more than 400 scientific papers and many books and book chapters. Mohamed's seven (!) chapters in the sixth edition of *Stoelting's Pharmacology & Physiology in Anesthetic Practice* reflect his academic rigor and clear writing. They also reflect his dedication to teaching; Mohamed was the first author to complete his chapters for this edition. His chapters in this edition reflect his academic breadth, ranging from analgesic pharmacology to neuromuscular physiology.

Those of you who were fortunate to know Mohamed will miss his enthusiasm for science, ready smile, and dry wit. I fondly recall discussing his elegant study of the mechanism that underlies anesthetic-induced cognitive dysfunction in neonatal rats. This is among my favorite papers in the anesthesiology literature. Mohamed demonstrated that the neurologic deficit in development induced by anesthesia in neonatal rats could be reversed with an enriched environment.

Sitting at a back table at a meeting on anesthetic mechanisms, Mohamed described how he created an enriched environment for a rat. How did he know what a baby rat would find entertaining? He leveraged his experience as a parent, creating a playroom for his baby rats. He placed a "play group" of six baby rats in a large space (preschool) and filled it with toys including running wheels and fun stuff for the rats to explore. Our discussion broke down into laughter about his baby rat playroom, with both of us concluding it might be more fun than the meeting we were attending. We were laughing so hard that we disrupted the speaker! Oops . . .

That was the last time I saw Mohamed.

Mohamed's scholarship, intellectual rigor, and ability to clearly explain complex concepts are fully evident in this edition of *Stoelting's Pharmacology & Physiology in Anesthetic Practice*. We will miss this amazing clinician, scientist, teacher, and friend.

Pamela Flood, MD, MA

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FOREWORD TO THE SIXTH EDITION

My journey with *Pharmacology and Physiology in Anesthetic Practice* began in the early 1980s with what seemed an impossible dream, a single-author anesthesia textbook devoted to the *daily application of principles of pharmacology and physiology in the care of patients*. Many yellow tablets later (my computer skills were in their infancy); an understanding family, residents, and faculty in the Department of Anesthesia at Indiana University School of Medicine; and the unwavering support and encouragement of a special friend and publisher, the first edition of *Pharmacology and Physiology in Anesthetic Practice* appeared in the fall of 1986.

The acceptance of the textbook by students, trainees, and practitioners over the years has been incredibly rewarding to me personally and served as the stimulus to create revisions for the next three editions with Simon C. Hillier, MB, ChB, joining me as a coeditor for the fourth edition that appeared in 2006.

It is clearly time for a new edition and a new approach if *Pharmacology and Physiology in Anesthetic Practice* is going to continue to meet its original goal of *providing an in-depth but concise and current presentation of those aspects of pharmacology and physiology that are relevant either directly or indirectly to the perioperative anesthetic management of patients*.

In this regard, I could not be more pleased and honored that Drs. Pamela Flood, James P. Rathmell, and Richard D. Urman agreed to act as coeditors of this multi-authored sixth edition. Their unique expertise and access to recognized authorities in the wide and expanding areas of pharmacology and physiology that impact the perioperative care of patients is clearly evident in this edition.

On behalf of myself and all our past (and future) readers, I thank the new coeditors and their authors for keeping *Stoelting's Pharmacology & Physiology in Anesthetic Practice* current with the times and fulfilling the dream I had more than 30 years ago.

Robert K. Stoelting, MD

PREFACE TO THE SIXTH EDITION

Robert Stoelting is among the best writers in our specialty. His signature textbook, *Pharmacology and Physiology in Anesthetic Practice*, resonated with residents and faculty, including us, because it was exceptionally well written. It has been the "go-to" reference since its first edition in 1986. Dr. Stoelting's clear prose succinctly covered the drugs we were using in our daily practice. His explanations of physiology were intuitive and sensible. Every chapter in the earlier editions spoke with the same voice, reflecting the many years he invested in refining his single-authored textbook. Even though Dr. Hillier joined him as coauthor of the fourth edition, the text continued to resonate as a single voice.

When first approached about revising the textbook for the fifth edition, we turned down the project. It seemed impossible to reproduce the clarity of Dr. Stoelting's work. However, the option for the publisher was to transform *Pharmacology and Physiology in Anesthetic Practice* into a conventional multi-authored textbook. Although it felt a bit like sacrilege to reduce one of the revered texts in our specialty to a "me too" multi-authored textbook, we agreed to take on the task.

The hybrid model developed for the fifth edition was undertaken by a small number of senior authors who were tasked with updating this classic text in their areas of expertise. This undertaking was daunting, but the model worked. We have maintained this structure for the sixth edition along with most of our authors.

We are proud to bring the sixth edition of *Stoelting's Pharmacology & Physiology in Anesthetic Practice* to anesthesiology residents, clinicians, and investigators. We have tried to maintain the succinct elegance of Dr. Stoelting's writing updated with the latest state-of-the-art knowledge and methods in anesthetic pharmacology and physiology.

Is everything in this book correct? No. The authors of each chapter have imperfect understanding; knowledge changes, and mistakes happen. Wikipedia brilliantly addresses this by allowing readers who catch errors to fix them. We can't implement the "Wikipedia approach" in a textbook, but we can come close by inviting you, the reader compulsive enough to read the Preface, to bring any errors, corrections, or suggestions to our attention. We invite our readers to become "peer reviewers," pointing us toward new information that should be included, out-of-date references, drugs no longer used, or missing content relevant to pharmacology and physiology in anesthesia practice. In this manner, readers will become collaborators for all future editions.

Finally, we have to acknowledge the efforts of our publishers, including Keith Donnellan, Ashley Fischer, Anthony Gonzalez, Tim Rinehart, and Harold Medina. No textbook comes to fruition without careful guidance, attention to detail, and occasional cajoling. In this case, they went full force on all three of us to maintain the gem that Bob Stoelting created.

Pamela Flood, MD, MA
James P. Rathmell, MD, MS
Richard D. Urman, MD, MBA

CONTENTS

CHAPTER 1

Basic Principles of Physiology

Pamela Flood • Lisa Wise-Faberowski • Steven L. Shafer

This chapter reviews the basic principles of the composition of the body, and the structure of cells. Although very basic, these principles are essential for everything that follows.

Body Composition

Water is the medium in which all metabolic reactions occur. Water accounts for about 60% of the weight in an adult man and about 50% of the body weight in an adult woman (**Figure 1.1**).[1] In a neonate, total body water may represent 70% of body weight. Total body water is less in women and obese individuals, reflecting the decreased water content of adipose tissue. Advanced age is also associated with increased fat content and decreased total body water (**Table 1.1**). Body fluids can be divided into intracellular and extracellular fluid depending on their location relative to the cell membrane (see **Figure 1.1**).[1] Approximately two-thirds of the total body fluid in an adult are contained inside the estimated 100 trillion cells of the body. The fluid in these cells, despite individual differences in constituents, is collectively designated *intracellular fluid*. *Extracellular fluid*, one-third of fluid outside the cells, is divided into interstitial fluid and plasma (intravascular fluid) by the capillary membrane (see **Figure 1.1**).[1]

Interstitial fluid is present in the spaces between cells. An estimated 99% of this fluid is held in the gel structure of the interstitial space. Plasma is the noncellular portion of blood. The average plasma volume is 3 L, a little over half of the blood volume of 5 L. Plasma is in dynamic equilibrium with the interstitial fluid through pores in the capillaries, the interstitial fluid serving as a reservoir from which water and electrolytes can be mobilized into the circulation. Loss of plasma volume from the intravascular space is minimized by colloid osmotic pressure exerted by the plasma proteins.

Other extracellular fluid that may be considered as part of the interstitial fluid includes cerebrospinal fluid, gastrointestinal fluid (because it is mostly resorbed), and fluid in potential spaces (pleural space, pericardial space, peritoneal cavity, synovial cavities). Excess amounts of fluid in the interstitial space manifest as peripheral edema.

The normal daily intake of water (drink and internal product of food metabolism) by an adult averages 2.5 L, of which about 1.5 L is excreted as urine, 100 mL is lost in sweat, and 100 mL is present in feces. Insensible water losses occur with respiration and diffusion through the skin. Inhaled air, saturated with water vapor (47 mm Hg at 37°C), is subsequently exhaled, accounting for an average daily water loss through the lungs of 300 to 400 mL. The water content of inhaled air decreases with decreases in ambient air temperature such that more endogenous water is required to achieve a saturated water vapor pressure at body temperature. As a result, insensible water loss from the lungs is greatest in cold environments and least in warm temperatures. The remaining 400 mL of insensible losses is by diffusion through the skin and is not perceived as sweat. Insensible water loss is limited by the mostly impermeable cornified layer of the skin. When the cornified layer is removed or interrupted, as after burn injury, the loss of water through the skin is greatly increased.

Blood Volume

Blood contains extracellular fluid, the plasma, and intracellular fluid, mostly held in erythrocytes. The body has multiple systems to maintain intravascular fluid volume, including renin-angiotensin system, and arginine vasopressin (antidiuretic hormone), that increase fluid resorption in the kidney and evoke changes in the renal tubules that lead to restoration of intravascular fluid volume (see Chapter 16).

The average blood volume of an adult is 5 L, compromising about 3 L of plasma and 2 L of erythrocytes. These volumes vary with age, weight, and gender. For example, in nonobese individuals, the blood volume varies in direct proportion to the body weight, averaging 70 mL/kg for lean men and women. The greater the ratio of fat to body weight,

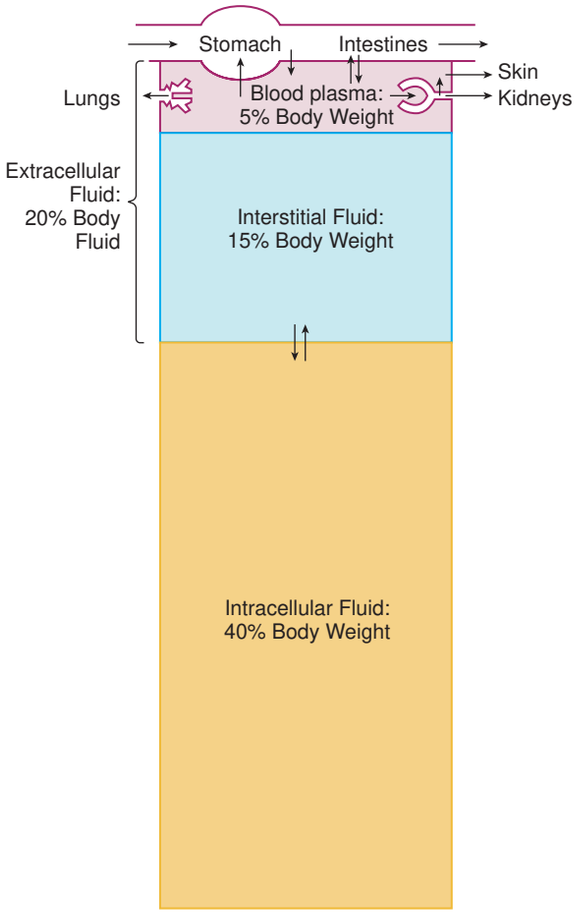

FIGURE 1.1 Body fluid compartments and the percentage of body weight represented by each compartment. The location relative to the capillary membrane divides extracellular fluid into plasma or interstitial fluid. Arrows represent fluid movement between compartments. *Reprinted with permission from Gamble JL.* Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid: A Lecture Syllabus. *6th ed. Cambridge, MA: Harvard University Press; 1954:9. Copyright © 1954 by the President and Fellows of Harvard College.*

however, the less is the blood volume in milliliter per kilogram because adipose tissue has a decreased vascular supply. The hematocrit or packed cell volume is approximately the erythrocyte fraction blood. The normal hematocrit is about 45% for men and postmenopausal women and about 38% for menstruating women, with a range of approximately ±5%.

TABLE 1.1
Total body water by age and gender

	Total body water	
Age (y)	Men (%)	Women (%)
18-40	61	51
41-60	55	47
>60	52	46

Constituents of Body Fluid Compartments

The constituents of intracellular and extracellular fluid are identical, but the quantity of each substance varies among the compartments (**Figure 1.2**).[2] The most striking differences are the low protein content in interstitial fluid compared with intracellular fluid and plasma and the fact that sodium and chloride ions are largely extracellular, whereas most of the potassium ions (approximately 90%) are intracellular. This unequal distribution of ions results in establishment of a potential (voltage) difference across cell membranes.

The constituents of extracellular fluid are carefully regulated by the kidneys so that cells are bathed in an osmotically neutral fluid containing the proper concentrations of electrolytes and nutrients. The normal amount of sodium and potassium in the body is about 58 mEq/kg and 45 mEq/kg, respectively. Trauma is associated with progressive loss of potassium through the kidneys. For example, a patient undergoing surgery excretes about 100 mEq of potassium in the first 48 hours postoperatively and, after this period, about 25 mEq daily. Plasma potassium concentrations are not good indicators of total body potassium content because most potassium is intracellular. There is a correlation, however, between the potassium and hydrogen ion content of plasma, the two increasing and decreasing together. In metabolic acidosis, there is net efflux of potassium out of the cells to compensate for the hydrogen ion influx and preserve the resting potential. As metabolic acidosis is treated, the plasma potassium will fall from that measured in the acidotic state.

Osmosis

Osmosis is the movement of water (solvent molecules) across a semipermeable membrane from a compartment in which the nondiffusible solute (ion) concentration is lower to a compartment in which the solute concentration is higher (**Figure 1.3**).[3] The lipid bilayer that surrounds all cells is freely permeable to water but is impermeable to ions. As a result, water rapidly moves across the cell membrane to establish osmotic equilibration, which happens almost instantly.

Cells control their size by controlling intracellular osmotic pressure. The maintenance of a normal cell volume and pressure depends on sodium-potassium adenosine triphosphatase (ATPase) (sodium-potassium exchange pump), which maintains the intracellular-extracellular ionic balance by removing three sodium ions from the cell for every two potassium ions brought into the cell. The sodium-potassium pump also maintains the transmembrane electrical potential and the sodium and potassium concentration gradients that power many cellular processes, including neuronal conduction.

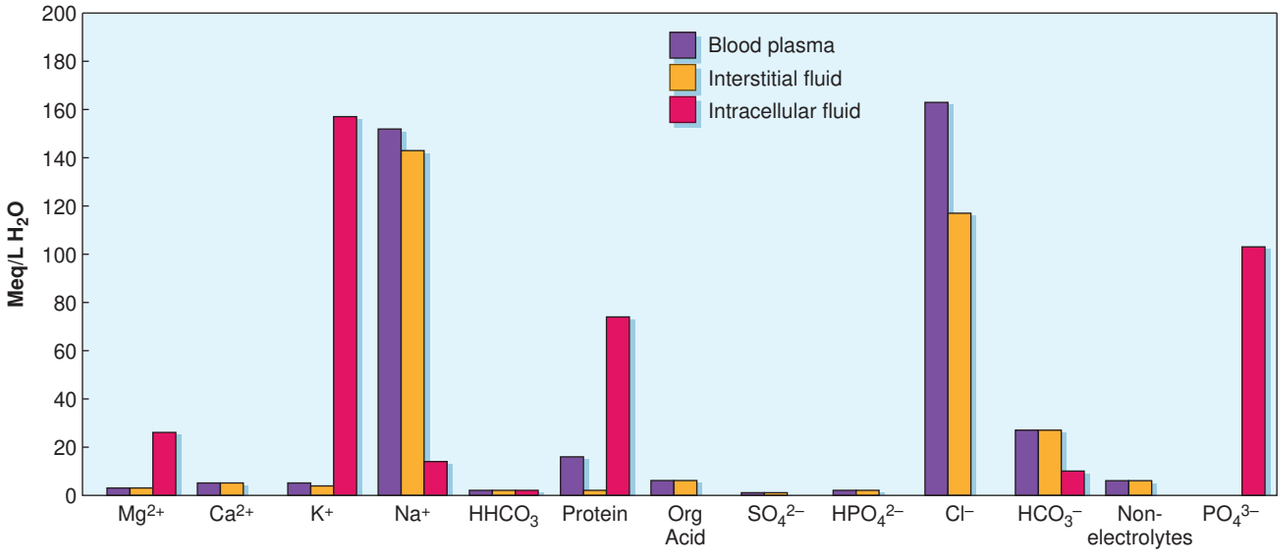

FIGURE 1.2 Electrolyte composition of body fluid compartments.

The osmotic pressure exerted by nondiffusible particles in a solution is determined by the number of particles in the solution (with each ion counting as 1 unit) and not the type of particles (molecular weight) (see **Figure 1.3**).[3] Thus, a 1-mol solution of glucose or albumin and 0.5-mol solution of sodium chloride exert the same osmotic pressure because the sodium chloride exists as independent sodium and chloride ions, each having a concentration of 0.5 mol.

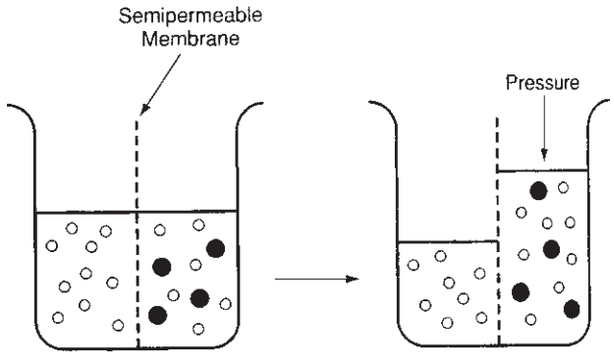

FIGURE 1.3 Diagrammatic representation of osmosis depicting water molecules (open circles) and solute molecules (solid circles) separated by a semipermeable membrane. Water molecules move across the semipermeable membrane to the area of higher concentration of solute molecules. Osmotic pressure is the pressure that would have to be applied to prevent continued movement of water molecules. *Republished with permission of McGraw Hill LLC from Ganong WF.* Review of Medical Physiology. *21st ed. New York, NY: Lange Medical Books/ McGraw-Hill; 2003; permission conveyed through Copyright Clearance Center, Inc.*

Osmole is the unit used to express osmotic pressure in solutes, but the denominator for osmolality is kilogram of *water*. *Osmolarity* is the correct terminology when osmole concentrations are expressed in liters of body fluid (eg, plasma) rather than kilograms of water. Because it is much easier to express body fluids in liters of fluid rather than kilograms of free water, almost all physiology calculations are based on osmolarity. Plasma osmolarity is important in evaluating dehydration, overhydration, and electrolyte abnormalities.

Normal plasma has an osmolarity of about 290 mOsm/L. All but about 20 mOsm of the 290 mOsm in each liter of plasma are contributed by sodium ions and their accompanying anions, principally chloride and bicarbonate. Proteins normally contribute <1 mOsm/L. The major nonelectrolytes of plasma are glucose and urea, and these substances can contribute significantly to plasma osmolarity when hyperglycemia or uremia is present, as suggested by the standard calculation of plasma osmolarity:

$$\text{Plasma osmolarity} = 2\,(Na^+) + 0.055\,(\text{glucose}) + 0.36\,(\text{blood urea nitrogen}).$$

Tonicity of Fluids

Packed erythrocytes must be suspended in **isotonic** solutions to avoid damaging the cells (**Figure 1.4**).[4] A 0.9% solution of sodium chloride is isotonic and remains so because there is no net movement of the osmotically active particles in the solution into cells, and the particles are not metabolized. A solution of 5% glucose in water is initially isotonic when infused, but glucose is metabolized, so the net effect is that of infusing a hypotonic solution. Lactated Ringer solution plus 5% glucose is initially hypertonic (about 560 mOsm/L), but as glucose is metabolized, the solution becomes less hypertonic.

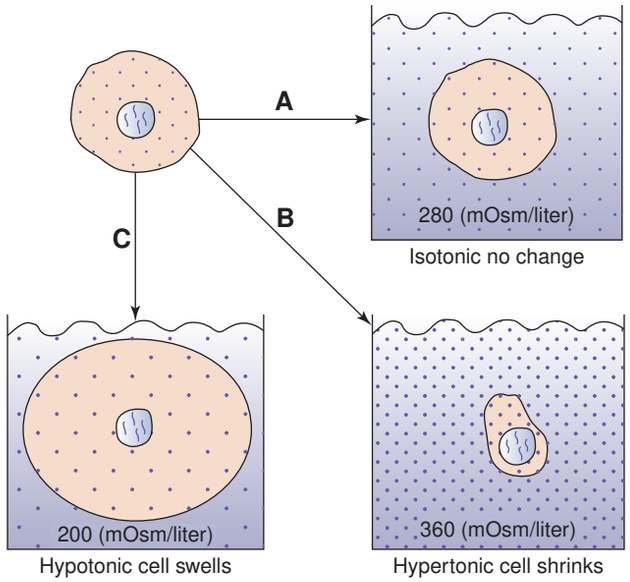

FIGURE 1.4 Effects of isotonic (A), hypertonic (B), and hypotonic (C) solutions on cell volume. *Reprinted from Guyton AC, Hall JE.* Textbook of Medical Physiology. *10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.*

Fluid Management

The goal of fluid management is to maintain normovolemia characterized by hemodynamic stability. Crystalloids consist of water, electrolytes, and occasionally glucose that freely distribute along a concentration gradient between the two extracellular spaces. After 20 to 30 minutes, an estimated 75% to 80% of an isotonic saline or a lactate-containing solution will have distributed outside the confines of the circulation, thus limiting the efficacy of these solutions in treating hypovolemia. The major goal of fluid resuscitation is to maintain microcirculatory perfusion to preserve the delivery of oxygen and glucose to the tissues. Measurement of systemic blood pressure or central venous pressure does not provide an accurate picture of specific organ micro perfusion. Indeed, microperfusion of individual organs it tightly regulated in most situations to prioritize tissue perfusion to the brain with other organs delegated to secondary status. A variety of techniques have been developed to measure microcirculation, the most common being sublingual with handheld microscopy.[5]

Hypotonic intravenous fluids equilibrate with extracellular fluid, causing it to become hypotonic with respect to intracellular fluid. When this occurs, osmosis rapidly increases intracellular water, causing cellular swelling. Increased intracellular fluid volume is particularly undesirable in patients with increased intracranial pressure or an intracranial mass. Protection from excessive fluid accumulation in the interstitial compartment is mediated by lymphatic flow, which can increase as much as tenfold but can be overwhelmed. The lymphatic system can be obstructed by surgery as after extensive axillary resection for breast cancer and tumor invasion causing distal tissue edema.

Hypertonic saline solutions (7.5% sodium chloride) have been useful for rapid intravascular fluid repletion during resuscitation as during hemorrhagic and septic shock. Hypertonic saline solutions compare favorably with mannitol for lowering intracranial pressure.[6] The primary effect of hypertonic saline solutions (increase systemic blood pressure and decrease intracranial pressure) most likely reflects increased intravascular fluid volume because of fluid shifts and movement of water away from uninjured region of the brain. In a secondary analysis of the data from the Resuscitation Outcomes Consortium Hypertonic Saline Trial Shock Study and Traumatic Brain Injury Study, the effect of hypertonic saline alone was compared with that of hypertonic saline plus mannitol on renal function after acute brain injury.[7] The combination was not superior to treatment with hypertonic saline alone. The use of hypertonic saline solutions is viewed as short-term treatment as hypertonicity and hypernatremia are likely with sustained administration.

Albumin should remain within the intracellular space longer than crystalloids in the setting of an intact vascular endothelial and blood–brain barrier. However, the vascular endothelium is commonly damaged by trauma, hyperglycemia, and sepsis, obviating this advantage.[8] While the administration of albumin makes sense, no randomized controlled trial has demonstrated long-term benefit over other solutions except perhaps in septic shock.[9]

Dehydration

Loss of water by gastrointestinal or renal routes or by diaphoresis is associated with an initial deficit in extracellular fluid volume. Intracellular water partly repletes this loss through osmosis, keeping the osmolarities in both compartments equal despite decreased absolute volume (dehydration) of both compartments. The ratio of extracellular fluid to intracellular fluid is greater in infants than adults, but the absolute volume of extracellular fluid is obviously less in infants. This is why dehydration develops more rapidly and is often more severe in the very young. Clinical signs of dehydration are likely when about 5% to 10% (severe dehydration) of total body water has been lost in a brief period of time. Physiologic mechanisms can usually compensate for acute loss of 15% to 25% of the intravascular fluid volume, whereas a greater loss places the patient at risk for hemodynamic decompensation.

Cell Structure and Function

The basic living unit of the body is the cell. It is estimated that the entire body consists of 38 trillion cells, 85% of which are (amazingly) erythrocytes. We cohabit our bodies with

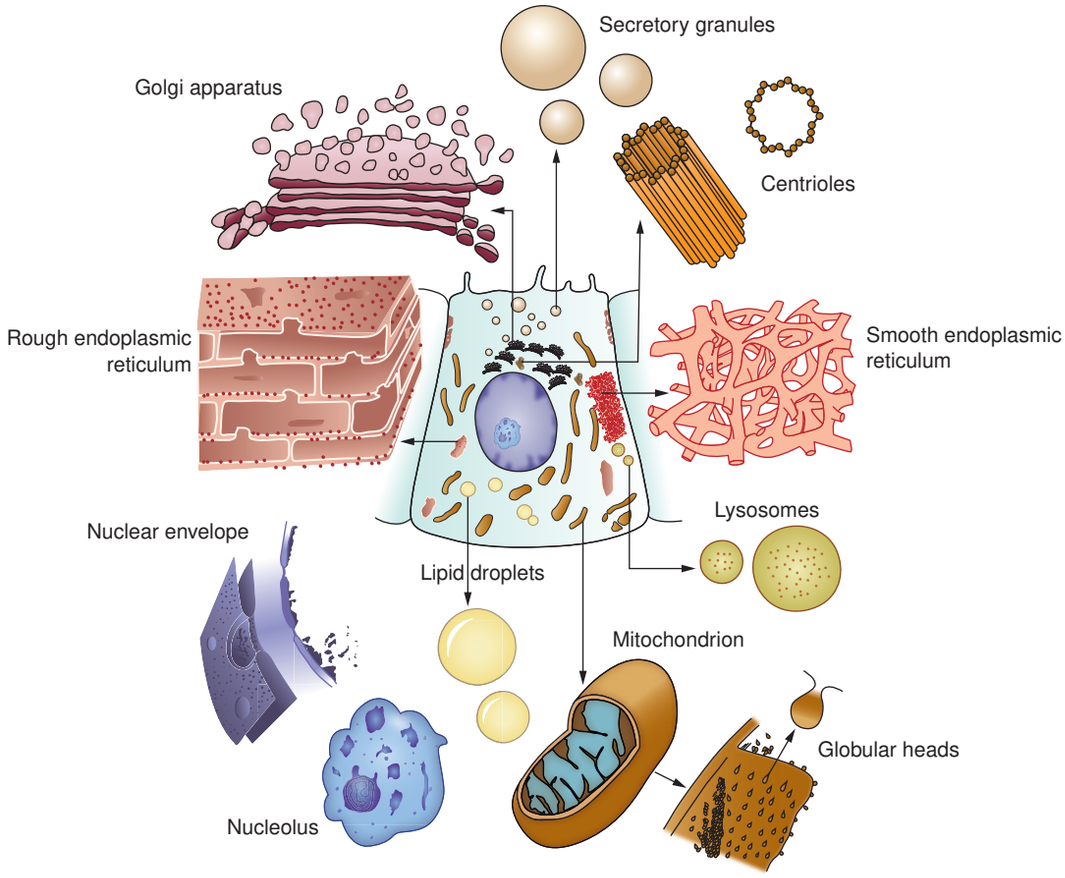

FIGURE 1.5 Schematic diagram of a hypothetical cell (center) and its organelles. *Republished with permission of McGraw Hill LLC from Junqueira LC, Carneiro J, Kelley RO.* Basic Histology. *7th ed. Norwalk, CT: Appleton & Lange, 1992; permission conveyed through Copyright Clearance Center, Inc.*

an approximately equal number of bacterial cells, which fortunately only contribute about 0.2 kg to our total mass.[10] Each organ is a mass of cells held together by intracellular supporting structures.

All mammalian cells literally burn nutrients (ie, carbohydrates, lipids, proteins) using intracellular oxygen to release energy necessary for cellular function. Almost every cell is within 25 to 50 microns of a capillary, assuring prompt diffusion of oxygen to cells. All cells exist in nearly the same composition of extracellular fluid. Our organs (lungs, kidneys, gastrointestinal tract) function to maintain a constant composition (homeostasis) of extracellular fluid.

Cell Anatomy

The principal components of cells include the nucleus (except for mature red blood cells) and the cytoplasm, which contains structures known as *organelles* (**Figure 1.5**).[11] The nucleus is separated from the cytoplasm by the nuclear membrane, and the cytoplasm is separated from surrounding fluids by a cell membrane. Organelles are also enclosed by membranes. All cellular membranes are lipid bilayers.

Cell Membrane

The lipid bilayer acts as a permeability barrier, allowing the cell to maintain a cytoplasmic composition different from extracellular fluid. Proteins and phospholipids are the most abundant constituents of cell membranes (**Table 1.2**). The lipid bilayer is interspersed with large

TABLE 1.2
Cell membrane composition

Phospholipids
Lecithins (phosphatidylcholines)
Sphingomyelins
Amino phospholipids (phosphatidylethanolamine)
Proteins
Structural proteins (microtubules)
Transport proteins (sodium-potassium ATPase)
Ion channels
Receptors
Enzymes (adenylate cyclase)

Abbreviation: ATPase, adenosine triphosphatase.

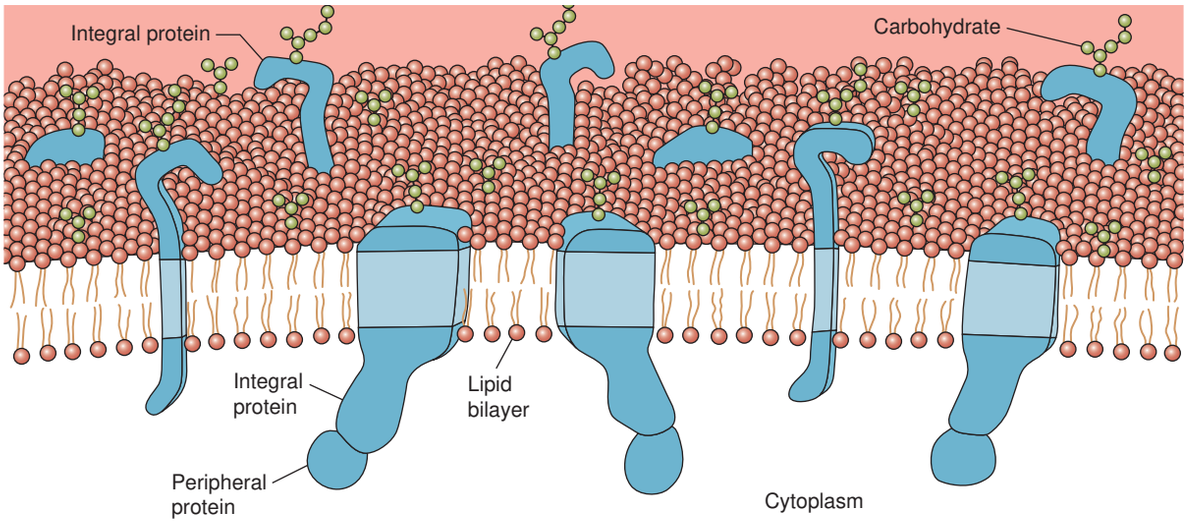

FIGURE 1.6 The cell membrane is a two molecule–thick lipid bilayer containing protein molecules that extend through the bilayer.

globular proteins (**Figure 1.6**).[12] Lipid bilayers are readily permeable to water, both through passive diffusion and through aquaporins, specialized proteins in the membrane that function as water channels described in the following text. Lipid bilayers are nearly impermeable to water-soluble substances, such as ions and glucose. Ions and charged water-soluble molecules require specialized channel and transport pumps to enter the intracellular environments. Conversely, fat-soluble substances (eg, steroids) and gases readily cross hydrophobic cell membranes.

There are several types of proteins in the cell membrane (see **Table 1.2**). In addition to structural proteins (microtubules), there are transport proteins (eg, sodium-potassium ATPase) that function as pumps, actively transporting ions across cell membranes. Other proteins function as passive channels for ions that can be opened or closed by changes in the conformation of the protein. There are proteins that function as receptors to bind ligands (hormones or neurotransmitters), thus initiating physiologic changes inside cells. Another group of proteins function as enzymes (adenylate cyclase), catalyzing reactions at the surface of cell membranes. The protein structure of cell membranes, especially the enzyme content, varies from cell to cell.

Transfer of Molecules Through Cell Membranes

Diffusion

Oxygen, carbon dioxide, and nitrogen move through cell membranes by diffusion through the lipid bilayer. Because diffusion is relatively slow over macroscopic distances, organisms have developed circulatory systems to deliver nutrients within reasonable diffusion ranges of cells (**Table 1.3**). Water is also able to diffuse through cells as described earlier, although not as freely as the gases.

Poorly lipid-soluble substances, such as glucose and amino acids, may pass through lipid bilayers by facilitated diffusion. For example, glucose combines with a carrier to form a complex that is lipid soluble. This lipid-soluble complex can diffuse to the interior of the cell membrane where glucose is released into the cytoplasm. The carrier then moves back to the exterior of the cell membrane, where it becomes available to transport more glucose from the extracellular fluid (**Figure 1.7**).[4] As such, the carrier renders glucose soluble in cell membranes that otherwise would prevent its passage. Insulin greatly speeds facilitated diffusion of glucose and some amino acids across cell membranes.

Endocytosis and Exocytosis

Endocytosis and exocytosis transfer molecules such as nutrients across cell membranes without the molecule actually passing through a cell membranes. The uptake of particulate matter (bacteria, damaged cells) by cells

TABLE 1.3
Predicted relationship between diffusion distance and time

Diffusion distance (mm)	Time required for diffusion
0.001	0.5 ms
0.01	50 ms
0.1	5 s
1	498 s
10	14 h

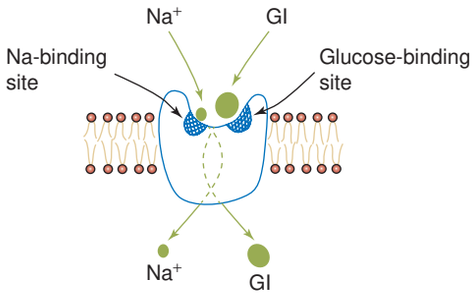

FIGURE 1.7 Glucose (Gl) can combine with a sodium (Na) cotransport carrier system at the outside surface of the cell membrane to facilitate diffusion (carrier-mediated diffusion) of Gl across the cell membrane. At the inside surface of the cell membrane, Gl is released to the interior of the cell and the carrier again becomes available for reuse. *Reprinted from Guyton AC, Hall JE.* Textbook of Medical Physiology. *10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.*

is phagocytosis, whereas uptake of materials in solution in the extracellular fluid is pinocytosis (**Figure 1.8**).[13] The process of phagocytosis is initiated when antibodies attach to damaged tissue and foreign substances (opsonization), facilitating binding to specialized proteins on the cell surface. Fusion of phagocytic or pinocytic vesicles with lysosomes allows intracellular digestion of materials to proceed. Neurotransmitters are ejected from cells by exocytosis from specialized presynaptic vesicles activated by an action potential. This process requires calcium ions and resembles endocytosis in reverse.

Sodium-Potassium Adenosine Triphosphatase

As mentioned previously, sodium-potassium ATPase, also known as the sodium-potassium pump, is an adenosine triphosphate (ATP)-dependent sodium and potassium transporter on the cell membrane that ejects three sodium ions from the cell in exchange for the import of two potassium ions (**Figure 1.9**).[4] This action maintains oncotic equilibration across the cell membrane, reducing the number of intracellular ions to balance the large

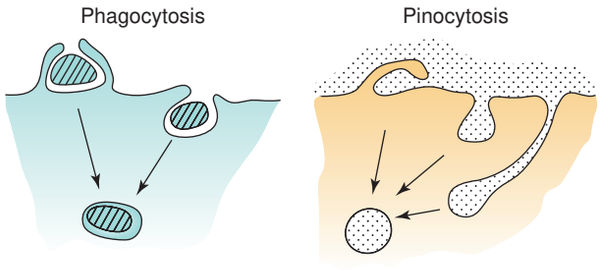

FIGURE 1.8 Schematic depiction of phagocytosis (ingestion of solid particles) and pinocytosis (ingestion of dissolved particles). *From Berne RM, Levy MN, Koeppen BM, et al.* Physiology. *5th ed. St Louis, MO: Mosby; 2004, Reprinted with permission from Bruce M. Koeppen, MD.*

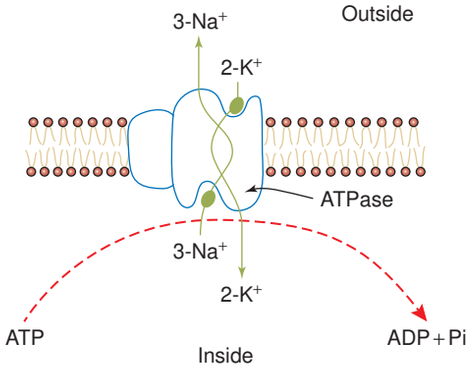

FIGURE 1.9 Sodium (Na)-potassium (K) adenosine triphosphatase (ATPase) is an enzyme present in all cells that catalyzes the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP). The resulting energy is used by the active transport carrier system (sodium pump) that is responsible for the outward movement of three sodium ions across the cell membrane for every two potassium ions that pass inward. Abbreviation: Pi, inorganic phosphate. *Reprinted from Guyton AC, Hall JE.* Textbook of Medical Physiology. *10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.*

number of protein and other intracellular constituents. It also is responsible for creating the transmembrane electrical potential, creating a net positive charge on the outside of the cell from the excess of positive sodium ions outside compared to number of positive potassium ions inside of the cell. Lastly, it creates the sodium gradients responsible for propagation of the action potential and the potassium gradient that rapidly restores the resting membrane potential after conduction of an action potential. In the brain, the sodium-potassium pump accounts for nearly 50% of energy consumption.[14]

Other ion transporters include hydrogen-potassium ATPases in the gastric mucosa and renal tubules, the transporter that exchanges protons for potassium ions. Calcium ATPases are responsible for maintaining very low cytoplasmic concentrations of calcium, either by ejecting it from the cell (plasma membrane calcium ATPase) or sequestering calcium in the endoplasmic reticulum via the sarcoplasmic/endoplasmic reticulum calcium ATPase.[15]

Ion Channels

Ion channels are transmembrane proteins that generate electrical signals the brain, nerves, heart, and skeletal muscles (**Figure 1.10**).[16] Ion channels use the energy stored in the chemical and electrical gradients created by sodium-potassium ATPase to rapidly initiate changes in transmembrane potential, causing conduction of an action potential.

Because of their charge, most ions are relatively insoluble in cell membranes. Ions pass through cell membranes primarily through "ion channels" in transmembrane proteins. Ion channels are intermolecular spaces that ex-

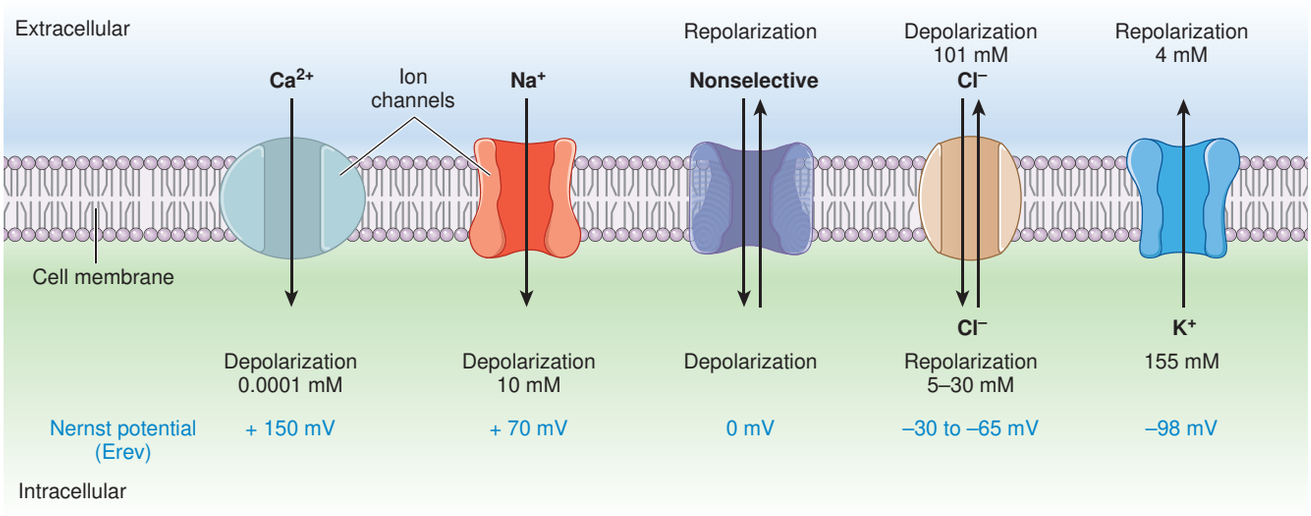

FIGURE 1.10 Ion channels that traverse the lipid bilayer to allow ion transport in response to a ligand or change in membrane potential. Sodium and calcium flow into the cell to facilitate depolarization while chloride and potassium have net outward flow to allow for repolarization. Non-selective channels carry multiple ions but favor repolarization at the cell's resting potential.

tend through the entire cell membrane. Some channels are highly specific with respect to ions allowed to pass (sodium, potassium), whereas other channels allow all ions below a certain size to pass (**Table 1.4**). Neurotransmitter receptors such as those for γ-aminobutyric acid, glycine, glutamate, and others are activated upon the binding of the transmitter to open or close the channel to their specific anion or cation. Movement of the ion alters the resting potential of the cell to facilitate or suppress the generation of an action potential.

Genes encoding the protein ion channels may be defective, leading to diseases such as cystic fibrosis (chloride channel defects), long Q-T interval syndrome (mutant potassium or [less commonly] sodium channels), hereditary nephrolithiasis (chloride channel), hereditary myopathies including myotonia congenital (chloride channel), and malignant hyperthermia (eg, the ryanodine receptor, the primary receptor releasing calcium from the sarcoplasmic reticulum)[17] or the α_1 subunit of the dihydropyridine receptor encoded by the CACNA1S gene.[18] The CACNA1S encoded calcium. Many drugs target ion channels, including common intravenous and inhalational anesthetics. Although details on the physiologic underpinning of most drugs is understood, the mechanism that underlies the action of inhalational anesthetics remains a well-studied mystery.[19,20] Ion channels are discussed further in detail in Chapter 3. Their interactions with general anesthetics are discussed in Chapter 4.

TABLE 1.4
Diameters of ions, molecules, and channels

	Diameter (nm)[a]
Channel (average)	0.80
Water	0.30
Sodium (hydrated)	0.51
Potassium (hydrated)	0.40
Chloride (hydrated)	0.39
Glucose	0.86

[a]1 nm = 10 Å.

Protein-Mediated Transport

Protein-mediated transport is responsible for movement of specific substrates across cell membranes. Indeed, carrier molecules are enzymes (specifically ATPases) that catalyze the hydrolysis of ATP. The most important of the ATPases is sodium-potassium ATPase, commonly called the sodium pump, which pumps sodium and potassium against their chemical gradients. Substances that are actively transported through cell membranes against a concentration gradient include ions (sodium, potassium, calcium, hydrogen, chloride, and magnesium), iodide (thyroid gland), carbohydrates, and amino acids.

P-glycoprotein is the primary transmembrane transporter, particularly for transporting drugs across the

blood–brain barrier. Notably, the transport of morphine out of the CNS significantly slows the rate of rise and activity of morphine in the CNS.[21] The ABC transporters (of which P-glycoprotein is a member) can be upregulated by long-term exposure to substrates including morphine and oxycodone contributing to tolerance.[22] Virtually all transport of molecules against concentration gradients requires the assistance of proteins, which utilize energy provided by ATP to pump the molecule against the concentration gradient.

Sodium Ion Cotransport

Despite the widespread presence of sodium-potassium ATPase, the active transport of sodium ions in some tissues is coupled to the transport of other substances. For example, a carrier system present in the gastrointestinal tract and renal tubules will transport sodium ions only in combination with a glucose molecule. As such, glucose is returned to the circulation, thus preventing its excretion. Sodium ion cotransport of amino acids is an active transport mechanism that supplements facilitated diffusion of amino acids into cells. Epithelial cells lining the gastrointestinal tract and renal tubules are able to reabsorb amino acids into the circulation by this mechanism, thus preventing their excretion.

Other substances, including insulin, steroids, and growth hormone, influence amino acid transport by the sodium ion cotransport mechanism. For example, estradiol facilitates transport of amino acids into the musculature of the uterus, which promotes uterine and metamorphosis during pregnancy.

Aquaporins

Aquaporins are protein channels that permit water to freely flux across cell membranes.[23] In the absence of aquaporins, diffusion of water might not be sufficiently rapid for some physiologic processes. Genetic defects in aquaporins are responsible for several clinical diseases, including some cases of congenital cataracts[24] and nephrogenic diabetes insipidus.[25]

Nucleus

The nucleus is mostly made up of the 46 chromosomes, except the nucleus of the egg cell, which contains 23. Each chromosome consists of a molecule of DNA covered with proteins including histones that tightly regulate DNA transcription. The nucleus is surrounded by a membrane that separates its contents from the cytoplasm. Nuclear pores allow transport of larger molecules, including RNA, and DNA, and proteins to pass between the nucleus and the cytoplasm.

The nucleolus is a non–membrane-bound structure within the nucleus responsible for the synthesis of ribosomes. Centrioles are present in the cytoplasm near the nucleus and coordinate the movement of chromosomes during cell division (**Figure 1.11**).

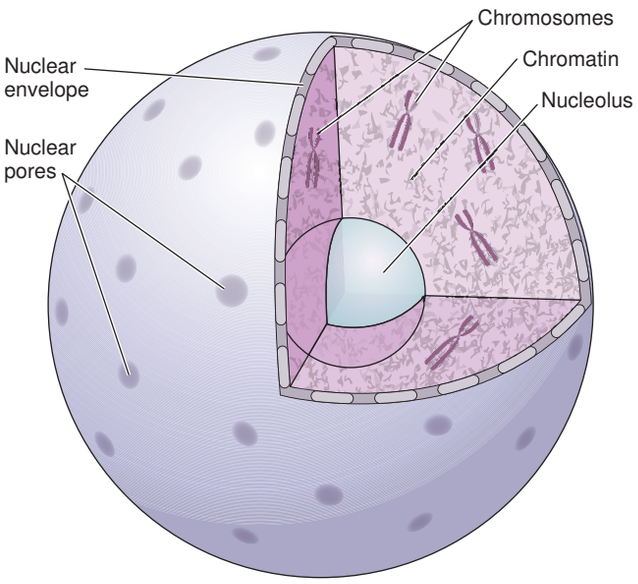

FIGURE 1.11 Contents of the cellular nucleus.

Structure and Function of DNA and RNA

The DNA consists of two complementary nucleotide chains composed of adenine, guanine, thymine, and cytosine (**Figure 1.12**).[26] The genetic message is determined by the sequence of nucleotides. The DNA is transcribed to RNA, which transfers the genetic message to the site of protein synthesis (ribosomes) in cytoplasm. All 3.2 billion base pairs of the human genome has been sequenced.[27] The protein encoding genes account for only 1% to 2% of our DNA. Our genome differs from that of chimpanzees by just 1%.[28] This explains so much!

The vast majority of our DNA consists of regulatory sequences, non-protein encoding RNA sequences (ribosomal RNA, transfer RNA and small nucleolar RNA), introns, and a considerable amount of DNA previously termed *junk* because it has no known function. Noncoding genes are transcribed to RNA but not translated to protein. There are short RNA sequences termed *microRNA* and long noncoding sequences called pseudogenes that can be transcribed from hundreds of base pairs. The physiologic functions are still being identified by include modulation of gene expression, protein function, and preservation of genomic stability in germ line cells.[29]

Cytoplasm

The cytoplasm consists of water, electrolytes, and proteins including enzymes, lipids, and carbohydrates. About 70% to 80% of the cell volume is water. Cellular chemicals are dissolved in the water, and these substances can diffuse to all parts of the cell in this fluid medium. Proteins are, next to water, the most abundant substance in most cells,

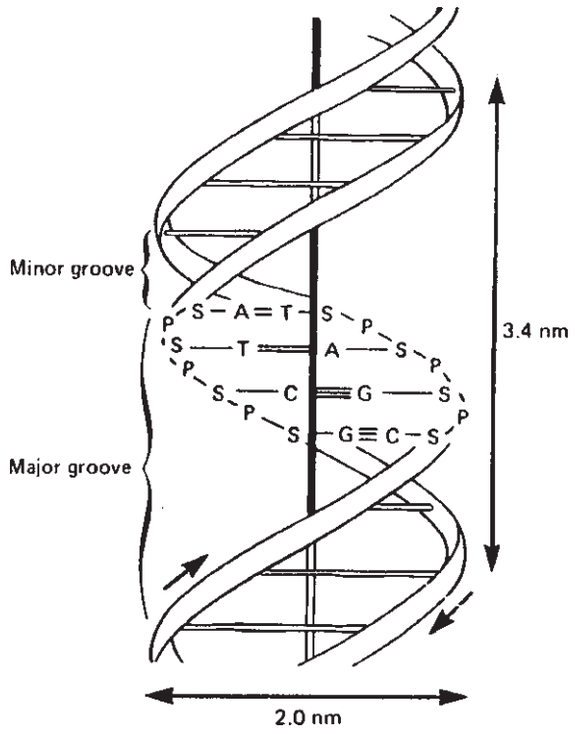

FIGURE 1.12 Double helical structure of DNA with adenine (A) bonding to thymine (T) and cytosine (C) to guanine (G). *Republished with permission from Murray RK*. Harper's Biochemistry. *23rd ed. Norwalk, CT: Appleton & Lange; 1990. Copyright © 1990 by Appleton & Lange.*

accounting for 10% to 20% of the cell mass. The cytoplasm contains numerous organelles with specific roles in cellular function.

Mitochondria

Mitochondria are the power-generating units of cells. They contain both the enzymes and substrates of the tricarboxylic acid cycle (Krebs cycle) and the electron transport chain. As a result, oxidative phosphorylation and synthesis of ATP are localized to mitochondria. The ATP leaves the mitochondria and diffuses throughout the cell, providing energy for cellular functions. Mitochondria consist of two lipid bilayers: the outer bilayer in contact with the cytoplasm and the inner layer that houses most of the biochemical machinery and the mitochondrial DNA. The space between these two membranes functions as a reservoir for protons created during electron transport. It is the movement of these protons back to the matrix, through the inner membrane, that drives the conversion of adenosine diphosphate to ATP, the primary form of intercellular energy, by ATP synthase.[30]

Increased need for ATP in the cell leads to an increase in the number of mitochondria. A number of diseases are known to be based on aberrant mitochondrial function.[31] The common element of mitochondrial diseases is aberrant cellular energetics. Mitochondria are exclusively inherited from the mother because sperm have no mitochondria. However, of the approximately 1,500 proteins responsible for mitochondrial function, only 13 are encoded by mitochondrial DNA. The balance is encoded in the nuclear DNA. Thus, the vast majority of mitochondrial diseases follow standard models of genetic inheritance.

Endoplasmic Reticulum

The endoplasmic reticulum is a complex lipid bilayer that wraps and folds creating tubules and vesicles in the cytoplasm. Ribosomes, composed mainly of RNA, attach to the outer portions of many parts of the endoplasmic reticulum membranes, serving as the sites for protein synthesis. The portion of the membrane containing these ribosomes is known as the *rough endoplasmic reticulum*. The part of the membrane that lacks ribosomes is the *smooth endoplasmic reticulum*. This smooth portion of the endoplasmic reticulum membrane functions in the synthesis of lipids, metabolism of carbohydrates, and other enzymatic processes. The sarcoplasmic reticulum is found in muscle cells, where it serves as a reservoir for calcium required for activation of the contractile apparatus.

Lysosomes

Lysosomes are lipid membrane enclosed organelles scattered throughout the cytoplasm. They function as an intracellular digestive system. Lysosomes are filled with digestive (hydrolytic) enzymes. When cells are damaged or die, these digestive enzymes cause autolysis of the remnants. Bactericidal substances in the lysosome kill phagocytized bacteria before they can cause cellular damage. These bactericidal substances include (1) lysozyme, which dissolves the cell membranes of bacteria; (2) lysoferrin, which binds iron and other metals that are essential for bacterial growth; (3) acid that has a pH of <4; and (4) hydrogen peroxide, which can disrupt some bacterial metabolic systems.

Lysosomal storage diseases are genetic disorders caused by inherited genetic defect in lysosomal function, resulting in accumulation of incompletely degradated macromolecules. There are more than 50 known lysosomal storage diseases, including Tay-Sachs, Gaucher, Fabry, and Niemann-Pick diseases.[32]

Golgi Apparatus

The Golgi apparatus is a collection of membrane-enclosed sacs that are responsible for storing proteins and lipids as well as performing postsynthetic modifications including glycosylation and phosphorylation. Proteins synthesized in the rough endoplasmic reticulum are transported to the Golgi apparatus, where they are stored in highly concentrated packets (secretory vesicles)

for subsequent release into the cell's cytoplasm, or transport to the surface for extracellular release via exocytosis. Exocytotic vesicles continuously release their content, whereas secretory vesicles store the packaged material until a triggering signal is received. Neurotransmitter release is a highly relevant (to anesthesia) example of regulated secretion. The Golgi apparatus is also responsible for creating lysosomes.

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CHAPTER 2

Basic Principles of Pharmacology

Pamela Flood • Steven L. Shafer

This chapter combines Dr. Stoelting's original elegant description of pharmacology with mathematical underpinnings first presented by Dr. Shafer[1] in 1997 and most recently in *Miller's Anesthesia*.[2,3] The combination of approaches sets a foundation for the pharmacology presented in the subsequent chapters. It also explains the fundamental principles of drug behavior and drug interaction that govern our daily practice of anesthesia.

Receptor Theory

A drug that *activates* a receptor by binding to that receptor is called an **agonist**. Most agonists bind through a combination of ionic, hydrogen, and van der Waals interactions (the sum of the attractive or repulsive forces between molecules), making them reversible. Rarely, an agonist will bind covalently to the receptor, rendering the interaction irreversible. Receptors are often envisioned as proteins that are either unbound or are bound to the agonist ligand. When the receptor is bound to the agonist ligand, the effect of the drug is produced. When the receptor is not bound, there is no effect. The receptor state is seen as binary: It is either unbound, resulting in one conformation, or it is bound, resulting in another conformation. Agonists are often portrayed as simply activating a receptor (**Figure 2.1**). In this view, the magnitude of the drug effect reflects the total number of receptors that are bound. In this simplistic view, the "most" drug effect occurs when every receptor is bound.

This simple view helps to understand the action of an antagonist (**Figure 2.2**). An **antagonist** is a drug that binds to the receptor without activating the receptor. Antagonists typically bind with ionic, hydrogen, and van der Waals interactions, rendering them reversible. Antagonists block the action of agonists simply by getting in the way of the agonist, preventing the agonist from binding to the receptor and producing the drug effect. **Competitive antagonism** is present when increasing concentrations of the antagonist progressively inhibit the response to the agonist. This causes a rightward displacement of the agonist dose-response (or concentration-response) relationship. **Noncompetitive antagonism** is present when, after administration of an antagonist, even high concentrations of agonist cannot completely overcome the antagonism. In this instance, either the agonist is bound irreversibly (and probably covalently) to the receptor site or it binds to a different site on the molecule and the interaction is allosteric (occurring at another site that fundamentally alters the activity of the receptor). Noncompetitive antagonism causes both a rightward shift of the dose-response relationship as well as a decreased maximum efficacy of the concentration versus response relationship.

Although this simple view of activated and inactivated receptors explains agonists and antagonists, it has a more difficult time with **partial agonists** and **inverse agonists** (**Figure 2.3**). A partial agonist is a drug that binds to a receptor (usually at the agonist site) where it activates the receptor but not as much as a full agonist. Even at supramaximal doses, a partial agonist cannot cause the full drug effect. Partial agonists may also have antagonist activity in which case they are also called **agonist-antagonists**. When a partial agonist is administered with a full agonist, it decreases the effect of the full agonist. For example, butorphanol acts as a partial agonist at the μ-opioid receptor. Given alone, butorphanol is a modestly efficacious analgesic. Given along with fentanyl, it will partly reverse the fentanyl analgesia. Individuals using high doses of full agonist opioids withdraw after receiving buprenorphine. Inverse agonists bind at the same site as the agonist (and likely compete with it), but they produce the opposite effect of the agonist. Inverse agonists "turn off" the constitutive activity of the receptor. The simple view of receptors as bound or unbound does not explain partial agonists or inverse agonists.

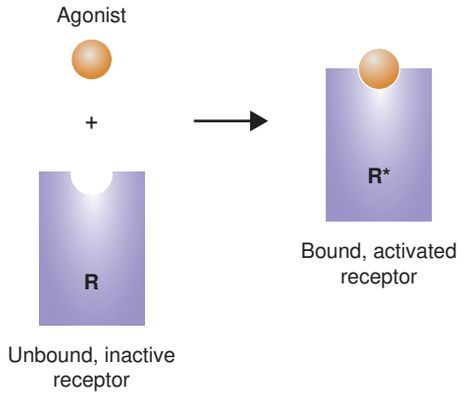

FIGURE 2.1 The interaction of a receptor with an agonist may be portrayed as a binary bound versus unbound receptor. The unbound receptor is portrayed as inactive. When the receptor is bound to the agonist ligand, it becomes the activated, *R**, and mediates the drug effect. This view is too simplistic, but it permits understanding of basic agonist behavior.

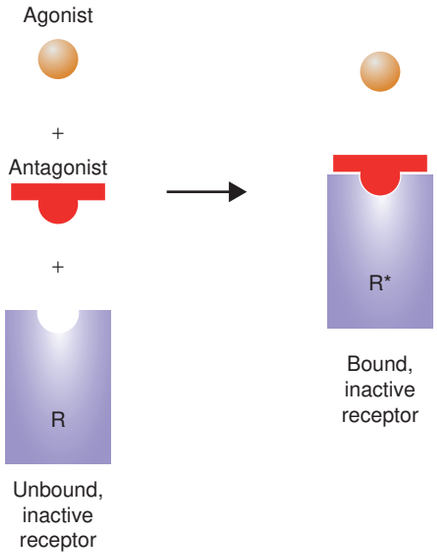

FIGURE 2.2 The simple view of receptor activation also explains the action of antagonist. In this case, the antagonist (red) binds to the receptor, but the binding does not cause activation. However, the binding of the antagonist blocks the agonist from binding, and thus blocks agonist drug effect. If the binding is reversible, this is competitive antagonism. If it is not reversible, then it is noncompetitive antagonism.

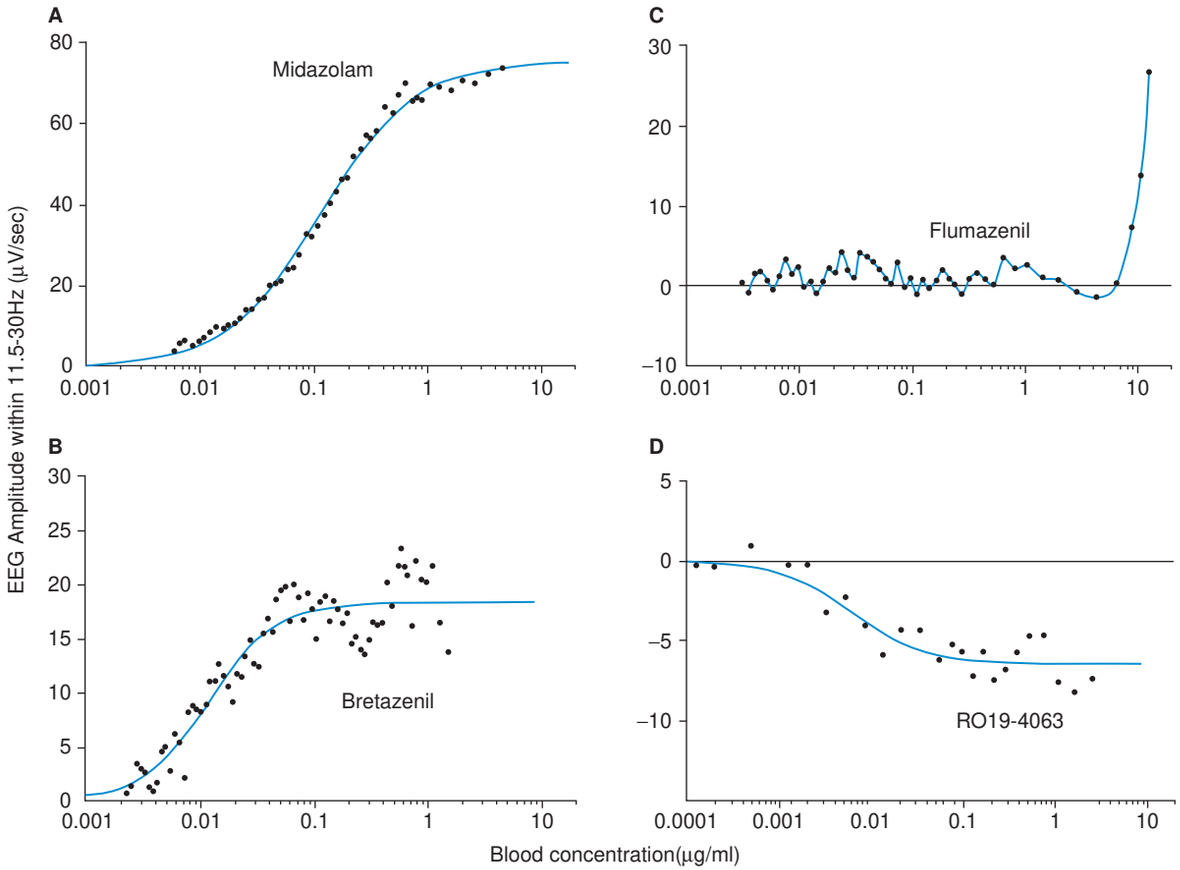

FIGURE 2.3 The concentration versus electroencephalogram (EEG) response relationship for four benzodiazepine ligands: midazolam (full agonist), bretazenil (partial agonist), flumazenil (competitive antagonist), and RO 19-4063 (inverse agonist). *Reprinted from Shafer SL. Principles of pharmacokinetics and pharmacodynamics. In: Longnecker DE, Tinker JH, Morgan GE, eds.* Principles and Practice of Anesthesiology. *2nd ed. St Louis, MO: Mosby-Year Book; 1997:1159, based on Mandema JW, Kuck MT, Danhof M. In vivo modeling of the pharmacodynamic interaction between benzodiazepines which differ in intrinsic efficacy.* J Pharmacol Exp Ther. *1992;261(1):56-61. Copyright © 1997 Elsevier. With permission.*

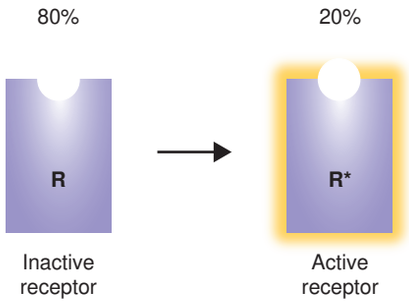

FIGURE 2.4 Receptors have multiple states, and they switch spontaneously between them. In this case, the receptor has just two states. It spends 80% of the time in the inactive state and 20% of the time in the active state in the absence of any ligand.

It turns out that receptors have many natural conformations, and they naturally fluctuate between these different conformations (**Figure 2.4**). Some of the conformations are associated with the pharmacologic effect, and some are not. In the example shown, the receptor only has two states: an inactive state and an active state that produces the same effect as if an agonist were bound to the receptor, although at a reduced level because the receptor only spends 20% of its time in this activated state.

In this view, ligands do not cause the receptor shape to change. That happens spontaneously. However, ligands change the ratio of active to inactive states by (thermodynamically) favoring one of the states. **Figure 2.5** shows the receptor as seen in **Figure 2.4** in the presence of an agonist, a partial agonist, an antagonist, and an inverse agonist. Presence of the full agonist causes the conformation of the active state to be strongly favored, causing the receptors to be in this state nearly 100% of the time. The partial agonist is not as effective in stabilizing the receptor in the active state, so the bound receptor only spends 50% of its time in this state. The antagonist does not favor either state; it just gets in the way of binding (as before; see **Figure 2.2**). The inverse agonist favors the inactive state, reversing the baseline receptor activity.

Using this information, we can now interpret the action of several ligands for the benzodiazepine receptor (see **Figure 2.3**). The actions include full agonism (midazolam), partial agonism (bretazenil), competitive antagonism (flumazenil), and inverse agonism (RO 19-4063). This range of actions can be explained by considering receptor states. Assume that the γ-aminobutyric acid (GABA) receptor has several conformations, one of which is particularly sensitive to endogenous GABA. Typically, there are some GABA receptors in this more sensitive conformation. As a full agonist, midazolam causes nearly all of the GABA receptors to be in the confirmation with increased sensitivity to GABA. Bretazenil does the same thing but not as well. Even when every benzodiazepine

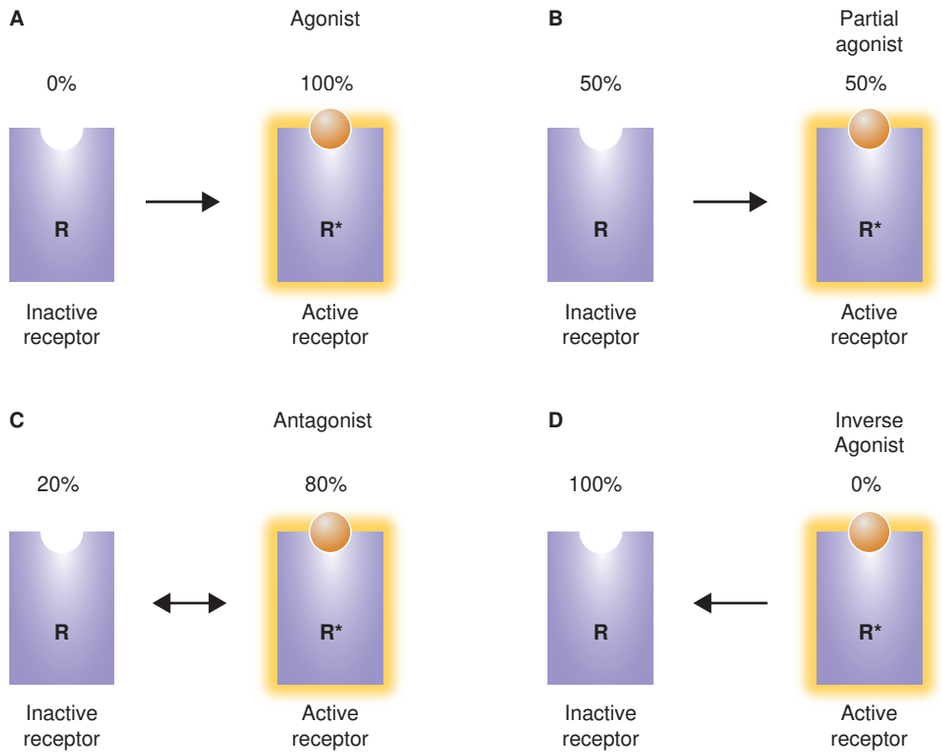

FIGURE 2.5 The action of agonists (A), partial agonists (B), antagonists (C), and inverse agonists (D) can be interpreted as changing the balance between the active and inactive forms of the receptor. In this case, in the absence of agonist, the receptor is in the activated state 20% of the time. This percentage changes based on nature of the ligand bound to the receptor.

receptor is occupied by bretazenil, fewer GABA receptors are in the more sensitive confirmation. Bretazenil simply does not favor that conformation as well as midazolam. When flumazenil is in the binding pocket, it does not change the relative probabilities of the receptor being in any conformation. Flumazenil just gets in the way of other drugs that would otherwise bind to the pocket. RO 19-4063 actually decreases the number of GABA receptors in the more sensitive conformation. Usually, some of them are in this more sensitive conformation, but that number is decreased by the inverse agonist RO 19-4063 (which was never developed as a drug because endogenous benzodiazepines, although anticipated, have not been described). The notion of receptors having multiple conformations with distinct activity, and drugs acting through favoring particular conformations, helps to understand the action of agonists, partial agonists, antagonists, and inverse agonists.

Receptor Action

The number for receptors in cell membranes is dynamic and increases (upregulates) or decreases (downregulates) in response to specific stimuli. For example, a patient with pheochromocytoma has an excess of circulating catecholamines. In response, there is a decrease in the numbers of β-adrenergic receptors in cell membranes in an attempt to maintain homeostasis. Likewise, prolonged treatment of asthma with a β-agonist may result in tachyphylaxis (decreased response to the same dose of β-agonist, often indistinguishable from **tolerance**) because of the decrease in β-adrenergic receptors. Conversely, lower motor neuron injury causes an increase in the number of nicotinic acetylcholine receptors in the neuromuscular junction, leading to an exaggerated response to succinylcholine. Changing receptor numbers is one of many mechanisms that contribute to variability in response to drugs.

Receptor Types

Receptors for drug action can be classified by location. Many of the receptors thought to be the most critical for anesthetic action are located in the lipid bilayer of cell membranes. For example, opioids, intravenous sedative hypnotics, benzodiazepines, β-blockers, catecholamines, and muscle relaxants (most of which are antagonists) all interact with membrane-bound receptors. Some receptors are intracellular proteins. Drugs such as caffeine, insulin, steroids, theophylline, and milrinone interact with intracellular proteins. Circulating proteins can also be drug targets. The coagulation cascade comprises an ensemble of circulating proteins, many of which are therapeutic targets for modifying coagulation.

There are also drugs that do not interact with proteins at all. Stomach antacids such as sodium citrate simply work by changing gastric pH. Chelating drugs work by binding divalent cations. Iodine kills bacteria by osmotic pressure (intracellular desiccation, which is why it is best to let iodine prep solutions dry), and intravenous sodium bicarbonate changes plasma pH. The mechanism of action of these drugs does not involve receptors per se, and hence, these drugs will not be further considered in this section.

Proteins are small machines whose cogs, cams, and wheels catalyze enzymatic reactions, permit ions to traverse cell membranes, exert mechanical force, or the myriad of other protein-based activities. When a drug binds to a receptor, it changes the activity of the machine, typically by enhancing its activity (eg, propofol increases the sensitivity of the $GABA_A$ receptor to GABA, the endogenous ligand), decreasing its activity (ketamine decreases the activity of the *N*-methyl-D-aspartate [NMDA] receptor), or triggering a chain reaction (opioid binding to the μ-opioid receptor activates an inhibitory G protein that decreases adenylyl cyclase activity). The protein's response to binding of the drug is responsible for the drug effect.

Pharmacokinetics

Pharmacokinetics is the quantitative study of the absorption, distribution, metabolism, and excretion of injected and inhaled drugs and their metabolites. *Pharmacokinetics describes what the body does to the drug*. Pharmacodynamics is the quantitative study of the body's response to a drug. *Pharmacodynamics describes what the drug does to the body*. This section introduces the basic principles of pharmacokinetics. The next section discusses the basic principles of pharmacodynamics.

Pharmacokinetics determines the concentration of a drug in the plasma or at the site of drug effect. Pharmacokinetic variability is a significant component of patient-to-patient variability in drug response. Pharmacokinetic variability may result from genetic modifications in metabolism; interactions with other drugs; or diseases of the liver, kidneys, or other organs of metabolism.[4]

The basic principles of pharmacokinetics are absorption, metabolism, distribution, and elimination. These processes are fundamental to all drugs. They can be described in basic physiologic terms or using mathematical models. Each serves a purpose. Physiology can be used to predict how changes in organ function will affect the disposition of drugs. Mathematical models can be used to calculate the concentration of drug in the blood or tissue following any arbitrary dose at any arbitrary time. We initially tackle the physiologic principles that govern distribution, metabolism, elimination, and absorption, in that order. We then turn to the mathematical models.

Distribution

Intravenously administered drugs mix with body tissues and are immediately diluted from the concentrated injectate in the syringe to the more dilute concentration

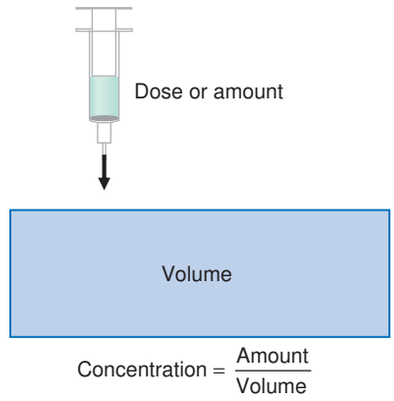

FIGURE 2.6 The central volume is the volume that intravenously injected drug initially mixes into. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds.* Miller's Anesthesia. *Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514, with permission. Copyright © 2010 Elsevier. With permission.*

measured in the plasma or tissue. This initial distribution (within 1 minute) after bolus injection is considered mixing within the "central compartment" (**Figure 2.6**). The central compartment is physically composed of those elements of the body that dilute the drug within the first minute after injection: the venous blood volume of the arm, the volume of the great vessels, the heart, the lung, and the upper aorta, and whatever uptake of drug occurs in the first passage through the lungs. Many of these volumes are fixed regardless of the drug that is given. The lungs are different. Drugs that are highly fat soluble may be avidly taken up in the first passage through the lung, reducing the concentration measured in the arterial blood. This results in an apparent increase in size of the central compartment. For example, first-pass pulmonary uptake of the initial dose of lidocaine, propranolol, meperidine, fentanyl, sufentanil, and alfentanil exceeds 65% of the dose.[5]

The body is a complex space, and mixing within the myriad body fluids and tissues is an ongoing process. The central compartment is the small initial mixing volume. Several minutes later, the drug will fully mix with the entire blood volume. However, it may take hours or even days for the drug to fully mix with all bodily tissues because some tissues have very low perfusion.

In the process of mixing, molecules are drawn to other molecules, some with specific binding sites. A drug that is polar will be drawn to water, where the polar water molecules find a low-energy state by associating with the charged aspects of the molecule. A drug that is nonpolar has a higher affinity for fat, where van der Waals binding provides numerous weak binding sites. Many anesthetic drugs are highly fat soluble and poorly soluble in water. High fat solubility means that the molecule will have a large volume of distribution because it will be preferentially taken up by fat, diluting the concentration in the plasma. The extreme example of this is propofol, which is almost inseparable from fat. The capacity of body fat to hold propofol is so vast that in some studies, the total volume of distribution of propofol has been reported as exceeding 5,000 L. Of course, nobody has a total volume of 5,000 L! It is important to understand that those 5,000 L refer to imaginary liters of plasma required to dilute the initial dose of propofol to achieve the measured concentration. Because propofol is so fat soluble, a large amount of propofol is held in the body's fatty tissues, with just a tiny fraction measured in the plasma.

Following bolus injection, the drug initially goes to the tissues that receive the bulk of arterial blood flow: the brain, heart, kidneys, and liver. These tissues are often called the **vessel-rich group**. The rapid blood flow to these highly perfused tissues ensures that the tissue drug concentration rapidly equilibrates with arterial blood. However, for highly lipid-soluble drugs, the capacity of the fat to hold the drug greatly exceeds the capacity of highly perfused tissues. Initially, the fat compartment is almost invisible because the blood supply to fat is quite limited. However, with time, the fat gradually absorbs more and more drug, sequestering it away from the highly perfused tissues. This redistribution of drug from the highly perfused tissue to the fat accounts for a substantial part of the offset of drug effect following a bolus of an intravenous anesthetic or fat-soluble opioid (eg, fentanyl). Muscles play an intermediate role in this process, having (at rest) blood flow that is intermediate between highly perfused tissues and fat, and also having intermediate solubility for lipophilic drugs.

Protein Binding

Most drugs are bound to some extent to plasma proteins, primarily albumin, α_1-acid glycoprotein, and lipoproteins.[6] Most acidic drugs bind to albumin, whereas basic drugs bind to α_1-acid glycoprotein. Protein binding effects both the distribution of drugs (because only the free or unbound fraction can readily cross cell membranes) and the apparent potency of drugs, again because it is the free fraction that determines the concentration of bound drug on the receptor.

The extent of protein binding parallels the lipid solubility of the drug. This is because drugs that are hydrophobic are more likely to bind to proteins in the plasma and to lipids in the fat. For intravenous anesthetic drugs, which tend to be quite potent, the number of available protein binding sites in the plasma vastly exceeds the number of sites actually bound. As a result, the fraction bound is not dependent on the concentration of the anesthetic and only dependent on the protein concentration.

Binding of drugs to plasma albumin is nonselective, and drugs with similar physicochemical characteristics may compete with each other and with endogenous substances for the same protein binding sites. For example,

sulfonamides can displace unconjugated bilirubin from binding sites on albumin, leading to the risk of bilirubin encephalopathy in the neonate.

Age, hepatic disease, renal failure, and pregnancy can decrease plasma protein concentration. Alterations in protein binding are important only for drugs that are highly protein bound (eg, >90%). For such drugs, the free fraction changes as an inverse proportion with a change in protein concentration. If the free fraction is 2% in the normal state, then in a patient with 50% decrease in plasma proteins, the free fraction will increase to 4%, a 100% increase.

Theoretically, an increase in free fraction of a drug may increase the pharmacologic effect of the drug, but in practice, it is far from certain that there will be any change in pharmacologic effect at all. The reason is that it is the unbound fraction that equilibrates throughout the body, including with the receptor. Plasma proteins only account for a small portion of the total binding sites for drug in the body. Because the free drug **concentration** in the plasma and tissues represents partitioning with all binding sites, not just the plasma binding sites, the actual free drug concentration that drives drug on and off receptors may change fairly little with changes in plasma protein concentration.

Metabolism

Metabolism converts pharmacologically active, lipid-soluble drugs into water-soluble and usually pharmacologically inactive metabolites. However, this is not always the case. For example, diazepam and propranolol may be metabolized to active compounds. Morphine-6-glucuronide, a metabolite of morphine, is a more potent opioid than morphine itself. In some instances, an inactive parent compound (prodrug) is metabolized to an active drug. This is the case with codeine, which is an exceedingly weak opioid. Codeine is metabolized to morphine, which is responsible for the analgesic effects of codeine.

Pathways of Metabolism

The four basic pathways of metabolism are (1) oxidation, (2) reduction, (3) hydrolysis, and (4) conjugation. Traditionally, metabolism has been divided into phase I and phase II reactions. Phase I reactions include oxidation, reduction, and hydrolysis, which increase the drug's polarity prior to the phase II reactions. Phase II reactions are conjugation reactions that covalently link the drug or metabolites with a highly polar molecule (carbohydrate or an amino acid) that renders the conjugate more water-soluble for subsequent excretion.

Hepatic microsomal enzymes are responsible for the metabolism of most drugs. Other sites of drug metabolism include the plasma (Hofmann elimination, ester hydrolysis), lungs, kidneys, and gastrointestinal tract and placenta (tissue esterases). Hepatic microsomal enzymes, which participate in the metabolism of many drugs, are located principally in hepatic smooth endoplasmic reticulum. These microsomal enzymes are also present in the kidneys, gastrointestinal tract, and adrenal cortex. Microsomes are vesicle-like artifacts reformed from pieces of the endoplasmic reticulum bilayer sliced apart as cells are cut up in a blender. Microsomal enzymes are those enzymes that are concentrated in these vesicle-like artifacts.

Phase I Enzymes

Enzymes responsible for phase I reactions include cytochrome P450 (CYP) enzymes, non-CYP enzymes, and flavin-containing monooxygenase enzymes. The CYP enzyme system is a large family of membrane-bound proteins containing a heme cofactor that catalyzes the metabolism of compounds. The P450 enzymes are predominantly hepatic microsomal enzymes, although there are also mitochondrial P450 enzymes. The designation CYP is derived from their characteristic absorption peak at 450 nm when heme is combined with carbon monoxide. The CYP system is also known as the mixed function oxidase system because it involves both oxidation and reduction steps; the most common reaction catalyzed by CYP is the monooxygenase reaction, for example, insertion of one atom of oxygen into an organic substrate while the other oxygen atom is reduced to water. The CYP functions as the terminal oxidase in the electron transport chain.

Individual CYP enzymes have evolved from a common protein.[7] The CYP enzymes, often called **CYPs**, that share more than 40% sequence homology are grouped in a family designated by a number (eg, "CYP2"), those that share more than 55% homology are grouped in a subfamily designated by a letter (eg, "CYP2A"), and individual CYP enzymes are identified by a third number (eg, "CYP2A6"). Ten isoforms of CYP are responsible for the oxidative metabolism of most drugs. The preponderance of CYP activity for anesthetic drugs is generated by CYP3A4, which is the most abundantly expressed P450 isoform, comprising 20% to 60% of total P450 activity. The P450 3A4 metabolizes more than one-half of all currently available drugs, including opioids (alfentanil, sufentanil, fentanyl), benzodiazepines, local anesthetics (lidocaine, ropivacaine), immunosuppressants (cyclosporine), and antihistamines (terfenadine).

Drugs can alter the activity of these enzymes through induction and inhibition. Induction occurs through increased expression of the enzymes. For example, phenobarbital induces microsomal enzymes and thus can render drugs less effective through increased metabolism. Conversely, other drugs directly inhibit enzymes, increasing the exposure to their substrates. Famously, grapefruit juice (not exactly a drug) inhibits CYP 3A4, possibly increasing the concentration of anesthetics and other drugs.

Oxidation

CYP enzymes are crucial for oxidation reactions. These enzymes require an electron donor in the form of reduced nicotinamide adenine dinucleotide and molecular oxygen for their activity. The molecule of oxygen is split, with one atom of oxygen oxidizing each molecule of drug and the other oxygen atom being incorporated into a molecule of water. Examples of oxidative metabolism of drugs catalyzed by CYP enzymes include hydroxylation, deamination, desulfuration, dealkylation, and dehalogenation. Demethylation of morphine to normorphine is an example of oxidative dealkylation. Dehalogenation involves oxidation of a carbon-hydrogen bond to form an intermediate metabolite that is unstable and spontaneously loses a halogen atom. Halogenated volatile anesthetics are susceptible to dehalogenation, leading to release of bromide, chloride, and fluoride ions. Aliphatic oxidation is oxidation of a side chain. For example, oxidation of the side chain of thiopental converts the highly lipid-soluble parent drug to the more water-soluble carboxylic acid derivative. Thiopental also undergoes desulfuration to pentobarbital by an oxidative step.

Epoxide intermediates in the oxidative metabolism of drugs are capable of covalent binding with macromolecules and may be responsible for some drug-induced organ toxicity, such as hepatic dysfunction. Normally, these highly reactive intermediates have such a transient existence that they exert no biologic action. When enzyme induction occurs, however, large amounts of reactive intermediates may be produced, leading to organ damage. This is especially likely to occur if the antioxidant glutathione, which is in limited supply in the liver, is depleted by the reactive intermediates.

Reduction

The CYP enzymes are also essential for reduction reactions. Under conditions of low oxygen partial pressures, CYP enzymes transfer electrons directly to a substrate such as halothane rather than to oxygen. This electron gain imparted to the substrate occurs only when insufficient amounts of oxygen are present to compete for electrons.

Conjugation

Conjugation with glucuronic acid involves CYP enzymes. Glucuronic acid is synthesized from glucose and added to lipid-soluble drugs to render them water-soluble. The resulting water-soluble glucuronide conjugates are then excreted in bile and urine. In premature infants, reduced microsomal enzyme activity interferes with conjugation, leading to neonatal hyperbilirubinemia and the risk of bilirubin encephalopathy. The reduced conjugation ability of the neonate increases the effect and potential toxicity of drugs that are normally inactivated by conjugation with glucuronic acid.

Hydrolysis

Enzymes responsible for hydrolysis of drugs, usually at an ester bond, do not involve the CYP enzymes system. Hydrolysis often occurs outside of the liver. For example, remifentanil, succinylcholine, esmolol, and the ester local anesthetics are cleared in the plasma and tissues via ester hydrolysis.

Phase II Enzymes

Phase II enzymes include glucuronosyltransferases, glutathione-S-transferases, *N*-acetyl-transferases, and sulfotransferases. Uridine diphosphate glucuronosyltransferase catalyzes the covalent addition of glucuronic acid to a variety of endogenous and exogenous compounds, rendering them more water-soluble. Glucuronidation is an important metabolic pathway for several drugs used during anesthesia, including propofol, morphine (yielding morphine-3-glucuronide and the pharmacologically active morphine-6-glucuronide), and midazolam (yielding the pharmacologically active α_1-hydroxymidazolam). Glutathione-S-transferase enzymes are primarily a defensive system for detoxification and protection against oxidative stress. *N*-acetylation catalyzed by *N*-acetyltransferase is a common phase II reaction for metabolism of heterocyclic aromatic amines (particularly serotonin) and arylamines, including the inactivation of isoniazid.

Hepatic Clearance

The rate of metabolism for most anesthetic drugs is proportional to drug concentration, rending the clearance of the drug constant (ie, independent of dose). This is a fundamental assumption for anesthetic pharmacokinetics. Exploring this assumption will provide insight into the critical role of clearance in governing the metabolism of drugs.

Although the metabolic capacity of the body is large, it is not possible that metabolism is *always* proportional to drug concentration because the liver does not have infinite metabolic capacity. At some rate of drug flow into the liver, the organ will be metabolizing drug as fast as the metabolic enzymes in the organ allow. At this point, metabolism can no longer be proportional to concentration because the metabolic capacity of the organ has been exceeded.

Understanding metabolism starts with a simple mass balance: The rate at which drug flows *out* of the liver must be the same as the rate at which drug flows *into* the liver minus the rate at which the liver metabolizes drug. The rate at which drug flows into the liver is liver blood flow, Q, times the concentration of drug flowing in, C_{inflow}. The rate at which drug flows out of the liver is liver blood flow, Q, times the concentration of drug flowing out, $C_{outflow}$. The rate of hepatic metabolism by the liver, R, is the difference between the drug concentration flowing into the liver and the drug concentration flowing out of the liver, times the rate of liver blood flow:

$$\text{Rate of drug metabolism} = R = Q(C_{inflow} - C_{outflow}) \quad \text{Equation 2.1}$$

This relationship is illustrated in **Figure 2.7**.

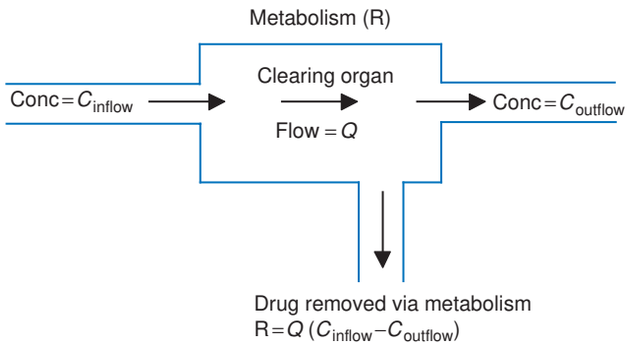

FIGURE 2.7 The relationship between drug rate of metabolism can be computed as the rate of liver blood flow times the difference between the inflowing and outflowing drug concentrations. This is a common approach to analyzing metabolism or tissue uptake across an organ in mass-balance pharmacokinetic studies. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds.* Miller's Anesthesia. *Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

Metabolism can be saturated because the liver does not have infinite metabolic capacity. A common equation used for this saturation processes is as follows:

$$\text{Response} = \frac{C}{C_{50} + C} \qquad \text{Equation 2.2}$$

"Response" in **Equation 2.2** varies from 0 to 1, depending on the value of *C*. In this context, Response is the fraction of maximal metabolic rate. Response = 0 means no metabolism, and response = 1 means metabolism at the maximal possible rate. *C* refers to whatever is driving the response. In this chapter, *C* means drug concentration. When *C* is 0, the response is 0. If *C* is greater than 0 but much less than C_{50}, the denominator is approximately C_{50} and the response is nearly proportional to *C*: Response $\approx \frac{C}{C_{50}}$. If we increase *C* even further to exactly C_{50}, then the response is $\frac{C_{50}}{C_{50} + C_{50}}$, which is simply 0.5. That is where the name "C_{50}" comes from: It is the concentration associated with 50% response. As *C* becomes much greater than C_{50}, the equation approaches $\frac{C}{C}$, which is 1. The shape of this relationship is shown in **Figure 2.8**. The relationship is nearly linear at low concentrations, but at high concentrations, the response saturates at 1.

To understand hepatic clearance, we must understand the relationship between hepatic metabolism and drug concentration. But what concentration determines the rate of metabolism: the concentration flowing into the liver, the average concentration within the liver, or the concentration flowing out of the liver? All have been used, but the most common views the rate of metabolism as a function of the concentration flowing *out* of the liver, $C_{outflow}$. The rationale for using $C_{outflow}$ is the same as the rationale for using end tidal anesthetic concentration to assess the steady state concentration in the lungs.

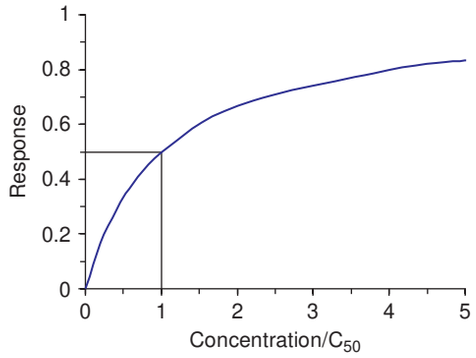

FIGURE 2.8 The shape of the saturation equation. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds.* Miller's Anesthesia. *Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

We can expand our equation of metabolism to include the observation that the rate of metabolism, *R*, approaches saturation at the maximum metabolic rate, *Vm*, as a function of $C_{outflow}$:

$$\text{Rate of drug metabolism} = R = Q\,(C_{inflow} - C_{outflow}) = Vm\,\frac{C_{outflow}}{Km + C_{outflow}} \qquad \text{Equation 2.3}$$

The saturation equation appears at the end of the Equation 2.3 equation. The *Vm* is the maximum possible metabolic rate. The saturation part of this equation, $\frac{C_{outflow}}{Km + C_{outflow}}$, determines fraction of the maximum metabolic rate. *Km*, the "Michaelis constant," is the outflow concentration at which the metabolic rate is 50% of the maximum rate (*Vm*). This relationship is shown in **Figure 2.9**. The *x*-axis is the outflow concentration, $C_{outflow}$, as a fraction *Km*. The *y*-axis is the rate of drug metabolism as a fraction of *Vm*. By normalizing the *x*- and *y*-axis in this manner, the relationship shown in **Figure 2.9** is true for all values of *Vm* and *Km*. As long as the outflow concentration is less than one-half of *Km* (true for almost all anesthetic drugs), there is a nearly proportional change in metabolic rate with a proportional change in outflow concentration. Another interpretation is that metabolism will be proportional to concentration as long as the metabolic rate is less than one-third of the maximum metabolic capacity.

So far, we have talked about the rate of metabolism and not about hepatic clearance. If the liver could completely extract the drug from the afferent flow, then clearance would equal liver blood flow, *Q*. However, the liver cannot remove every last drug molecule. There is always some drug in the effluent plasma. The fraction of inflowing drug extracted by the liver is $\frac{C_{inflow} - C_{outflow}}{C_{inflow}}$. This is called the **extraction ratio**. Clearance is the amount of blood completely cleared of drug per unit time. We can

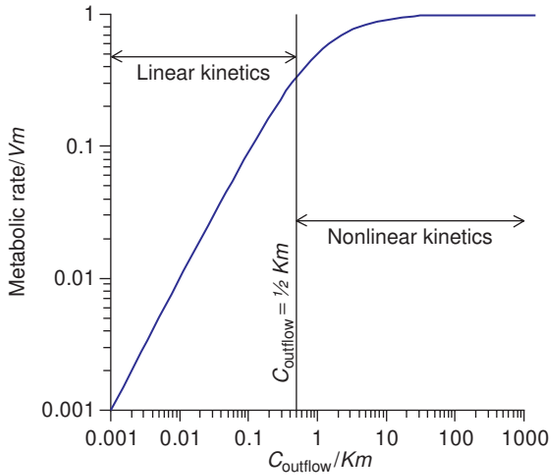

FIGURE 2.9 The relationship between concentration, here shown as a fraction of the Michaelis constant (*Km*), and drug metabolism, here shown as a fraction of the maximum rate (*Vm*). Metabolism increases proportionally with concentration as long as the outflow concentration is less than half *Km*, which corresponds to a metabolic rate that is roughly one-third of the maximal rate. Metabolism is proportional to concentration, meaning that clearance is constant, for typical doses of all intravenous drugs used in anesthesia. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds.* Miller's Anesthesia. *Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

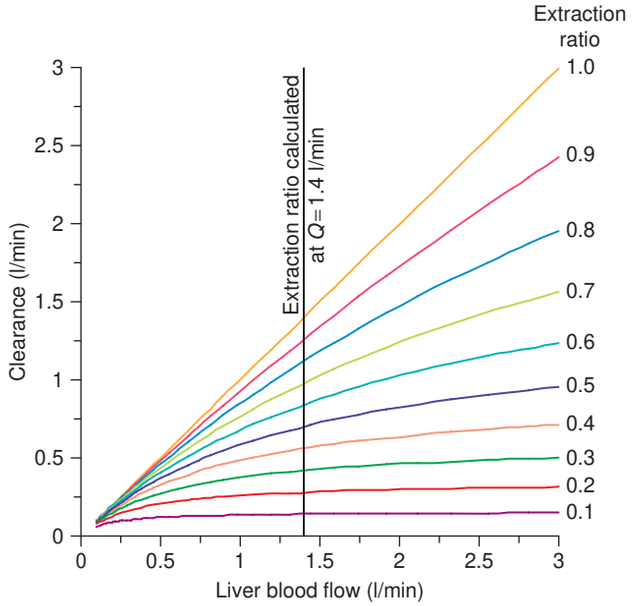

FIGURE 2.10 The relationship between liver blood flow (Q), clearance, and extraction ratio. For drugs with a high extraction ratio, clearance is nearly identical to liver blood flow. For drugs with a low extraction ratio, changes in liver blood flow have almost no effect on clearance. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds.* Miller's Anesthesia. *Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

calculate clearance as the liver blood flow times the extraction ratio:

$$\text{Clearance} = Q \times ER = Q\left(\frac{C_{inflow} - C_{outflow}}{C_{inflow}}\right) \quad \text{Equation 2.4}$$

With this basic understanding of clearance, let us divide each part of Equation 2.3 by C_{inflow}:

$$\frac{\text{Rate of drug metabolism}}{C_{inflow}} = \frac{R}{C_{inflow}} = Q\left(\frac{C_{inflow} - C_{outflow}}{C_{inflow}}\right) = \frac{C_{outflow}}{C_{inflow}}\left(\frac{Vm}{Km + C_{outflow}}\right) \quad \text{Equation 2.5}$$

The third term in the above equation is clearance as defined in Equation 2.4: *Q* times the extraction ratio. Thus, each term in Equation 2.4 must be clearance. Let us consider them in order.

The first term tells us that Clearance $= \frac{\text{Rate of drug metabolism}}{C_{inflow}}$. This indicates that clearance is a proportionality constant that relates inflowing (eg, arterial) concentration to the rate of metabolism. If we want to maintain a given steady-state arterial drug concentration, we must infuse drug at the same rate that it is being metabolized. With this understanding, we can rearrange the equation to say the following: Infusion rate = metabolic rate = Clearance × C_{inflow}. Thus, the infusion rate to maintain a given arterial concentration (C_{inflow}) is the clearance times the desired concentration.

The third and fourth terms

$$\text{Clearance} = Q\left(\frac{C_{inflow} - C_{outflow}}{C_{inflow}}\right)$$

and

$$\text{Clearance} = \frac{C_{outflow}}{C_{inflow}}\left(\frac{Vm}{Km + C_{outflow}}\right)$$

are particularly interesting when taken together. Remembering that $\frac{C_{inflow} - C_{outflow}}{C_{inflow}}$ is the extraction ratio, these equations relate clearance to liver blood flow and the extraction ratio, as shown in **Figure 2.10**.[8] For drugs with an extraction ratio of nearly 1 (eg, propofol), a change in liver blood flow produces a nearly proportional change in clearance. For drugs with a low extraction ratio (eg, alfentanil), clearance is nearly independent of the rate of liver blood flow. This makes intuitive sense. If nearly 100% of the drug is extracted by the liver, then the liver has tremendous metabolic capacity for the drug. In this case, flow of drug to the liver is what limits the metabolic rate. Metabolism

is "flow limited." The reduction in liver blood flow that accompanies anesthesia can be expected to reduce clearance. However, moderate changes in hepatic metabolic function per se will have little impact on clearance because hepatic metabolic capacity is overwhelmingly in excess of demand.

Conversely, for drugs with an extraction ratio considerably less than 1, clearance is limited by the capacity of the liver to take up and metabolize the drug. This is called "capacity-limited" clearance. When clearance is capacity limited, changes in liver blood flow (as might be caused by the anesthetic state itself) have little influence on the clearance because the liver can only handle a fraction of the drug flowing through it. It does not matter if liver blood flow is doubled, or cut in half, because the liver's enzymatic capacity is "maxed out" regardless of the amount of drug flowing through it.

When clearance is flow limited, it is generally unaffected by modest changes in hepatic capacity. However, when clearance is capacity limited, changes in liver metabolic capacity produce nearly proportional changes in clearance rate. For these drugs, clearance can be significantly decreased by hepatic disease or increased by enzymatic induction. This relationship can be seen in **Figure 2.11**.

Figure 2.11 allows us to also see how extraction ratio helps identify flow-limited from capacity-limited drugs. The vertical line at $Vm = 1$ shows the extraction ratio for each line (labeled to the left), based on a liver blood flow of 1.4 L per minute. Changes in *Vm*, as might be caused by liver disease (reduced *Vm*) or enzymatic induction (increased *Vm*) have little effect on drugs with a high extraction ratio. However, drugs with a low extraction ratio have a nearly linear change in clearance with a change in intrinsic metabolic capacity (*Vm*).

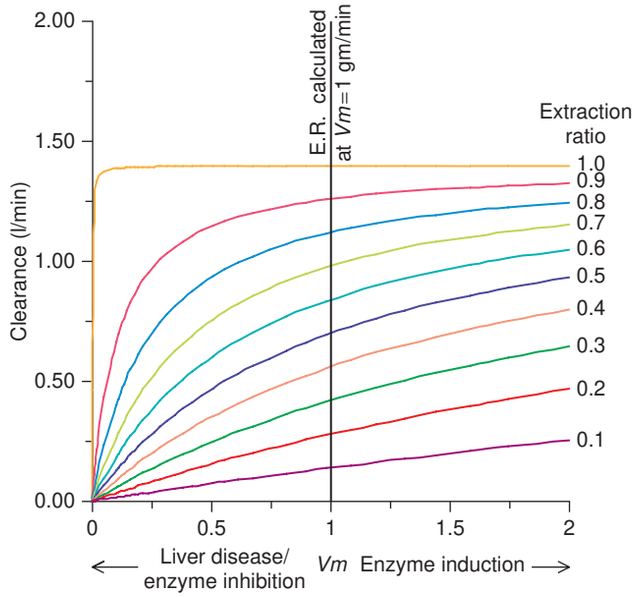

FIGURE 2.11 Changes in maximum metabolic velocity (*Vm*) have little effect on drugs with a high extraction ratio (ER) but cause a nearly proportional decrease in clearance for drugs with a low extraction ratio. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds.* Miller's Anesthesia. *Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

Vm and *Km* are usually not known and condensed into a single term, $\frac{Vm}{Km}$. This term summarizes the hepatic metabolic capacity and is called **intrinsic clearance**. Because clearance $= \frac{C_{outflow}}{C_{inflow}}\left(\frac{Vm}{Km + C_{outflow}}\right)$, consider what happens if hepatic blood flow increases to infinity (this is a thought experiment—do not try this at home). At super high hepatic blood flow, $C_{outflow}$ becomes indistinguishable from C_{inflow} because the finite hepatic capacity only metabolizes an infinitesimal fraction of the drug flowing through the liver. As a result, clearance becomes $\frac{Vm}{Km + C_{outflow}}$. This is clearance when blood flow is infinitely fast. There must be a linear portion, where metabolism is proportional to concentration. We can solve for clearance in the "linear range" by solving for $C_{inflow} = C_{outflow} = 0$, $\frac{Vm}{Km}$. This is the intrinsic clearance, Cl_{int}. It can be demonstrated algebraically from the definition of Cl_{int} that in the linear range (ie, when $km >> C_{outflow}$), Cl_{int} is related to the extraction ratio and hepatic blood flow:

$$ER = \frac{Cl_{int}}{Q + Cl_{int}} \qquad \text{Equation 2.6}$$

This relationship between intrinsic clearance and extraction ratio is shown in **Figure 2.12**, calculated at a hepatic blood flow of 1,400 mL per minute. It shows that the intrinsic clearance for drugs like propofol with an extraction

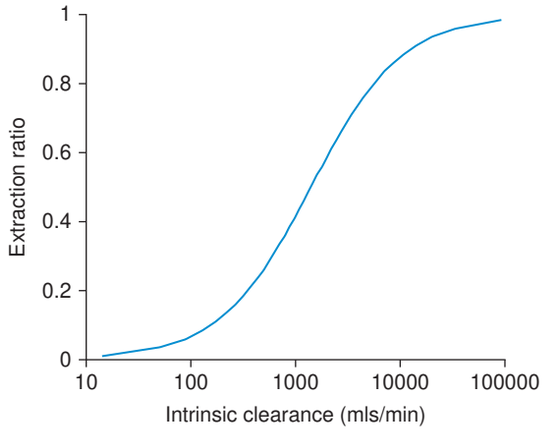

FIGURE 2.12 The extraction ratio as a function of the intrinsic calculated for a liver blood flow of 1,400 mL per minute. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds.* Miller's Anesthesia. *Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

ratio of approximately 1 is enormous, somewhere around 100 L per minute!

Finally, we can combine Equation 2.6 with Equation 2.5 to solve for the relationship between hepatic clearance and Cl_{int}:

$$\text{Hepatic Clearance} = \frac{Q\,Cl_{int}}{Q + Cl_{int}} \qquad \text{Equation 2.7}$$

In general, true hepatic clearance and extraction ratio are more useful concepts for anesthetic drugs than the intrinsic clearance. However, intrinsic clearance is introduced here because it is occasionally used in pharmacokinetic analyses of drugs used during anesthesia.

So far, we have focused on linear pharmacokinetics, that is, the pharmacokinetics of drugs whose metabolic rate at clinical doses is less than $Vm/3$. The clearance of such drugs is generally expressed as a constant (eg, propofol clearance = 1.6 L per minute). Some drugs, such as phenytoin, exhibit saturable pharmacokinetics (ie, have such low Vm that typical doses exceed the linear portion of **Figure 2.9**). The clearance of drugs with saturable metabolism is a function of drug concentration, rather than a constant flow (ie, volume per unit time). There are almost no drugs with saturable clearance in anesthesia, so they will not be discussed in greater detail. However, the clearance for these drugs as a function of concentration can be calculated from Equations 2.5 and 2.7.

Renal Clearance

Renal excretion of drugs involves (1) glomerular filtration, (2) active tubular secretion, and (3) passive tubular reabsorption. The amount of drug that enters the renal tubular lumen depends on the fraction of drug bound to protein and the glomerular filtration rate (GFR). Renal tubular secretion involves active transport processes, which may be selective for certain drugs and metabolites, including protein-bound compounds. Reabsorption from renal tubules removes drug that has entered tubules by glomerular filtration and tubular secretion. This reabsorption is most prominent for lipid-soluble drugs that can easily cross cell membranes of renal tubular epithelial cells to enter pericapillary fluid. Indeed, a highly lipid-soluble drug, such as thiopental, is almost completely reabsorbed such that little or no unchanged drug is excreted in the urine. Conversely, production of less lipid-soluble metabolites limits renal tubule reabsorption and facilitates excretion in the urine.

The rate of reabsorption from renal tubules is influenced by factors such as pH and rate of urine flow in the renal tubules. Passive reabsorption of weak bases and acids is altered by urine pH, which influences the fraction of drug that exists in the ionized form. For example, weak acids are excreted more rapidly in alkaline urine. This occurs because alkalinization of the urine results in more ionized drug that cannot easily cross renal tubular epithelial cells, resulting in less passive reabsorption.

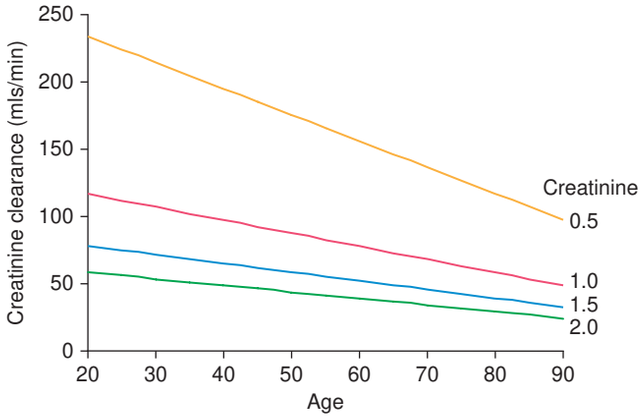

FIGURE 2.13 Creatinine clearance as a function of age and serum creatinine based on the equation of Cockcroft and Gault. *Derived from Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine.* Nephron. *1976;16:31-41.*

Renal blood flow is inversely correlated with age, as is creatinine clearance, which is closely related to GFR because creatinine is water-soluble and not resorbed in the tubules. Creatinine clearance can be predicted from age and weight according to the equation of Cockcroft and Gault[9]:

Men:

$$\text{Creatinine Clearance (mL/min)} = \frac{[140 - \text{age(years)}] \times \text{weight(kgs)}}{72 \times \text{serum creatinine (mg\%)}} \qquad \text{Equation 2.8}$$

Women:

85% of the above equation.

Equation 2.8 shows that age is an independent predictor of creatinine clearance. Elderly patients with normal serum creatinine have about half the GFR than younger patients. This can be seen graphically in **Figure 2.13**.

Absorption

Classically, pharmacokinetics is taught as "absorption, distribution, metabolism, and elimination." Because most anesthetic drugs are administered intravenously, and inhaled anesthetic pharmacokinetics are discussed elsewhere, this order has been changed in this textbook to put absorption at the end of the list. Absorption is not particularly relevant for most anesthetic drugs.

Ionization

Most drugs are weak acids or bases that are present in both ionized and nonionized forms in solution. The nonionized molecule is usually lipid soluble and can diffuse across cell membranes including the blood–brain barrier,

TABLE 2.1
Characteristics of nonionized and ionized drug molecules

	Nonionized	Ionized
Pharmacologic effect	Active	Inactive
Solubility	Lipids	Water
Cross lipid barriers (gastrointestinal tract, blood–brain barrier, placenta)	Yes	No
Renal excretion	No	Yes
Hepatic metabolism	Yes	No

renal tubular epithelium, gastrointestinal epithelium, placenta, and hepatocytes (**Table 2.1**). As a result, it is usually the nonionized form of the drug that is pharmacologically active, undergoes reabsorption across renal tubules, is absorbed from the gastrointestinal tract, and is susceptible to hepatic metabolism. Conversely, the ionized fraction is poorly lipid soluble and cannot penetrate lipid cell membranes easily (see **Table 2.1**). A high degree of ionization thus impairs absorption of drug from the gastrointestinal tract, limits access to drug-metabolizing enzymes in the hepatocytes, and facilitates excretion of unchanged drug, as reabsorption across the renal tubular epithelium is unlikely.

Determinants of Degree of Ionization

The degree of drug ionization is a function of its dissociation constant (pK) and the pH of the surrounding fluid. When the pK and the pH are identical, 50% of the drug exists in both the ionized and nonionized form. Small changes in pH can result in large changes in the extent of ionization, especially if the pH and pK values are similar. Acidic drugs, such as barbiturates, tend to be highly ionized at an alkaline pH, whereas basic drugs, such as opioids and local anesthetics, are highly ionized at an acid pH. Acidic drugs are usually supplied in a basic solution to make them more soluble in water and basic drugs are usually supplied in an acidic solution for the same reason, unless the pH affects drug stability, as is the case for most ester local anesthetics.

Ion Trapping

Because it is the nonionized drug that equilibrates across lipid membranes, a concentration difference of total drug can develop on two sides of a membrane that separates fluids with different pHs[10] because the ionized concentrations will reflect the local equilibration between ionized and nonionized forms based on the pH. This is an important consideration because one fraction of the drug may be more pharmacologically active than the other fraction.

Systemic administration of a weak base, such as an opioid, can result in accumulation of ionized drug (ion trapping) in the acid environment of the stomach. A similar phenomenon occurs in the transfer of basic drugs, such as local anesthetics, across the placenta from mother to fetus because the fetal pH is lower than maternal pH. The lipid-soluble nonionized fraction of local anesthetic crosses the placenta and is converted to the poorly lipid-soluble ionized fraction in the more acidic environment of the fetus. The ionized fraction in the fetus cannot easily cross the placenta to the maternal circulation and thus is effectively trapped in the fetus. At the same time, conversion of the nonionized to ionized fraction maintains a gradient for continued passage of local anesthetic into the fetus. The resulting accumulation of local anesthetic in the fetus is accentuated by the acidosis that accompanies fetal distress.

The kidneys are the most important organs for the elimination of unchanged drugs or their metabolites. Water-soluble compounds are excreted more efficiently by the kidneys than are compounds with high lipid solubility. This emphasizes the important role of metabolism in converting lipid-soluble drugs to water-soluble metabolites. Drug elimination by the kidneys is correlated with endogenous creatinine clearance or serum creatinine concentration. The magnitude of change in these indices provides an estimate of the necessary change adjustment in drug dosage. Although age and many diseases are associated with a decrease in creatinine clearance and requirement for decreased dosing, pregnancy is associated with an increase in creatinine clearance and higher dose requirements for some drugs.

Ion trapping and extraction ratio featured, somewhat unexpectedly, in the trial of Conrad Murray for the death of Michael Jackson. The initial defense strategy was to blame Michael Jackson for his death, claiming that he drank a mixture of propofol and lidocaine when Conrad Murray stepped out of the room. We already know why the propofol claim is bogus. As discussed earlier, the extraction ratio for propofol is nearly 1. The extraction ratio does not care if the propofol enters the liver from the hepatic artery or portal vein. The liver will just as happily remove all the propofol from the portal vein as from the hepatic artery. As a result, any propofol that is swallowed will be metabolized in the liver before ever reaching the systemic circulation.

The defense also observed that the concentration of lidocaine in Michael Jackson's stomach was 22.9 μg/mL, far exceeding the concentration of lidocaine in Michael Jackson's blood of 0.8 μg/mL. Surely this was evidence that Michael Jackson drank a mixture of lidocaine and propofol! Nope. It is just ion trapping, nothing more.

We can quantitate the extent of ion trapping using the Henderson-Hasselbalch equation:

$$pH = pK_a + log_{10}\left(\frac{[A^-]}{[HA]}\right) \qquad \text{Equation 2.9}$$

This assumes that the dissociating moiety is an acid that releases a proton. However, lidocaine is a proton receptor,

requiring we use the form of the Henderson-Hasselbalch equation adapted for bases:

$$pOH = pK_b + log_{10}\left(\frac{[BH^+]}{[B]}\right) \qquad \text{Equation 2.10}$$

where pOH is the negative logarithm (base 10) of the hydroxide ion concentration, pKb is the base dissociation constant (readily calculated as 14 − pKa), [B] is the concentration of the base (uncharged lidocaine), and [BH^+] is the concentration of the conjugate acid (protonated lidocaine). We can rearrange the second equation to calculate the ratio of [BH^+] / [B] as $10^{pOH - pKb}$.

The pH of blood is 7.4, the pH of the stomach is 1 to 3.5, and the pKa of lidocaine is 8.01. Therefore, the pOH of blood is 6.6, the pOH of the stomach is 10.5 to 13, and the pKb of lidocaine is 5.99.

Figure 2.14 was presented in pretrial testimony to explain the mathematics of ion trapping. The left shows blood, where the total lidocaine was measured on autopsy as 0.84 μg/mL. From the Henderson-Hasselbalch equation, we can calculate that the uncharged moiety was 0.17 μg/mL and the balance was charged. Because the uncharged moiety establishes equilibrium across gastric epithelium, we expect the lidocaine concentration in the stomach to be the same, 0.17 μg/mL. Knowing this, and the gastric pH, we can calculate the charged lidocaine concentration at equilibrium would have been 5,357 μg/mL, about 200 times higher than actually measured on autopsy. Of course, the system was not in equilibrium at the time of autopsy, which is why the stomach concentration was only 22.9 μg/mL, not 5,357 μg/mL. However, all that we know about Michael Jackson is that charged lidocaine accumulated in his stomach, exactly as expected from ion trapping.

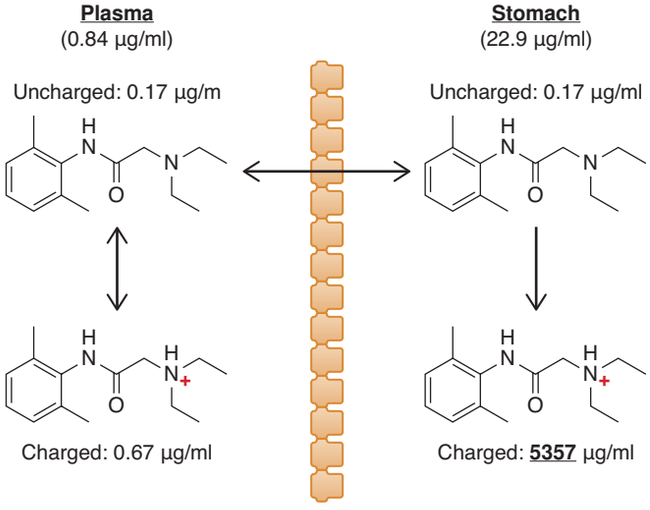

FIGURE 2.14 Ion trapping can result in significant sequestration of drugs based on local pH. The molecule shown is lidocaine, which has a nitrogen group that can accept protons in an acidic environment. Only neutrally changed lidocaine equilibrates across membranes. The figure is taken from the trial of Conrad Murray for the death of Michael Jackson. The defense claimed that the measured lidocaine concentration in the stomach, 22 μg/mL, proved that Mr. Jackson drank a mixture of lidocaine and propofol. However, the measured concentration can be entirely explained by ion trapping, which was not even close to the equilibrium concentration of 5,357 μg/mL.

Route of Administration and Systemic Absorption of Drugs

Drugs administered by intravenous injection or inhalation reach the systemic circulation almost instantly. However, for drugs not administered by these two routes, there is an initial delay between administering the drug (eg, swallowing a pill or applying a patch) and appearance of the drug in the systemic circulation. The rate of systemic absorption determines the magnitude of the drug effect and duration of action. Changes in the rate of systemic absorption rate may require adjusting the dose or time interval between repeated drug doses.

Systemic absorption, regardless of the route of drug administration, depends on the drug's solubility. Local conditions at the site of absorption alter solubility, particularly in the gastrointestinal tract. Blood flow to the site of absorption also affects the rate of systemic transfer. For example, increased blood flow evoked by rubbing or applying heat at the subcutaneous or intramuscular injection site enhances systemic absorption, whereas decreased blood flow due to vasoconstriction impedes drug absorption. Finally, the area of the absorbing surface available for drug absorption is an important determinant of drug entry into the circulation.

Oral Administration

Oral administration of a drug is often the most convenient and inexpensive route of administration. Disadvantages of the oral route include (1) emesis caused by irritation of the gastrointestinal mucosa by the drug, (2) destruction of the drug by digestive enzymes or acidic gastric fluid, and (3) irregularities in absorption in the presence of food or other drugs. Furthermore, drugs may be metabolized by enzymes or bacteria in the gastrointestinal tract before systemic absorption can occur.

With oral administration, the onset of drug effect is largely determined by the rate and extent of absorption from the gastrointestinal tract. The principal site of most drug absorption after oral administration is the small intestine due to the large surface area of this portion of the gastrointestinal tract. Changes in the pH of gastrointestinal fluid that favor the presence of a drug in its nonionized (lipid-soluble) fraction thus favor systemic absorption. Some absorption occurs in the stomach, where the fluid is obviously acidic, enhancing the absorption of weak acids such as aspirin. However, most drug absorption occurs in the alkaline environment of the small intestine. The alkalinity enhances absorption of weak bases such as

opioids, but even weak acids are mostly absorbed in the small intestine because of the large surface area.

First-Pass Hepatic Effect

Drugs absorbed from the gastrointestinal tract enter the portal venous blood and thus pass through the liver before entering the systemic circulation for delivery to tissue receptors. This is known as the **first-pass hepatic metabolism**. For drugs that undergo extensive hepatic extraction and metabolism (propranolol, lidocaine), it is the reason for large differences in the pharmacologic effect between oral and intravenous doses. As mentioned earlier, it is also the reason that propofol exerts no pharmacologic effect when swallowed—none gets past the liver.

Sublingual, Buccal, and Nasal Administration

The sublingual or buccal route of administration permits a rapid onset of drug effect because this blood bypasses the liver, preventing first-pass metabolism for the initial dose. Drugs absorbed from the oral cavity flow into the superior vena cava. Evidence of the value of bypassing the first-pass hepatic effect is the efficacy of sublingual nitroglycerin. Sublingual nitroglycerin works quickly, while oral nitroglycerin tablets are ineffective because of extensive first-pass hepatic metabolism. It is also why oral transmucosal fentanyl citrate results in a rapid rise in fentanyl concentration for "breakthrough" cancer pain where rapid onset of pain relief is clinically important. Oral fentanyl has an extraction ratio of about 50%, which greatly limits the utility of oral administration. Buccal administration is an alternative to sublingual placement of a drug; it is better tolerated and less likely to stimulate salivation. Buccal buprenorphine is an example of effective buccal administration.

The nasal mucosa also provides an effective absorption surface for certain drugs. For example, in 2019, the US Food and Drug Administration approved nasally administered s-ketamine for treatment resistant depression. Nasally administered naloxone is now widely available to emergency medical technicians for treatment of opioid overdose. The nasal route affords very rapid reversal of opioid overdose.

Transdermal Administration

Transdermal administration of drugs provides sustained therapeutic plasma concentrations of the drug and decreases the likelihood of loss of therapeutic efficacy due to peaks and valleys associated with conventional intermittent drug injections. This route of administration is devoid of the complexity of continuous infusion techniques, and the low incidence of side effects (because of the small doses used) contributes to high patient compliance. Characteristics of drugs that favor predictable transdermal absorption include (1) combined water and lipid solubility, (2) molecular weight of <1,000, (3) pH 5 to 9 in a saturated aqueous solution, (4) absence of histamine-releasing effects, and (5) daily dose requirements of <10 mg. Scopolamine, fentanyl, clonidine, estrogen, progesterone, and nitroglycerin can be delivered with commercially approved transdermal systems. For some drugs, such as scopolamine and nitroglycerine, the sustained plasma concentrations provided by transdermal absorption result in tolerance and loss of therapeutic effect.

The rate-limiting step in transdermal absorption of drugs is diffusion across the stratum corneum of the epidermis. Initial absorption occurs along sweat ducts and hair follicles that function as diffusion shunts. Differences in the thickness and chemistry of the stratum corneum are reflected in the skin's permeability to drug absorption. For example, skin may be 10 to 20 micron thick on the back and abdomen compared with 400 to 600 micron on the palmar surfaces of the hands. This explains part of the variability in transdermal delivery. This is the reason that scopolamine patches are placed behind the ear. It has nothing to do with the proximity to the semicircular canals. The postauricular zone, because of its thin epidermal layer and somewhat higher temperature, is the only region of skin sufficiently permeable for predictable and sustained absorption of scopolamine.

The stratum corneum sloughs and regenerates over about 7 days, placing an upper limit on the adhesion duration of transdermal delivery systems. Contact dermatitis at the site of transdermal patch applications occurs in a significant number of patients and is another reason to limit the duration of patch placement.

Rectal Administration

Drugs administered into the proximal rectum are absorbed into the superior hemorrhoidal veins and subsequently transported via the portal venous system to the liver. Thus, rectally administered drugs undergo the same first pass metabolism as orally administered drugs. However, if the drugs are placed more distal (eg, closer to the anus), then they may be absorbed directly into the systemic circulation, bypassing the liver. This is one of the reasons that rectal drug delivery is exceptionally unpredictable. Furthermore, drugs may cause irritation of the rectal mucosa. Patients have limited enthusiasm for this route of drug delivery.

Pharmacokinetic Models

In the following section, several common, useful pharmacokinetic models are derived. Although it is not necessary for every clinician to be able to derive these models, a consideration of where they come from takes them out of the "black box" and allows consideration of their representative parts.

Zero- and First-Order Processes

The consumption of oxygen and production of carbon dioxide are processes that happen at a constant rate. These are called **zero-order processes**. The rate of change (dx/dt) for a zero-order process is $\frac{dx}{dt} = k$. This says the rate of change is constant. If x represents an amount of drug and t

represents time, then the units of k are amount/time. If we want to know the value of x at time t, $x(t)$, we can compute it as the integral of this equation from time 0 to time: t, $x(t) = x_0 + k \cdot t$, where x_0 is the value of x at time 0. This is the equation of a straight line with a slope of k and an intercept of x_0.

Many processes occur at a rate proportional to the amount. For example, the interest payment on a loan is proportional to the outstanding balance. The rate at which water drains from a bathtub is proportional to amount (height) of water in the tub. These are examples of first-order processes. The rate of change in a first-order process is only slightly more complex than for a zero-order process, $\frac{dx}{dt} = k \cdot x$. In this equation, x has units of amount, so the units of k are 1/time. The value of x at time t, $x(t)$, can be computed as the integral from time 0 to time t: $x(t) = x_0\, e^{kt}$, where x_0 is the value of x at time 0. If $k > 0$, $x(t)$ increases exponentially to infinity. If $k < 0$, $x(t)$ decreases exponentially to 0. In pharmacokinetics, k is negative because concentrations decrease over time. For clarity, the minus sign is usually explicit, so k is expressed as a positive number. Thus, the identical equation for pharmacokinetics, with the minus sign explicitly written, is

$$x(t) = x_0\, e^{-kt} \qquad \text{Equation 2.11}$$

Figure 2.15A shows the exponential relationship between x and time. X continuously decreases over time. Taking the natural logarithm of both sides of $x(t) = x_0\, e^{-kt}$ gives

$$\begin{aligned} \ln\left[x(t)\right] &= \ln\left(x_0 \cdot e^{-kt}\right) \\ &= \ln\left(x_0\right) + \ln\left(e^{-kt}\right) \\ &= \ln\left(x_0\right) - k \cdot t \end{aligned} \qquad \text{Equation 2.12}$$

This is the equation of a straight line, as shown in **Figure 2.15B**, where the vertical axis is ln $[x(t)]$, the horizontal axis is t, the intercept is $\ln(x_0)$, and the slope of the line is $-k$. How long will it take for x to go from some value, x_1, to half that value, $x_{½}$? Because k is the slope of a straight line relating $\ln(x)$ to time, it follows that

$$k = \frac{\Delta \ln(x)}{\Delta t} = \frac{ln(x) - ln\left(\frac{x}{2}\right)}{t_{½}} = \frac{ln\left(\frac{x}{\left(\frac{x}{2}\right)}\right)}{t_{½}} = \frac{ln(2)}{t_{½}} \approx \frac{0.693}{t_{½}} \qquad \text{Equation 2.13}$$

where $t_{½}$ is the "half-life," the time required for a 50% decrease in x. The natural log of 2 is close enough to 0.693 to be considered an equality in subsequent equations here.

Thus, the relationship of the slope (or "rate constant"), k, to half-life, $t_{½}$ is $k = \frac{0.693}{t_{½}}$. If we measure the time it takes for x to fall by 50%, $t_{½}$, then we know the rate constant, k. Conversely, if we know k, the rate constant, we can easily calculate the time it will take for x to fall by 50% as

$$t_{½} = \frac{0.693}{k} \qquad \text{Equation 2.14}$$

Physiologic Pharmacokinetic Models

It is possible to analyze volumes and clearances for each organ in the body and construct models of pharmacokinetics by assembling the organ models into physiologically and anatomically accurate models of the entire animal. **Figure 2.16** shows such a model for thiopental in rats.[11] However, models that work with individual tissues are mathematically cumbersome and do not offer a better prediction of plasma drug concentration than models that lump the tissues into a few compartments. If the goal is to determine how to give drugs in order to obtain therapeutic plasma drug concentrations, then all that is needed is to mathematically relate dose to plasma concentration. For this purpose, "compartmental" models are usually adequate.

Compartmental Pharmacokinetic Models

Compartmental models are built on the same basic concepts as physiologic models. The "one-compartment model" (**Figure 2.17A**) contains a single volume and a single clearance, as though we were buckets of fluid. For anesthetic drugs, we resemble several buckets connected by pipes. These are usually modeled using two- or three-compartment models (**Figure 2.17B,C**). The volume to the left in the two-compartment model and in the center of the three-compartment model is the central volume. This is the volume where we inject our intravenous drugs and also the volume we measure when we draw blood samples. The other volumes are peripheral volumes of distribution. The sum of the all volumes is the volume of distribution at steady state, Vd_{ss}. The clearance

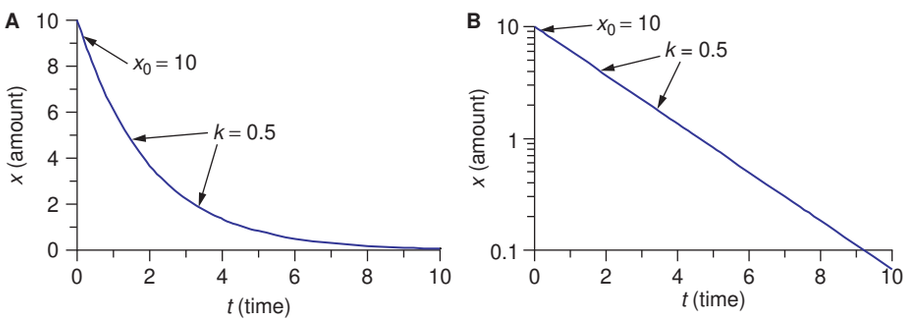

FIGURE 2.15 Exponential decay curve, as given by $x(t) = x_0 e^{-kt}$, plotted on standard axis (A) and a logarithmic axis (B).

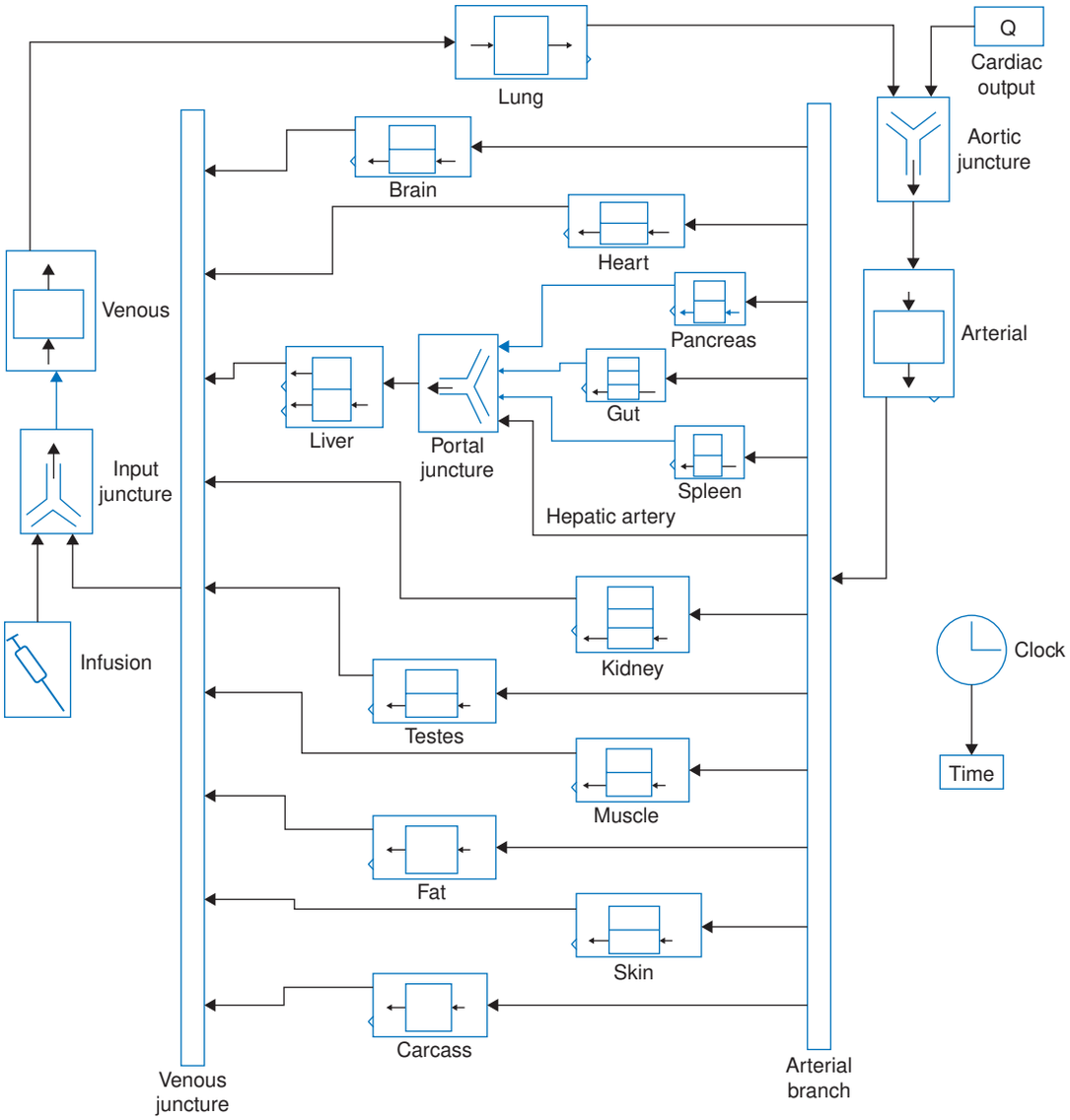

FIGURE 2.16 Physiologic model for thiopental in rats. The pharmacokinetics of distribution into each organ has been individually determined. The components of the model are linked by zero-order (flow) and first-order (diffusion) processes. *Reprinted by permission from Springer: Ebling WF, Wada DR, Stanski DR. From piecewise to full physiologic pharmacokinetic modeling: applied to thiopental disposition in the rat.* J Pharmacokinetic Biopharm. *1994;22(4):259-292. Copyright © 1994 Plenum Publishing Corporation.*

for drugs permanently removed from the central compartment is the "systemic clearance," so named because it is the process that clears drug from the entire system. The clearances between the central compartment and the peripheral compartments are the "intercompartmental" clearances. Although the concept of compartments yields useful mathematics for planning dosing, when experimental animals were flash frozen at different times following administration of anesthetic drugs, and characterized using physiologic models, none of the compartments identified in two and three compartment models could be anatomically identified.[12] Other than clearance, none of the parameters of compartment models readily translates into any anatomic structure or physiologic process.

One-Compartment Model

Bolus Pharmacokinetics

Returning to the one-compartment bucket, let us call the amount of drug poured into the bucket x_0 (x at time 0).

Remembering that the definition of concentration is amount divided by volume, by definition concentration immediately following a bolus dose, C_0 is:

$$C_0 = x_0/V \qquad \text{Equation 2.15}$$

where x_0 is the amount at time 0 (i.e., the amount of the bolus dose) and V is the volume of the compartment. We can rearrange equation 2.15 to calculate the bolus dose for any desired target concentration, C_T:

$$\text{Dose} = C_T \times V \qquad \text{Equation 2.16}$$

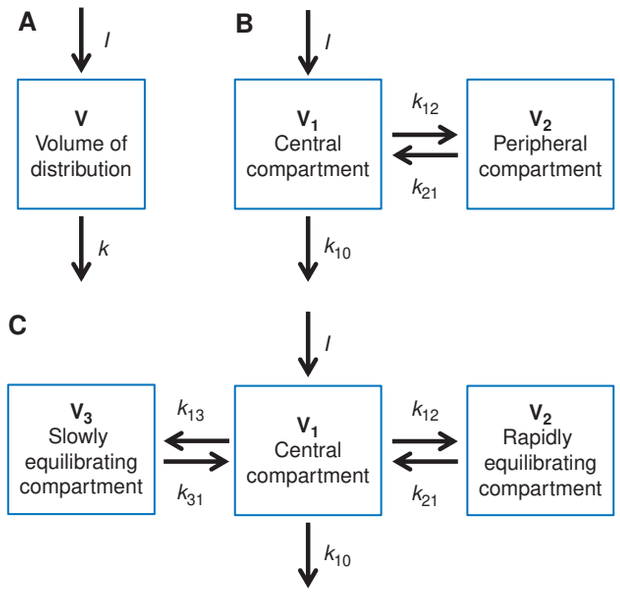

FIGURE 2.17 Standard one- (A), two- (B), and three-compartment (C) mammillary pharmacokinetic models. *I* represents any input into the system (eg, bolus or infusion). The volumes are represented by *V* and the rate constants by *k*. The subscripts on rate constants indicate the direction of flow, noted as $k_{\text{from to}}$.

Let us assume that the fluid is being drained through a pipe at a constant rate, which we will call **clearance**, *Cl*. What is the rate, *dx*/*dt*, that drug *x* is leaving the bucket? It is the concentration of drug times the rate of flow through the pipe:

$$\frac{dx}{dt} = Concentration \cdot Cl = \frac{x}{V} \cdot Cl = x \cdot \frac{Cl}{V} \qquad \text{Equation 2.17}$$

We will come back to this equation many times.

Because *Cl*/*V* is a constant, and the rate $x \times Cl/V$ is obviously proportional to x, $\frac{dx}{dt}$ is a first-order process. We know that a first order process can be expressed as $\frac{dx}{dt} = k\,x$. Since $\frac{dx}{dt} = x\frac{Cl}{V} = k\,x$, it follows that $k = \frac{Cl}{V}$. This can be rearranged to yield a fundamental identity of linear pharmacokinetics:

$$Cl = k \times V \qquad \text{Equation 2.18}$$

What does this identity tell us about the relationship between half-life, volume, and clearance? Rearranging the above equation as $k = \frac{Cl}{V}$ and remembering that $t_{½} = \frac{0.693}{k}$, we can conclude that half-life is proportional to volume and inversely proportional to clearance.

$$t_{½} = 0.693\,\frac{V}{Cl} \qquad \text{Equation 2.19}$$

Consider two alternative models, one with a large volume and a small clearance (**Figure 2.18A**), and one with a small volume and a large clearance (**Figure 2.18B**). It is (hopefully) intuitively obvious that following bolus injection, concentrations will fall more quickly (shorter half-life) with the larger clearance and smaller volume as predicted by Equation 2.16 and shown in figure 2.18B.

Because this is a first-order process, let us calculate the concentration of drug that remains in the bucket as drug is being cleared following bolus injection. Using the equation that describes first-order processes, $x(t) = x_0\,e^{-kt}$, $x(t)$ is the amount of drug at time *t*, x_0 is the amount of drug right after bolus injection, and *k* is the rate constant (*Cl*/*V*). If we divide both sides by *V*, and remember that *x*/*V* is the

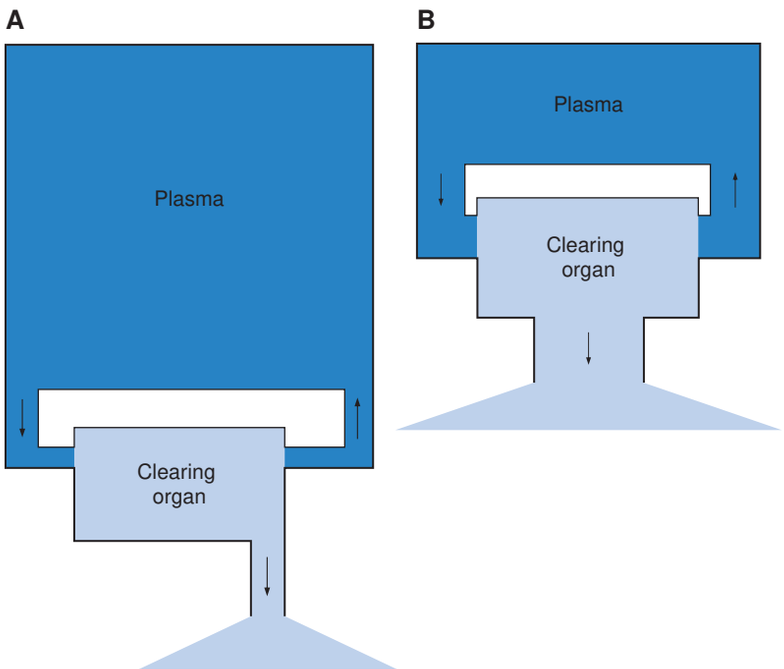

FIGURE 2.18 The relationship between volume and clearance and half-life can be envisioned by considering two settings: a big volume and a small clearance (A) and a small volume with a big clearance (B). Drug will be eliminated faster in the latter case.

definition of concentration, we get the equation that relates concentration following an intravenous bolus to time and initial concentration:

$$C(t) = C_0\, e^{-kt} \qquad \text{Equation 2.20}$$

This equation defines the "concentration over time" curve for a one-compartment model after a bolus of drug and has the log linear shape seen in **Figure 2.15B**.

In a typical experiment, we start with the concentrations, as seen in **Figure 2.15**, and calculate clearance in one of two ways. First, we can calculate V by rearranging the definition of concentration, V = dose/initial concentration = $dose/C_0$. If you know the dose and you measure C_0 in the experiment, you can calculate V. If you then fit the log (C) line versus time line to a straight line, you can directly measure the slope, $-k$. You can then calculate clearance as $k \cdot V$.

A more general solution is to consider the integral of the concentration over time curve, $C(t) = C_0\, e^{-kt}$, known in pharmacokinetics as the area under the curve, or AUC:

$$\begin{aligned} AUC &= \int_0^\infty C_0\, e^{-kt} dt \\ &= \int_0^\infty \frac{x_0}{V}\left(e^{-\frac{Cl}{V}t}\right) dt \text{ (substituting for } C_0 \text{ and } k) \\ &= \frac{x_0}{V} \times \frac{V}{Cl} \text{ (evaluating the above integral)} \\ &= \frac{x_0}{Cl} \end{aligned} \qquad \text{Equation 2.21}$$

We can rearrange the right side and the last term on the left side to solve for clearance, Cl:

$$Cl = \frac{x_0}{AUC} \qquad \text{Equation 2.22}$$

Because x_0 is the dose of drug, clearance equals the dose divided by the AUC. This fundamental property of *linear* pharmacokinetic models applies to one-compartment models, to multicompartment models, and to any type of intravenous drug dosing (provided the *total* dose administered is used as the numerator). It directly follows that AUC is proportional to dose for linear models (ie, models where Cl is constant).

The term *linear pharmacokinetics* has been used multiple times, starting with **Figure 2.9** showing that in the "linear" portion, metabolism was clearly proportional to concentrations. Now that the basic concepts have been introduced, we can define "linear" more precisely. If metabolism is proportional to concentration, as seen in **Figure 2.9**, then metabolism, defined as $\frac{dx}{dt}$ is therefore a first-order process defined by a rate constant k times x. Since $k = \frac{Cl}{V}$, k is constant, and V is constant, then clearance, Cl, must also be constant. In other words, clearance does not change with dose, concentration, time, or anything else. When clearance is constant, the pharmacokinetics are said to be "linear" because a linear (eg, proportional) increase in dose results in a linear (eg, proportional) increase in concentration. More intuitively stated, if you double the dose, you double the concentration. It also means that if you give a dose now, and another dose in an hour, the concentrations after the second dose what you would expect from the second dose alone, "linearly" added to the residual concentrations from the first dose. This is also called the principle of superposition.

Occasionally the term *linear* is confusing because the curves of concentration over time are typically exponentially increasing or decreasing rather than straight lines. That is not what linear implies because concentrations over time are virtually never straight lines. Linear pharmacokinetics are "linear" with respect to *dose*, but never with respect to time.

Infusion Pharmacokinetics

If you give an infusion at a rate of I (for *I*nput), the plasma concentration will rise as long as the rate of drug going into the body, I, exceeds the rate at which drug leaves the body, $C \cdot Cl$, where C is the drug concentration. Once, $I = C \cdot Cl$, drug is going in and coming out at the same rate, and the body is at steady state. We can calculate the concentration at steady state by observing that the rate of drug going in must equal the rate of drug coming out. At steady state, the drug concentration is C_{ss}. Based on Equation 2.17, drug is leaving the system at the rate $C_{ss} \cdot Cl$. Because at steady state, the infusion rate equals the metabolic rate, the infusion rate, I, must therefore equal the metabolic rate, $C_{ss} \cdot Cl$.

This can be rearranged to give the concentration of drug at steady state during an infusion:

$$C_{ss} = \frac{I}{Cl} \qquad \text{Equation 2.23}$$

Thus, the steady-state concentration during an infusion is the rate of drug input divided by the clearance. It follows that if we want to calculate the infusion rate that will achieve a given target concentration, C_T, at steady state, then the infusion rate must be $C_T \cdot Cl$.

$C_{ss} \cdot \frac{I}{Cl}$ is similar in form to the equation describing the concentration following a bolus injection: $C_0 = \frac{x_0}{V}$ as shown in equation 2.15. Thus, volume is a scalar relating bolus dose to initial concentration, and clearance is a scalar relating infusion rate to steady-state concentration. It follows that the initial concentration following a bolus is independent of the clearance, and the steady-state concentration during a continuous infusion is independent of the volume.

During an infusion, the rate of change in the amount of drug, x, is rate of inflow, I, minus the rate of outflow, $k \cdot x$, which is represented as $\frac{dx}{dt} = I - kx$. We can calculate x at any time t as the integral from time 0 to time t.

Assuming that we are starting with no drug in the body (ie, $x_0 = 0$), the result is $x(t) = \frac{I}{k}(1 - e^{-kt})$. If we divide both sides by volume, V, and remember that $Cl = k \cdot V$, we can solve this equation for concentration: $C(t) = \frac{I}{Cl}(1 - e^{-kt})$. This is the equation for concentration during an infusion in a one-compartment model.

As $t \to \infty$, $e^{-kt} \to 0$, the equation $x(t) = \frac{I}{k}(1 - e^{-kt})$ reduces to $x_{ss} = \frac{I}{k}$. During an infusion, the amount in the body approaches x_{ss} (steady state) asymptotically, only reaching it at infinity. However, we can calculate how long it takes to get to half of the steady-state amount, $\frac{x_{ss}}{2}$. If $x_{ss} = \frac{I}{k}$, then $\frac{x_{ss}}{2} = \frac{I}{2k}$. Because $\frac{I}{2k}$ is the amount of drug when we are halfway to steady state, we can substitute that for the amount of drug in our formula, $x(t) = \frac{I}{k}(1 - e^{-kt})$, giving us $\frac{I}{2k} = \frac{I}{k}(1 - e^{-kt})$, and solve that for t. The solution is $t½ = \frac{\ln(2)}{k}$. This is the time to rise to half of the steady state concentration. Recall that $t_{½}$, the half time to decrease to 0 following a bolus injection, was $\frac{\ln(2)}{k}$. We again have a parallel between boluses and infusions. Following a bolus, it takes 1 half-life to reduce the concentrations by half, and during an infusion, it takes 1 half-life to increase the concentration halfway to steady state. Similarly, it takes 2 half-lives to reach 75%, 3 half-lives to reach 87.5%, and 5 half-lives to reach 97% of the steady-state concentration. By 4 to 5 half-lives, we typically consider the patient to be at steady state, although the concentrations only asymptotically approach the steady-state value.

Absorption Pharmacokinetics

When drugs are given intravenously, every molecule reaches the systemic circulation. When drugs are given by a different route, such as orally, transdermally, or intramuscularly, the drug must first reach the systemic circulation. Oral drugs may be only partly absorbed. What is absorbed then has to get past the liver ("first-pass hepatic metabolism") before reaching the systemic circulation. Transdermally applied drugs may be rubbed off, removed with soap or alcohol, or be sloughed off with the stratum corneum without being absorbed. The dose of drug that eventually reaches the systemic circulation with alternative routes of drug delivery is the administered dose times f, the fraction "bioavailable."

Alternative routes of drug delivery are often modeled by assuming the drug is absorbed from a reservoir or depot, usually modeled as an additional compartment with a monoexponential rate of transfer to the systemic circulation, $A(t) = f \cdot D_{oral} \cdot k_a \cdot e^{-k_a t}$, where $A(t)$ is the absorption rate at time t, f is the fraction bioavailable, D_{oral} is the dose taken orally (or intramuscularly, applied to the skin, etc). The k_a is the absorption rate constant. Because the integral of $k_a\, e^{-k_a t}$ is 1, the total amount of drug absorbed is $f \cdot D_{oral}$. To compute the concentrations over time, we first reduce the problem to differential equations and integrate. The differential equation for the amount, x, with oral absorption into a one-compartment disposition model is

$$\frac{dx}{dt} = \text{inflow} - \text{outflow} = A(t) - k \cdot x = f \cdot D_{oral} \cdot k_a \cdot e^{-k_a t} - k \cdot x \qquad \text{Equation 2.24}$$

This is simply the rate of absorption at time t, $A(t)$, minus the rate of exit, $k \cdot x$. The amount of drug, x, in the compartment at time t is the integral of this from 0 to time t:

$$x(t) = \frac{D_{oral} f k_a}{k - k_a}\left(e^{-k_a t} - e^{-kt}\right) \qquad \text{Equation 2.25}$$

This equation describes the amount of drug in the systemic circulation following first-order absorption from a depot, such as the stomach, an intramuscular injection, the skin, or even an epidural dose. To describe the concentrations, rather than amounts of drug, it is necessary to divide both sides by V, the volume of distribution.

Multicompartment Models

The previous section used one-compartment model to introduce concepts of rate constants and half-lives and relate them to the physiologic concepts of volume and clearance. Unfortunately, none of the drugs used in anesthesia can be accurately characterized by one-compartment models because anesthetic drugs distribute extensively into peripheral tissues. To describe the pharmacokinetics of intravenous anesthetics, we must extend the one-compartment model to account for this distribution.

The plasma concentrations over time following an intravenous bolus resemble the curve in **Figure 2.19**. In

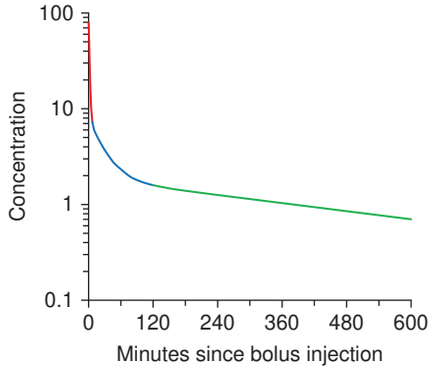

FIGURE 2.19 Typical time course of plasma concentration following bolus injection of an intravenous drug, with a rapid phase (red), an intermediate phase (blue), and a slow log-linear phase (green). The simulation was performed with the pharmacokinetics of fentanyl. *Reprinted with permission from Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamics evaluation.* J Pharmacol Exp Ther. *1987;240(1):159-166. Copyright © 1987 by The American Society for Pharmacology and Experimental Therapeutics.*

contrast to **Figure 2.15**, **Figure 2.19** is not a straight line even though it is plotted on a log *y*-axis. This curve has the characteristics common to most drugs when given by intravenous bolus. First, the concentrations continuously decrease over time. Second, the rate of decline is initially steep but becomes less steep over time until we get to a portion that is "log-linear."

Many anesthetic drugs appear to have three distinct phases, as suggested by **Figure 2.19**. There is a "rapid distribution" phase (*red* in **Figure 2.19**) that begins immediately after bolus injection. Very rapid movement of the drug from the plasma to the rapidly equilibrating tissues characterizes this phase. Often, there is a second "slow distribution" phase (*blue* in **Figure 2.19**) that is characterized by movement of drug into more slowly equilibrating tissues and return of drug to the plasma from the most rapidly equilibrating tissues. The terminal phase (*green* in **Figure 2.19**) is a straight line when plotted on a semilogarithmic graph. The distinguishing characteristic of the terminal elimination phase is that the plasma concentration is lower than the tissue concentrations, and the relative proportion of drug in the plasma and peripheral volumes of distribution remains constant. During this "terminal phase," drug returns from the rapid and slow distribution volumes to the plasma and is permanently removed from the plasma by metabolism or excretion.

The presence of three distinct phases following bolus injection is a defining characteristic of a mammillary model with three compartments. (A mammillary model consists of a central compartment with peripheral compartments connecting to it. There are no interconnections among other compartments.) It is possible to develop "hydraulic" models, as shown in **Figure 2.20**, for intravenous drugs.[13] In this model, there are three tanks, corresponding (from left to right) with the slowly equilibrating peripheral compartment, the central compartment (the plasma, into which drug is injected), and the rapidly equilibrating peripheral compartment. The horizontal pipes represent intercompartmental clearance or (for the pipe draining onto the page) metabolic clearance. The volumes of each tank correspond with the volumes of the compartments for fentanyl. The cross-sectional areas of the pipes correlate with fentanyl systemic and intercompartmental clearances. The height of water in each tank corresponds to drug concentration.

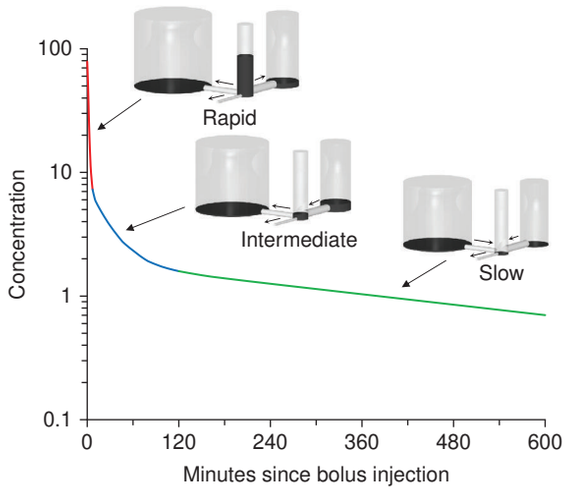

FIGURE 2.20 Hydraulic equivalent of the model in **Figure 2.19**. *Adapted with permission from Youngs EJ, Shafer SL. Basic pharmacokinetic and pharmacodynamic principles. In: White PF, ed.* Textbook of Intravenous Anesthesia. *Baltimore, MD: Lippincott Williams & Wilkins; 1997:10.*

We can follow the processes that decrease drug concentration over time following bolus injection. Initially, drug flows from the central compartment to both peripheral compartments and is eliminated via the drain pipe through metabolic clearance. Because there are three places for drug to go, the central compartment concentration decreases very rapidly. At the transition between the red and the blue lines, there is a change in the role of the most rapidly equilibrating compartment. At this transition, the central compartment concentration falls below the concentration in the rapidly equilibrating compartment, and the direction of flow between them is reversed. After this transition (*blue line*), drug in the plasma only has two places to go: the slowly equilibrating compartment or out the drain pipe. These processes are partly offset by the return of drug to the plasma from the rapidly equilibrating compartment, which slows the decrease in plasma concentration. Once the concentration in the central compartment falls below both the rapidly and slowly equilibrating compartments (*green line*), then the only method of decreasing the plasma concentration is clearance out the drain pipe. Drug accumulated in the rapidly and slowly equilibrating compartments acts as an enormous drag on the system, and the little drain pipe now is working against the entire body store of drug.

Curves that continuously decrease over time, with a continuously increasing slope (ie, curves that look like **Figures 2.19** and **2.20**), can be described by a sum of negative exponentials, as shown in **Figure 2.21**, which shows how three single exponential curves are added together to get a sum of exponentials that describes the plasma concentrations over time after bolus injection:

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \qquad \text{Equation 2.26}$$

where t is the time since the bolus; $C(t)$ is the drug concentration following a bolus dose; and A, α, B, β, C, and γ are parameters of a pharmacokinetic model. A, B, and C are called **coefficients**, whereas α, β, and γ are called **exponents**. Following a bolus injection, all six of the parameters (A, α, B, β, C, and γ) will be greater than 0.

The main reason that polyexponential equations are used is that they work. These equations describe reasonably accurately the plasma concentrations observed after bolus injection, except for the misspecification in the first few minutes mentioned previously.

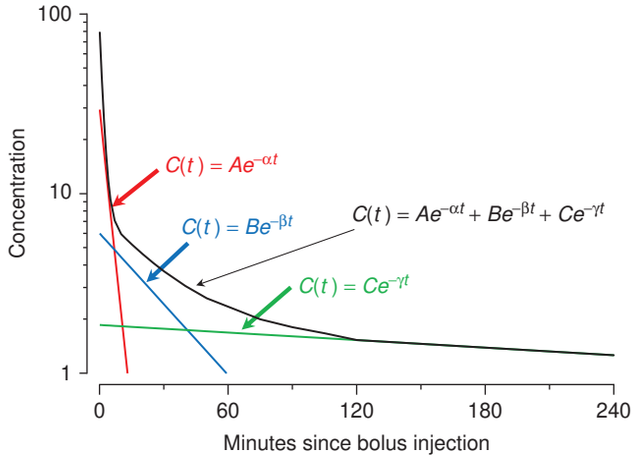

FIGURE 2.21 The polyexponential equation that describes the decline in plasma concentration for most intravenous anesthetics is the algebraic sum of the exponential terms that represent rapid phase shown in red, intermediate phase shown in blue and slow phase shown in green.

Polyexponential equations permit us to use the one-compartment ideas just developed, with some generalization of the concepts. $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$ says that the concentrations over time are the algebraic sum of three separate functions, $Ae^{-\alpha t}$, $Be^{-\beta t}$, and $Ce^{-\gamma t}$. Typically, $\alpha > \beta > \gamma$ by about 1 order of magnitude. At time 0 ($t = 0$), Equation 2.22 reduces to $C_0 = A + B + C$. In other words, the sum of the coefficients A, B, and C equals the concentration immediately following a bolus. It thus follows that $A + B + C =$ bolus amount / V_1.

Constructing pharmacokinetic models represents a trade-off between accurately describing the data, having confidence in the results, and mathematical tractability. Adding exponents to the model usually provides a better description of the observed concentrations. However, adding more exponent terms usually decreases our confidence in how well we know each coefficient and exponential and *greatly* increases the mathematical burden of the models. This is why most pharmacokinetic models are limited to two or three exponents.

Polyexponential models can be mathematically transformed from the admittedly unintuitive exponential form $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$ to a more easily visualized compartmental form, as shown in Figures 2.17 and 2.20. Micro-rate constants, expressed as k_{ij}, define the rate of drug transfer from compartment i to compartment j. Compartment 0 is the compartment outside the model, so k_{10} is the micro-rate constant for irreversible removal of drug from the central compartment (analogous to k for a one-compartment model).

The intercompartmental micro-rate constants (k_{12}, k_{21}, etc) describe the movement of drug between the central and peripheral compartments. Each peripheral compartment has two micro-rate constants, one for drug entry and one for drug exit. The micro-rate constants for the two- and three-compartment models can be seen in **Figure 2.17**. The differential equations describing the rate of change for the amount of drug in compartments 1, 2, and 3 follow directly from the micro-rate constants. For the two-compartment model, the differential equations for each compartment are as follows:

$$\frac{dx_1}{dt} = I + x_2k_{21} - x_1k_{10} - x_1k_{12}$$
$$\frac{dx_2}{dt} = x_1k_{12} - x_2k_{21} \qquad \text{Equation 2.27}$$

where I is the rate of drug input. For the three-compartment model, the differential equations for each compartment are as follows:

$$\frac{dx_1}{dt} = I + x_3k_{31} + x_2k_{21} - x_1k_{10} - x_1k_{12} - x_1k_{13}$$
$$\frac{dx_2}{dt} = x_1k_{12} - x_2k_{21}$$
$$\frac{dx_3}{dt} = x_1k_{13} - x_3k_{31} \qquad \text{Equation 2.28}$$

For the one-compartment model, k was both the rate constant and the exponent. For multicompartment models, the relationships are more complex. The interconversion between the micro-rate constants and the exponents becomes exceedingly complex as more exponents are added because every exponent is a function of every micro-rate constant and vice versa. Individuals interested in such interconversions can find them in the Excel spreadsheet "convert.xls," which can be downloaded from https://github.com/StevenLShafer/Pharmacokinetics/blob/master/convert.xls. This is useful because publications on pharmacokinetics may use one or another system, and it is difficult to compare without converting the exponents to micro-rate constants.

The Time Course of Drug Effect

The plasma is not the site of drug effect for anesthetic drugs. There is a time lag between plasma drug concentration and effect site drug concentration. Consider the different rate of onset for fentanyl and alfentanil. **Figure 2.21** is from work by Stanski and colleagues.[14,15] The black bar in **Figure 2.22A** shows the duration of a fentanyl infusion.[14] Rapid arterial samples document the rise in fentanyl concentration. The time course of electroencephalogram effect (spectral edge) lags 2 to 3 minutes behind the rapid rise in arterial concentration. This lag is called **hysteresis**. The plasma concentration peaks at the moment the infusion is turned off. Following the peak plasma concentration (and the Disney logo that appears at peak plasma concentration), the plasma fentanyl concentration rapidly decreases. However, the offset of fentanyl drug effect lags well behind the decrease in plasma concentration. **Figure 2.22B** shows the same study design in

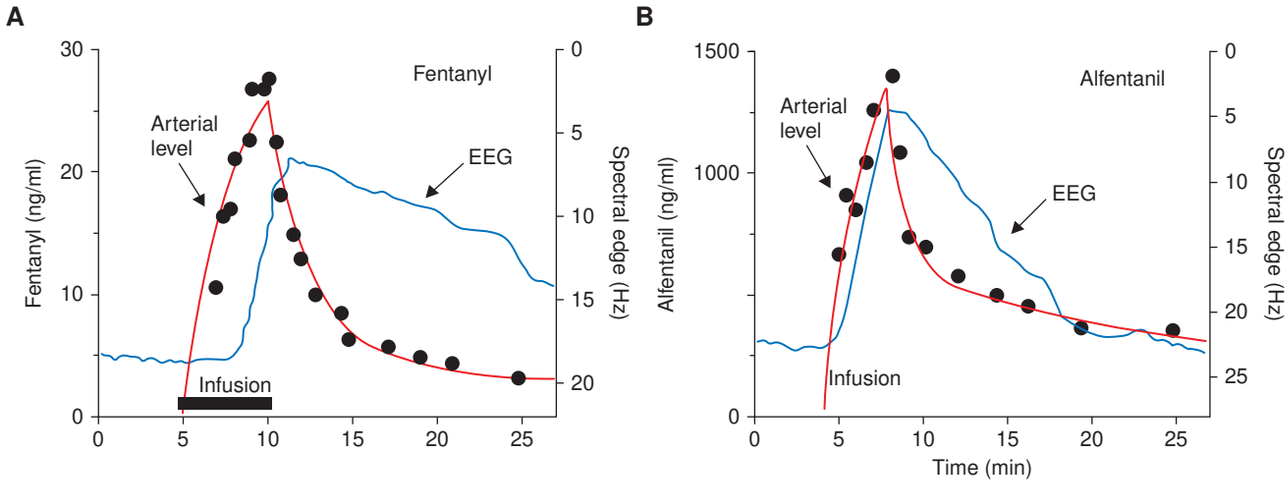

FIGURE 2.22 Fentanyl and alfentanil arterial concentrations (circles) and electroencephalographic (EEG) response (irregular line) to an intravenous infusion. Alfentanil shows a less time lag between the rise and fall of arterial concentration and the rise and fall of EEG response than fentanyl because it equilibrates with the brain more quickly. *Reprinted with permission from Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil.* Anesthesiology. *1985;62(3):234-241. Copyright © 1985 American Society of Anesthesiologists, Inc.*

a patient receiving alfentanil. Because of alfentanil's rapid blood–brain equilibration, there is less hysteresis (delay) with alfentanil than with fentanyl.

The relationship between the plasma and the site of drug effect is modeled with an "effect site" model, as shown in **Figure 2.23**.[16] The site of drug effect is connected to the plasma by a first-order process. The equation that relates effect site concentration to plasma concentration is

$$\frac{dCe}{dt} = k_{e0} \cdot Cp - k_{e0} \cdot Ce \qquad \text{Equation 2.29}$$

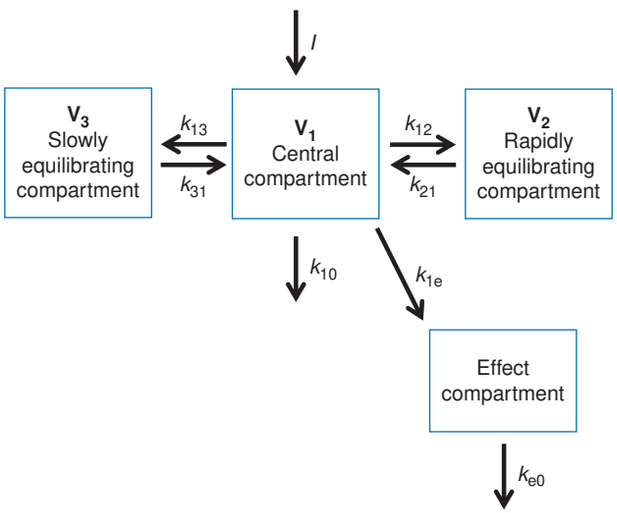

FIGURE 2.23 The three-compartment model from **Figure 2.16** with an added effect site to account for the equilibration delay between the plasma concentration and the observed drug effect. The effect site has a negligible volume. As a result, the only parameter that affects the delay is k_{e0}.

where *Ce* is the effect site concentration and *Cp* is the plasma drug concentration. k_{e0} is the rate constant for elimination of drug from the effect site. It is most easily understood in terms of its reciprocal, $0.693/k_{e0}$, the half-time for equilibration between the plasma and the site of drug effect.

Figure 2.24 shows the plasma and effect site concentrations predicted by the model (see **Figure 2.22**) for fentanyl and alfentanil. The plasma concentrations (*black lines*) are not very different. However, the effect site concentrations (*red lines*) show that alfentanil equilibrates more quickly. There are two consequences. First, the peak effect is sooner (obviously). Second, the rapid equilibration of alfentanil allows the brain to "see" the initial high plasma concentrations, producing a relatively greater rise in effect site concentrations than observed with fentanyl. This permits alfentanil to deliver relatively more "bang" for a bolus.

The constant k_{e0} has a large influence on the rate of rise of drug effect, the rate of offset of drug effect, the time to peak effect,[17] and the dose that is required to produce the desired drug effect.

Dose Calculations

Bolus Dosing

We noted previously that we can rearrange the definition of concentration to find the amount of drug required to produce any desired target concentration for a known volume, amount = $C_T \times$ volume. Many introductory pharmacokinetic texts suggest using this formula to calculate the loading bolus required to achieve a given concentration. The problem with applying this concept to

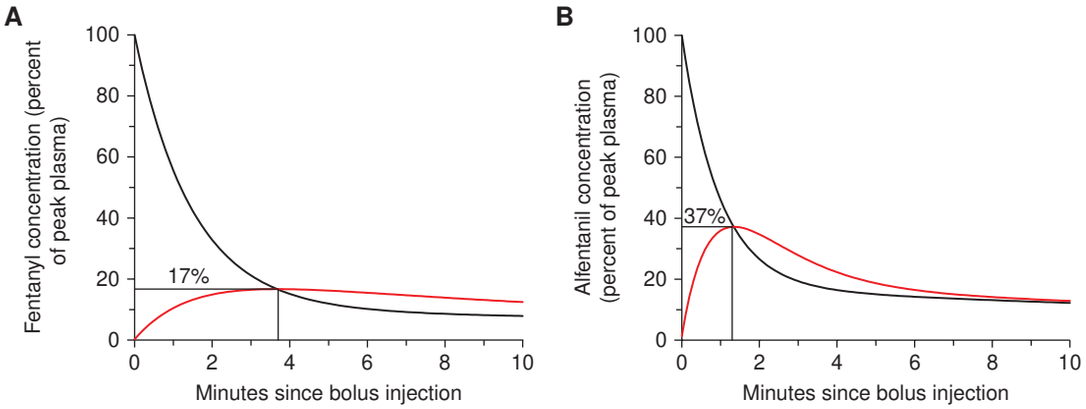

FIGURE 2.24 Plasma (black line) and effect site (red line) concentrations following a bolus dose of fentanyl (A) or alfentanil (B). *Adapted with permission from Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection.* Anesthesiology. *1991;74(1):53-63. Copyright © 1991 American Society of Anesthesiologists, Inc.*

the anesthetic drugs is that there are several volumes: V_1 (central compartment); V_2 and V_3 (the peripheral compartments); and Vd_{ss}, the sum of the individual volumes. V_1 is usually much smaller than Vd_{ss}, and so it is tempting to say that the loading dose should be something between $C_T \times V_1$ and $C_T \times Vd_{ss}$.

That proves to be a useless suggestion. Consider the initial dose of fentanyl. The C_{50} for fentanyl to attenuate hemodynamic response to intubation (when combined with an intravenous hypnotic) is approximately 2 ng/mL. The V_1 and Vd_{ss} for fentanyl are 13 L and 360 L, respectively. The dose of fentanyl thus ranges from a low of 26 μg (based on the V_1 of 13 L) to a high 720 μg (based on the Vd_{ss} of 360 L). A fentanyl bolus of 26 μg achieves the desired concentration in the plasma for an initial instant (**Figure 2.25**).

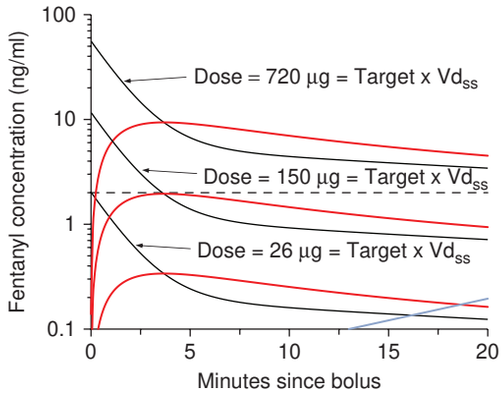

FIGURE 2.25 The volume of the central compartment of fentanyl is 13 L. The volume of distribution at steady state is 360 L. For a target concentration of 2 μg/L (dotted line), the dose calculated on V_1, 26 μg, results in a substantial undershoot. The dose calculated using Vd_{ss}, 720 μg, produces a profound overshoot. Only a dose based on $Vd_{peak\ effect}$, 150 μg, produces the desired concentration in the effect site. The black lines show plasma concentration over time. Red lines show effect site concentration over time.

Unfortunately, the plasma levels almost instantly decrease below the desired target, and the effect site levels are never close to the desired target. A fentanyl bolus of 720 μg, not surprisingly, produces an enormous overshoot in the plasma levels that persists for hours. It is absurd to use equations to calculate the fentanyl dose if the resulting recommendation is "pick a dose between 26 and 720 μg."

Conventional approaches to calculate a bolus dose are designed to produce a specific *plasma* concentration. This makes little sense because the plasma is not the site of drug effect. By knowing the k_{e0} (the rate constant for elimination of drug from the effect site) of an intravenous anesthetic, we can design a dosing regimen that yields the desired concentration *at the site of drug effect*. If we do not want to overdose the patient, we should select the bolus that produces the desired peak concentration in the effect site.

The decline in plasma concentration after the bolus, up to the time of peak effect, can be thought of as a dilution of the bolus into a larger volume than the volume of the central compartment. One interesting characteristic of the equilibration between the plasma and the effect site is that at the time of peak effect, the plasma and the effect site concentrations are the same (if they were not the same, then it would not be the peak because there would be a gradient driving drug in or out of the effect site). This introduces the concept of Vd_{pe}, the apparent volume of distribution at the time of peak effect.[18] The size of this volume can be readily calculated from the observation that the plasma and effect site concentrations are the same at the time of peak effect:

$$Vd_{pe} = \frac{\text{bolus amount}}{C_{pe}} \qquad \text{Equation 2.30}$$

where C_{pe} is the plasma concentration at the time of peak effect. We can arrange this equation to calculate the dose that provides the desired peak effect site concentration: bolus dose $= C_T \times Vd_{pe}$. For example, the Vd_{pe} for fentanyl is 75 L. Producing a peak fentanyl effect site concentration

TABLE 2.2
Volume of distribution at the time of peak effect[a]

Drug	V_1 (L)	Vd_{pe} (L)
Fentanyl	12.7	75
Alfentanil	2.19	5.9
Sufentanil	17.8	89
Remifentanil	5.0	17
Propofol	6.7	37
Thiopental	5.6	14.6
Midazolam	3.4	31

Abbreviations: V_1, volume of the central compartment; Vd_{pe}, apparent volume of distribution at the time of peak effect.
[a]Reprinted from Glass PSA, Shafer SL, Reves JG. Intravenous drug delivery systems. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. *Miller's Anesthesia*. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:825-858. Copyright © 2010 Elsevier. With permission.

of 2 ng/mL requires 150 μg for the typical patient, which produces a peak effect in 3.6 minutes. This is a much more reasonable dosing guideline than the previous recommendation of picking a dose between 26 and 760 μg. **Table 2.2** lists V_1 and Vd_{pe} for fentanyl, alfentanil, sufentanil, remifentanil, propofol, thiopental, and midazolam. **Table 2.3** lists the time to peak effect and the $t_{½}\ k_{e0}$ (half-life at the site of drug effect) of the commonly used intravenous anesthetics. Of course, individuals may differ from the typical patient. The individual characteristics that drive the differences may be known (age, weight, renal or hepatic dysfunction) in which case they can be built into the pharmacokinetic model if they are found to be significant. On the other hand, they may be unknown, in which case pharmacodynamic monitoring is required to fine tune dosing.

TABLE 2.3
The time to peak effect and $t_{½}\ k_{e0}$ following a bolus dose[a]

Drug	Time to peak drug effect (min)	$T_{½}\ k_{e0}$ (min)[b]
Fentanyl	3.6	4.7
Alfentanil	1.4	0.9
Sufentanil	5.6	3.0
Remifentanil	1.6	1.3
Propofol	2.2	2.4
Thiopental	1.6	1.5
Midazolam	2.8	4.0
Etomidate	2.0	1.5

[a]Reprinted from Glass PSA, Shafer SL, Reves JG. Intravenous drug delivery systems. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. *Miller's Anesthesia*. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:825-858. Copyright © 2010 Elsevier. With permission.
[b]$t_{½}\ k_{e0} = 0.693/k_{e0}$, the effect site half-life, where k_{e0} is the rate constant for elimination of drug from the site of drug effect and $t_{½}\ k_{e0}$ is the time required for the concentration at the site of drug effect to fall to half of its value.

Maintenance Infusion Rate

As explained previously, to maintain a given target concentration, C_T, drug must be delivered at the same rate that drug is exiting the body. Thus, the maintenance infusion rate at steady state is maintenance infusion rate $= C_T \times Cl$. However, this equation only applies after peripheral tissues have fully equilibrated with the plasma, which may require many hours. At all other times, this maintenance infusion rate underestimates the infusion rate to maintain a target concentration.

In some situations, this simple rate calculation may be acceptable. For example, if an infusion at this rate is used after a bolus based on Vd_{pe} (apparent volume of distribution at time of peak effect), and the drug has a long delay between the bolus and peak effect, then much of the distribution of drug into the tissues may have occurred by the time of peak effect site concentration. In this case, the maintenance infusion rate calculated as clearance times target concentration may be satisfactory because Vd_{pe} is sufficiently higher than V_1 to account for the distribution of drug into peripheral tissues. Unfortunately, most drugs used in anesthesia have sufficiently rapid plasma-effect site equilibration that Vd_{pe} does not adequately encompass the distribution process, making this approach unsuitable.

The pharmacokinetically sound approach should account for tissue distribution. Initially, the infusion rate is higher than $C_T \cdot Cl$ because it is necessary to replace the drug that gets taken up by peripheral tissues. However, the net flow of drug into peripheral tissues decreases over time. Therefore, the infusion rate required to maintain any desired concentration must also decrease over time. Following bolus injection, the equation to maintain the desired concentration is:

$$\text{Maintenance infusion rate} = C_T \times V_1 \times (k_{10} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t})$$

Equation 2.31

This equation indicates that a high infusion rate is initially required to maintain C_T. Over time, the infusion rate gradually decreases (**Figure 2.26**). At equilibrium ($t = \infty$), the infusion rate decreases to $C_T\ V_1\ k_{10}$, which is the same as $C_T \times Cl$.

No anesthetic in history has ever been so boring as to merit mentally solving such an equation while administration of an anesthetic. Fortunately, there are simple techniques that can be used in place of solving such a complex expression.

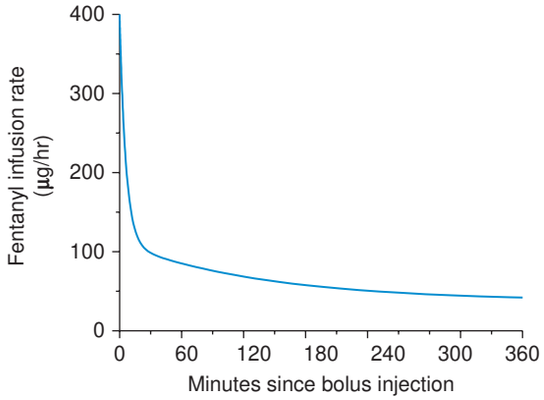

FIGURE 2.26 Fentanyl infusion rate to maintain a plasma concentration of 1 μg per hour. The rate starts off quite high because fentanyl is avidly taken up by body fat. The necessary infusion rate decreases as the fat equilibrates with the plasma.

Figure 2.27 is a nomogram in which the Equation 2.14 has been solved, showing the infusion rates over time necessary to maintain any desired concentration of fentanyl, alfentanil, sufentanil, and propofol. This nomogram is complex, and we don't use it even though one of us (SLS) created this nomogram. The point in including it is to show how infusion rates must be turned down over time as drug accumulates. The *y*-axis represents the target concentration, C_T. The suggested target initial concentrations (shown in *red*) are based on the work of Vuyk and colleagues[19] and appropriately scaled for fentanyl and sufentanil. The *x*-axis is the time since the beginning of the anesthetic. The intersections of the target concentration line and the diagonal lines indicates the infusion rate appropriate at each point in time. For example, to maintain a fentanyl concentration of 1.0 ng/mL, the appropriate rates are 3.0 μg/kg/hour at 15 minutes, 2.4 μg/kg/hour at 30 minutes, 1.8 μg/kg/hour at 60 minutes, 2.1 μg/kg/hour at 120 minutes, and 0.9 μg/kg/hour at 180 minutes.

Another approach to determine infusion rates for maintenance of anesthesia to a desired target concentration is through the use of a specialized slide rule.[20] **Figure 2.28** illustrates such a slide rule for propofol. As described by Bruhn et al,[20] "The bolus dose required to reach a given target plasma concentration is the product of the (weight-related) distribution volume and required concentration. Similarly, the infusion rate at a particular time point is the product of target concentration, body weight, and a correction factor that depends on the time elapsed from the start of the initial infusion. This factor can be determined for each time point using a PK simulation program."

The best approach is through the use of target-controlled drug delivery. With target-controlled drug delivery, the user simply sets the desired plasma or effect site concentration. Based on the drug's pharmacokinetics and the mathematical relationship between patient covariates (eg, weight, age, gender) and individual pharmacokinetic parameters, the computer calculates the dose of drug necessary to rapidly achieve and then maintain any desired concentration. Most critically, it can raise and lower concentrations in a controlled fashion, a calculation that cannot be captured in any simple nomogram. Such computerized controlled drug delivery systems are now widely available.

An alternative approach is to use stanpumpR, which can be found online at http://stanpumpR.io. stanpumpR is an online, open-source (see https://github.com/StevenLShafer/stanpumpR) pharmacokinetic simulator for intravenous anesthetic drugs and oral opioids. It was primarily developed by one of the authors (SLS) and remains in active development. **Figure 2.29** shows the screen of stanpumpR simulating an anesthetic with a propofol bolus and infusion, a fentanyl bolus, a remifentanil infusion, and two boluses of rocuronium. stanpumpR can be used to model specific anesthetic strategies before anesthesia or to model an ongoing anesthetic to see approximately what the drug levels are for the administered drugs.

Context-Sensitive Half-time

Special significance is often ascribed to the smallest exponent, which determines the slope of the final log-linear portion of the curve. When the medical literature refers to the half-life of a drug, unless otherwise stated, the half-life is based on the terminal half-life (ie, 0.693/smallest exponent). However, the terminal half-life for drugs with more than one exponential term is nearly impossible to interpret. The terminal half-life sets an upper limit on the time required for the concentrations to decrease by 50% after drug administration. Usually, the time for a 50% decrease will be much faster than that upper limit. A more useful concept is the "context-sensitive half-time," shown in **Figure 2.30**,[21] which is the time for the plasma concentration to decrease by 50% from an infusion that maintains a constant concentration. The "context" is the duration of the infusion. The context-sensitive half-time increases with longer infusion durations because it takes longer for the concentrations to fall if drug has accumulated in peripheral tissues.

The context-sensitive half-time is based on the time for a 50% decrease, which was chosen both to provide an analogy to half-life, and because, very roughly, a 50% reduction in drug concentration appears necessary for recovery after administration of most intravenous hypnotics at the termination of surgery. Of course, decreases other than 50% may be clinically relevant. Additionally, the context-sensitive half-time does not consider plasma-effect site disequilibrium and thus may be misleading for drugs with very slow plasma-effect site equilibration. A related but more clinically relevant representation is the context-sensitive effect site decrement time, as shown

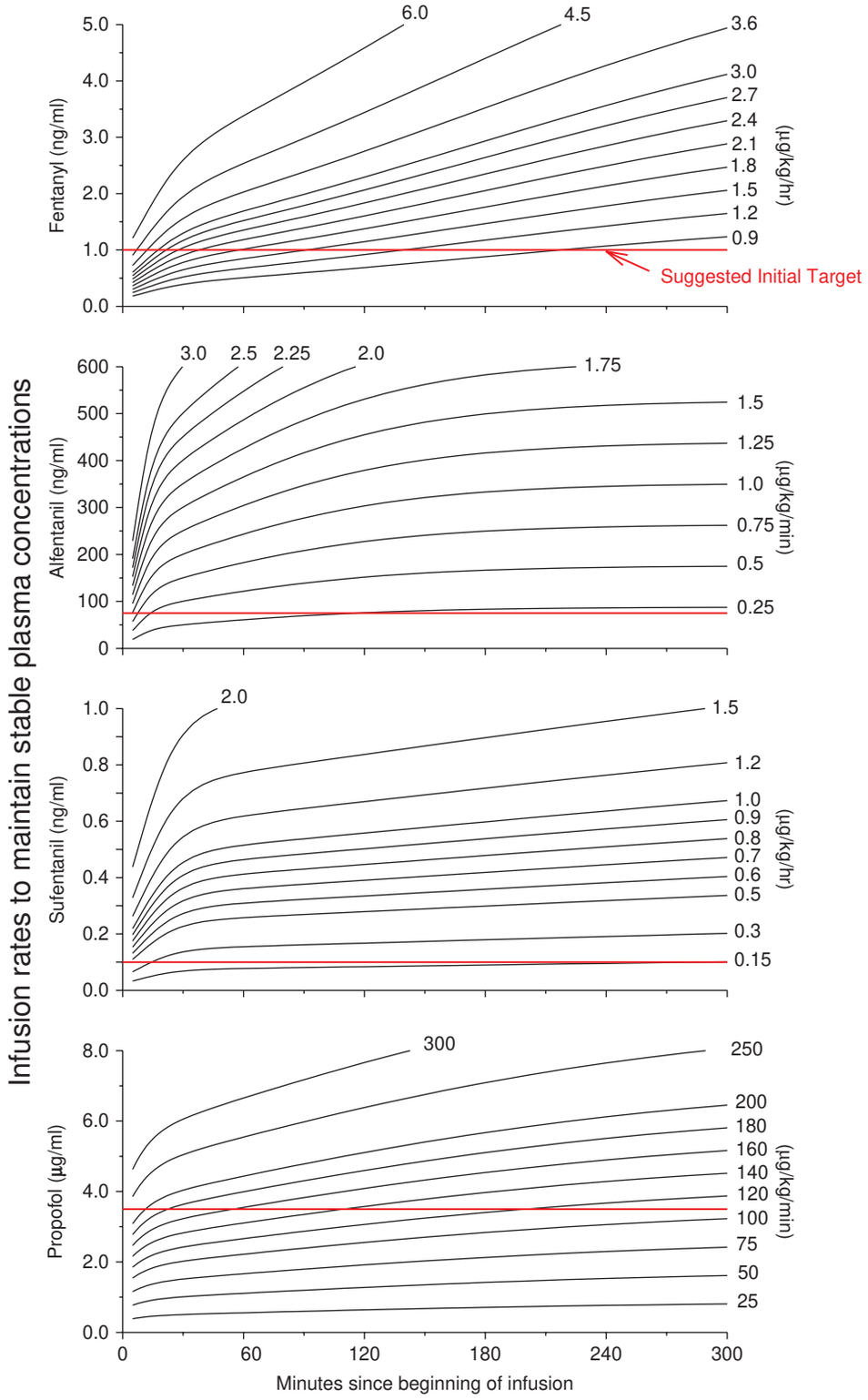

FIGURE 2.27 Dosing nomogram, showing the infusion rates (numbers on the perimeter) required to maintain stable concentrations of fentanyl (1.0 µg/mL), alfentanil (75 µg/mL), sufentanil (0.1 µg/mL), and propofol (3.5 ng/mL).

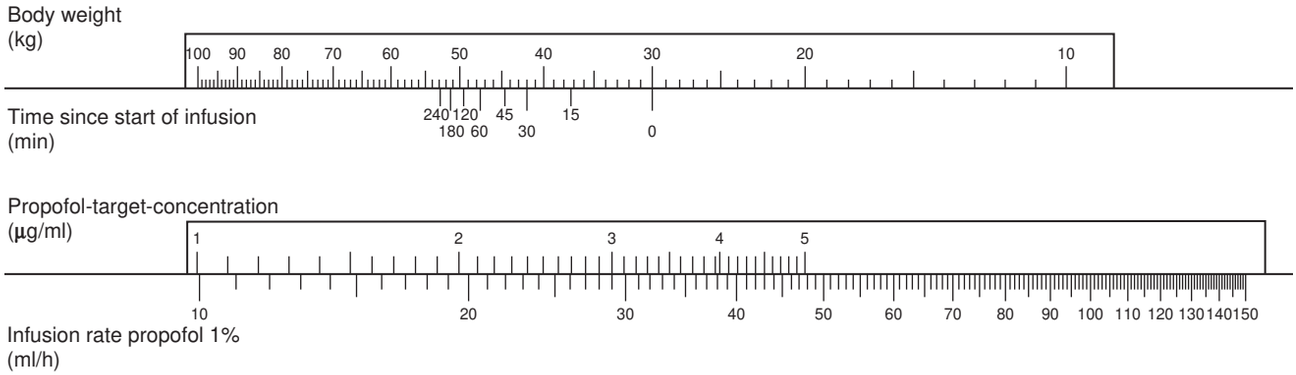

FIGURE 2.28 Propofol slide ruler to calculate maintenance infusion rate, based on the patient's weight and the time since the start of the infusion, as proposed by Bruhn and colleagues. To make use of the calculator, make a photocopy and cut in to top (body weight), middle (time since start of infusion/propofol target concentration), and bottom (infusion rate propofol 1%) sections—calculation requires sliding the middle piece in relationship to the top and bottom segments, which are fixed. *Adapted with permission from Bruhn J, Bouillon TW, Röpcke H, et al. A manual slide rule for target-controlled infusion of propofol: development and evaluation.* Anesth Analg. *2003;96(1):142-147. Copyright © 2003 International Anesthesia Research Society.*

in **Figure 2.31**.[22] For example, the upper black line in **Figure 2.31** is the context-sensitive 20% effect site decrement time for fentanyl, that is, the time required for fentanyl effect site concentrations to fall by 20%, based on the duration of a fentanyl infusion. Context-sensitive half-time and effect site decrement times are more useful than elimination half-time in characterizing the clinical responses to drugs.[23]

Pharmacodynamics

Pharmacodynamics is the study of the intrinsic sensitivity or responsiveness of the body to a drug and the mechanisms by which these effects occur. Thus, pharmacodynamics may be viewed as what the drug does to the body. Structure-activity relationships link the actions of drugs to their chemical structure and facilitate the design of drugs with more desirable pharmacologic properties. The intrinsic sensitivity is determined by measuring plasma concentrations of a drug required to evoke specific pharmacologic responses. The intrinsic sensitivity to drugs varies among patients and within patients over time with changes in physiology such as aging, disease, and injury. As a result, at similar plasma concentrations of a drug, some patients show a therapeutic response, others show no response, and others develop toxicity.

The basic principles of receptor theory were covered in the first section of this chapter. This section focuses on methods of evaluating clinical drug effects such as dose-response curves, efficacy, potency, the median effective dose (ED_{50}), the median lethal dose (LD_{50}), and the therapeutic index.

Concentration Versus Response Relationships

The most fundamental relationship in pharmacology is the concentration (or dose) versus response curve, shown in **Figure 2.32**. This is the time-independent relationship between exposure to the drug (*x*-axis) and the measured effect (*y*-axis). The exposure can be the concentration, the dose, the area under the concentration versus time curve, or any other measure of drug exposure that is clinically meaningful. The measured effect can be an absolute response (eg, twitch height), a normalized response (eg, percentage of twitch depression), a population response (eg, fraction of subjects moving at incision), or any physiologic response (chloride current). The standard equation for this relationship is the "Hill" equation, sometimes called the **sigmoid-E_{max} relationship**:

$$Effect = E_0 + (E_{max} - E_0)\frac{C^{\gamma}}{{C_{50}}^{\gamma} + C^{\gamma}} \qquad \text{Equation 2.32}$$

In this equation, E_0 is the baseline effect in the absence of drug, and E_{max} is the maximum possible drug effect. C is typically concentration or dose, although other measures of drug exposure (eg, dose, peak concentration, area under the concentration vs time curve) can be used. C_{50} is the concentration associated with 50% of peak drug effect and is a measure of drug potency. The term $\frac{C^{\gamma}}{{C_{50}}^{\gamma} + C^{\gamma}}$ is a modification of the saturation equation $\frac{C}{C_{50} + C}$ presented in the prior section. Previously, it did not have an exponent. However, when used in pharmacodynamic models, the exponent γ, also called the **Hill coefficient**, appears.

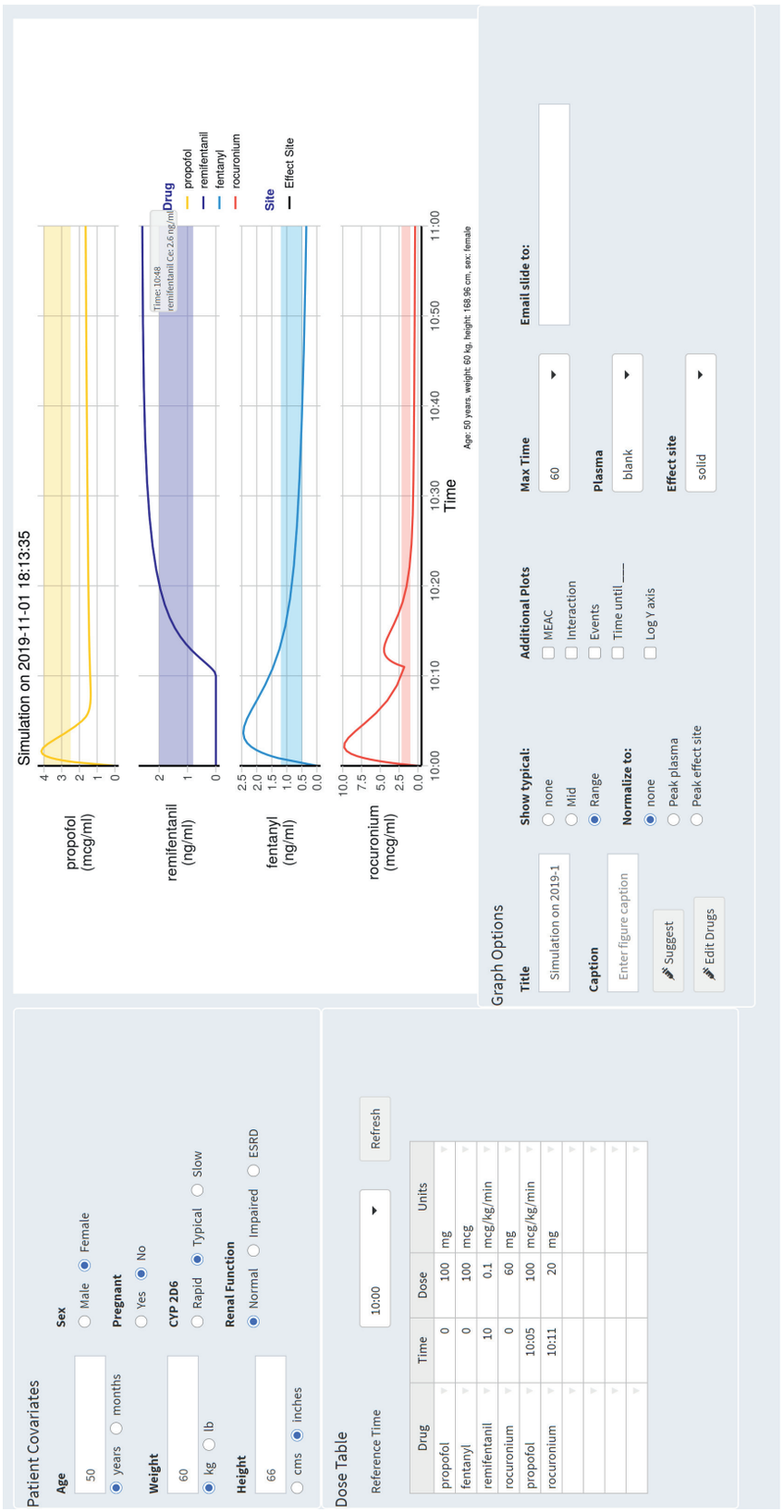

FIGURE 2.29 stanpumpR (https://stanpumpR.io) is a pharmacokinetic (PK)/pharmacodynamic (PD) simulation program for anesthesia. The program implements published PK/PD models for alfentanil, dexmedetomidine, etomidate, fentanyl, hydromorphone, ketamine, lidocaine, methadone, midazolam, morphine, naloxone, oxycodone, oxytocin, pethidine, propofol, remifentanil, rocuronium, and sufentanil.