Chapter 1
Pharmacokinetics and Pharmacodynamics of Anesthetics

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Contents

Introduction

Our understanding of the numerous barriers and cascades that govern drug kinetic and dynamic behavior of clinical response(s) continues to grow in complexity as the inextricable link between pharmacokinetics (PK) and pharmacodynamics (PD) becomes increasingly apparent. Colloquially, PK is described as "what the body

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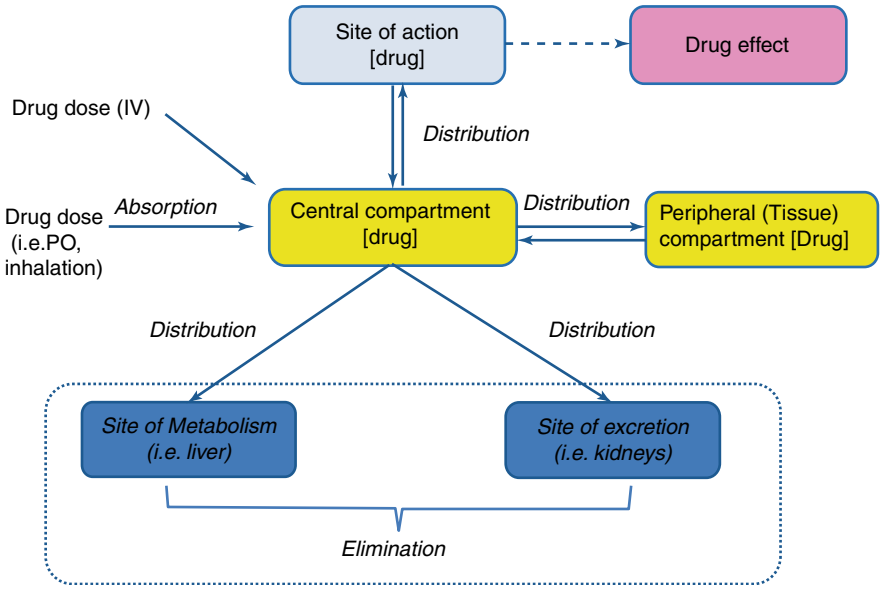

Fig. 1.1 The relationship among the pharmacokinetic processes of absorption, distribution, metabolism, and excretion with the central, peripheral, and site of action compartments

does to the drug" and PD is described as "what the drug does to the body." The key element to those phrases is "what is changing?": In PK, it is the drug concentration; in PD, it is the "body" or the physiological and pharmacological systems and cascades that convert drug concentrations into responses. More precisely, PK encompasses all of the kinetic processes from the drug released from its dosage form (e.g., i.v., p.o., i.m., extended release) to the delivery of the drug to its site or tissue responsible for initiating the translation of drug concentration/exposure into a response (shown as the solid arrows in Fig. 1.1). And where PK ends, PD begins by explaining the time-course translation/transduction of drug concentration into a "biological signal" or "messenger" (e.g., intracellular Ca^{2+} concentration) that ultimately leads to the end desired response or effect (e.g., increased pain relief) (shown as the broken line arrow in Fig. 1.1).

Upon closer examination, PK includes even the kinetics of drug released from the dosage form prior to absorption—such as drug being transferred from syringe to systemic circulation (i.e., i.v. bolus) or the complex disintegration, solvation, and dissolution of drug released by an advanced drug delivery system (ADDS) into the gastrointestinal (GI) tract milieu for permeation (passive diffusion and active or facilitated transport) across the GI endothelial barrier to the systemic circulation. Additional terms associated with the PK of a drug include absorption, distribution, excretion, and metabolism (see Fig. 1.1). A general term describing the sum of drug excretion and metabolism is elimination. An even more general PK term, disposition, describes the kinetic time course of drug distribution, excretion, and metabolism. The input function of drug (e.g., i.v. bolus, p.o.) combined with the disposition

is the drug PK. *Most importantly*, *clinicians can generally only control the input function of drugs*, *while the* "*body*" *or physiology controls the disposition*.

An essential hypothesis of PK is that there is a quantitative relationship between drug concentration and pharmacological effect [1]. Clinical PK incorporates the fundamentals of PK to dose calculations, infusion rates, predictions of drug concentrations, dosing intervals, and time to eliminate the drug from the body. The primary objective of clinical PK is to maximize efficacy while minimizing toxicities, through a process called therapeutic drug monitoring (TDM). A complete TDM protocol entails monitoring-defined therapeutic endpoints (which include plasma drug concentration if appropriate) and adverse reactions. Adjustments of doses can be guided by TDM to provide individualized regimens. Clinical PK can be affected by numerous covariates, such as age, genetics, gender, race, comorbid disease states, and concomitant medications, resulting in drug interactions. These factors should be considered into the dosing regimen for each patient.

Absorption

The absorption of a drug is largely dependent on the route of delivery. Drugs can be administered by depot type of routes: oral, inhaled, subcutaneous, intramuscular, sublingual, rectal, intraocular, intranasal, vaginal, and transdermal. Although intravenous and intra-arterial technically do have an aspect of absorption (i.e., release of drug from a syringe or i.v./i.a. bag), these routes deliver drug directly into the systemic circulation and are a special subset of PK input (i.e., instantaneous absorption processes having a bioavailability of 1.0). The physicochemical properties (i.e., solubility, pKa, ionization, polarity, molecular weight, partition coefficient) play a critical role in the absorption of drugs. The route of delivery impacts the rate of absorption as well as the extent of absorption. Bioavailability is defined as the rate and extent of drug absorption or the percentage or fraction of the parent compound that reaches systemic (plasma) circulation. The bioavailability of the same drug in the same patient may be different depending on the route of administration. Drug references frequently provide the bioavailabilities of drugs and are typically denoted as F. The extent of absorption, but not the rate, can be described by the parameter area under the curve (AUC). In an acute setting, the rate of absorption, generally k_a, tends to be more important, whereas the extent of absorption tends to be more important in chronic use medications. The salt factor (S) is the fraction of a dose that is the active base form of the drug and pragmatically can be viewed as an attenuation of F (e.g., "effective dose" = F*S*dose). Probably, the most frequently used routes of administration of drugs in anesthesiology are oral, intravenous/intra-arterial, inhaled, and local (epidural, interscalene, etc.).

The absolute bioavailability, F, is determined by comparing the availability for any given extravascular (e.v.) route of administration measured against an i.v. point of reference of availability of the drug administered intravenously (Eq. 1.1):

Table 1.1 Partition coefficients of commonly used inhaled anesthetics

	Isoflurane	Sevoflurane	Desflurane	Nitrous oxide
Blood/gas partition coefficient	1.46	0.69	0.42	0.47
Brain/blood partition coefficient	1.6	1.70	1.29	1.1
Muscle/blood partition coefficient	2.9	3.13	2.02	1.2
Fat/blood partition coefficient	45	47.5	27.2	2.3

$$F = \frac{\mathrm{AUC}_{\mathrm{e.v.}} / \mathrm{Dose}_{\mathrm{e.v.}}}{\mathrm{AUC}_{\mathrm{i.v}} / \mathrm{Dose}_{\mathrm{i.v.}}} \tag{1.1}$$

Since anesthetics and pain management medications can be delivered via numerous routes of administration, the value of F is important in determining the "effective dose" for these e.v. drugs. The physicochemical properties, previously mentioned, of the drug affect the drug's ability to partition from lipid to aqueous phases, and therefore, *F*. Food, drug interactions, and gastrointestinal (GI) motility can all affect drug solubility and absorption. First-pass metabolism, which is pre-systemic metabolism of the drug, can occur in the GI tract and the liver prior to reaching systemic circulation. All of these factors can affect F and the route will sometimes dictate the countersalt needed, thus affecting *S*, as well.

For inhaled anesthetics, three major factors influencing absorption are solubility in the blood, alveolar blood flow, and the partial pressure gradient between alveolar gas and venous blood. The solubility of inhaled anesthetics in blood is described by blood/gas partition coefficients (Table 1.1). The inhaled anesthetics are absorbed almost completely and rapidly through the lungs. A lower blood/gas partition coefficient indicates a more rapid onset and dissipation of anesthetic action.

Volume of Distribution

The volume of distribution V_d is a PK parameter characterizing the extent of drug distribution into the tissue from the blood. The physicochemical properties of a drug, plasma protein binding, and tissue binding influence V_d. It has also been termed *apparent* volume of distribution because it does not correlate with an actual physiological volume compartment in the human body, but rather, it is the inferred volume in which the drug appears to be dissolved. It is inferred because as Eq. 1.2 shows, the clinician knows the dose given and Cp (drug plasma concentration) is measured; the V_d is inferred or calculated from the two values of dose and Cp. The lower limit for nearly all drugs is 3 L or the actual average volume of human plasma. As the apparent or inferred volume of distribution increases in size, the interpretation begins to focus on the distribution of drug into extravascular tissues. The apparent or inferred V_d can be calculated using Eq. 1.2:

$$V_d = \frac{\text{Dose}_{\text{i.v.}}}{\text{Cp}} \tag{1.2}$$

If the plasma concentration Cp of a drug is small immediately following a single-bolus dose, this generally indicates substantial drug permeation into the tissue(s), and the resultant V_d is >40–80 L, indicating extensive distribution into the tissue. In contrast, if V_d is small (close to 3 L), a large fraction of the drug is assumed to reside in the blood plasma, thus suggesting a little amount of drug has permeated into the extravascular tissue(s). While V_d provides insight as to whether the drug is residing in the blood or tissue, its value does not determine which specific tissue compartment the drug permeates into.

V_d is useful in determining the loading dose necessary to achieve a targeted Cp. The usual loading dose equation is Loading Dose = $V_d \times \text{Cp}_{\text{target}}$. For drugs that have a large V_d, a greater loading dose is necessary to achieve the targeted Cp. Drugs with a small V_d require a reduced loading dose to obtain the targeted Cp.

As shown in Table 1.1, the inhaled anesthetics have high brain/blood, muscle/blood, and fat/blood partition coefficients. In particular, most inhaled anesthetics distribute extensively into the fat tissues.

Clearance

Clearance is an independent PK parameter quantifying the rate the body is able to eliminate a drug. More specifically, clearance is the volume of blood that is completely cleared of the drug per unit time. The units are in volume/time, usually liters per hour (L/h) or milliliters per minute (mL/min). While the liver is primarily responsible for drug metabolism and the kidneys are primarily responsible for parent drug and metabolite excretion (filtration and secretion), other routes of elimination include the chemical decomposition, feces, skin, and lungs. Hepatic metabolism and elimination are components of drug clearance. Total clearance is characterized by Eq. 1.3:

$$\text{Cl}_{\text{Total}} = \text{Cl}_{\text{Hepatic}} + \text{Cl}_{\text{Renal}} + \text{Cl}_{\text{Other}} \tag{1.3}$$

Total clearance Cl_{Total} is used in most dose calculations without taking into account the specific route of elimination. Clearance is an important parameter because it controls the steady-state concentration Cp_{ss} as shown in Eq. 1.4:

$$\text{Cp}_{\text{ss}} = \frac{(S)(F)(\text{Dose}/\tau)}{\text{Cl}} \tag{1.4}$$

S is the salt factor, F is the bioavailability, and tau (τ) is the dosing interval.

Metabolism

Drug metabolism occurs primarily in the liver, though metabolism can also occur at other sites such as the gastrointestinal wall, kidneys, and blood-brain barrier. Metabolism can be characterized as phase I or phase II reactions. Phase I reactions include oxidation, epoxidation, dealkylation, and hydroxylation reactions catalyzed by the cytochrome P450 enzyme system. A majority of the cytochrome P450 enzymes reside in the microsomes of hepatocytes where it metabolizes the highest number of substrates (chemical, drugs, and pollutants) in the body. Phase II reactions are glucuronidation and sulfation processes.

Many drug interactions involve the cytochrome P450 enzyme system. Certain drugs, termed inducers, may increase the activity of specific cytochrome P450 isozymes, leading to increased metabolism of drugs which are substrates of that particular isozyme. The reduction in plasma concentration of the drug substrates may lead to decreased therapeutic effects. Other drugs are inhibitors of cytochrome P450 enzymes, decreasing the metabolism of drugs that are substrates. The increase in substrate plasma concentration may result in not only enhanced pharmacological effects but also enhanced toxicological effects. Clinicians are encouraged to consider dosing adjustments based on known drug interactions to achieve therapeutic effects while minimizing adverse reactions.

Excretion

Excretion frequently refers to the irreversible clearance of a drug typically through the kidneys. The three major physiological processes occurring in the kidneys governing renal excretion are glomerular filtration, active secretion, and reabsorption. The glomerular filtration of an adult patient may be estimated by the Cockcroft-Gault equation [3] (Eq. 1.5):

$$\mathrm{Cl_{Cr}}\left(\mathrm{mL/min}\right)=\frac{\left(140-\mathrm{age}\right)\times\mathrm{IBW}}{72\times\mathrm{SCr}}\left(\mathrm{Multiplied\,by\,0.85\,if\,female}\right) \qquad (1.5)$$

Cl_{Cr} is the creatinine clearance in mL/min, the age of the patient is in years, SCr is the serum creatinine, and IBW is the ideal body weight of the patient in kilograms (kg). For female patients, the resultant Cl_{Cr} is multiplied by 85 % to account for lower muscle mass typically exhibited by females. The Cockcroft-Gault equation utilizes serum creatinine, which is a by-product of muscle metabolism and is freely filtered by the glomerulus. Creatinine is not actively secreted nor is it reabsorbed. For drugs that are primarily eliminated via the renal route, dose adjustments may be made on the basis of creatinine clearance (Cl_{Cr}) and are provided by drug package inserts or drug information references.

Elimination Rate Constant and Half-Life

The dependent parameter K is a first-order rate constant. It is a function of V_d and Cl. K can be described as the percentage or fraction of the amount of drug that is cleared from the body per unit time. The units are typically expressed as 1/h (hr^{-1}) or 1/min (min^{-1}). As shown in Eq. 1.6, K can be viewed as a proportionality constant between V_d and Cl:

$$K = \frac{\mathrm{Cl}}{V_d} \tag{1.6}$$

A large K value indicates rapid elimination of the drug. If two drug concentrations are drawn within the same dosing interval, K can be determined using Eq. 1.7 [4]:

$$K = \frac{\mathrm{Ln}\left(\mathrm{Cp}_1 / \mathrm{Cp}_2\right)}{\Delta t} \tag{1.7}$$

Ln is natural log and Δt is the time elapsed between Cp_1 and Cp_2. The determination of K is integral to calculating half-life, $t_{1/2}$, as shown in Eq. 1.8:

$$t_{1/2} = \frac{\mathrm{Ln}(2)}{\mathrm{K}} = \frac{(V_d) * \mathrm{Ln}(2)}{\mathrm{Cl}} \tag{1.8}$$

Equation 1.8 also shows the relationship among $t_{1/2}$ and V_d and Cl. The $t_{1/2}$ is the amount of time it takes for the drug currently in the body to reduce by 50 %. The $t_{1/2}$ can also predict the amount of time it takes for a patient to achieve steady-state drug concentrations (assuming no loading dose and the same dose was administered at the same interval). For example, after one $t_{1/2}$, Cp is 50 % of the final steady-state Cp_{ss}. Under these conditions, a patient is considered to be clinically at steady state if the drug concentration is >90 % of the true steady-state level. As shown in Table 1.2, it would take approximately 3.3 half-lives for a patient to achieve 90 % of

Table 1.2 The number of half-lives and the expected percent of true steady-state concentration Cp_{ss} or percent of drug eliminated

Number of $t_{1/2}$	Percent of Cp_{ss} or percent eliminated
1	50
2	75
3	87.5
4	93.8
5	96.9
6	98.5
7	99.2

the true steady state. Conversely, it would take 3.3 half-lives for a patient to eliminate 90 % of the drug once the administration of the drug has ceased. To note, $t_{1/2}$ determines the dosing interval, but V_d and Cl determine the size of the dose.

Pharmacodynamics

The time-course conversion of drug concentration (Ce) into a pharmacological effect (response) is pharmacodynamics. The *biosensor process* is the detection of the drug's presence, Ce. Frequently, the *biosensor process* is the receptor system on the cell's surface. The white and black *biosensor process* rectangles indicate that the drug (Ce) either stimulates (white) or inhibits (black) the zero-order and first-order constants k_{in} or k_{out}, respectively. The *biosignal* is similar to the second messenger, in that it directs the end response. While the pathway in between the *biosignal* and the *response* can contain nonlinear and time-varying processes (circadian, drug-induced—such as drug tolerance), it still is the *biosignal* that is responsible for the end response. Alterations of k_{in} or k_{out} are frequently the sites for the nonlinearities or time-varying processes. This model is known as an "indirect" model and is relatively general; the most important aspect of this model is that a change in Cp is not instantaneously realized as a change in response (Fig. 1.2). Somewhere along the pathway of D, drug, diffusing out of Cp in to Ce or in the translation of D binding

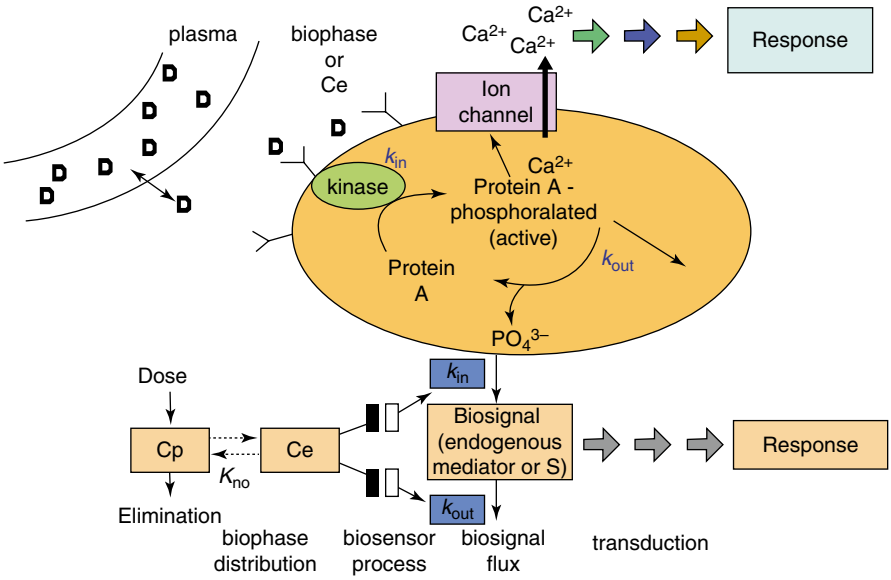

Fig. 1.2 The indirect model (*bottom*) is laid over a generic diagram of how cells (*top*) generally convert drug (*D*) into a pharmacological or physiological response (*response*). In this example, phosphorylated protein A acts as the biosignal responsible for the end response

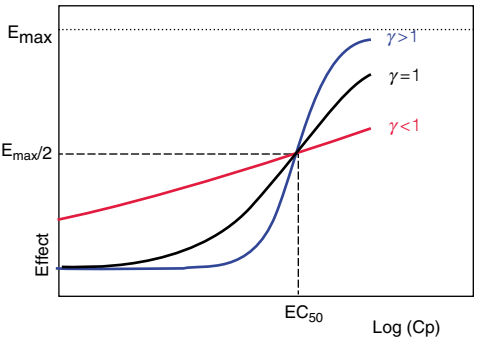

Fig. 1.3 Comparison of three different values of γ for the same E_{max} model with baseline. E_0, E_{max}, and EC_{50} are kept constant for all three plots to show the behavior of γ

to the receptors to produce the response, there is a rate-limiting step that causes the response to lag behind changes in Cp.

A subset model of the indirect model is the direct model. In the direct model, the pharmacodynamic system very rapidly converts the Ce concentration of drug to response relative to the rate at which the Ce or Cp steady state is achieved. Or in other words, there is no time lag, as in the indirect model, between changes in Cp or Ce and response. Typical direct models have the form of $E = E_0 \pm \frac{E_{max}\,Cp^{\gamma}}{EC_{50}^{\gamma} + Cp^{\gamma}}$, where E_0 is the endogenous baseline (i.e., value of E in the absence of drug), E_{max} is the maximal effect achievable, EC_{50} is the concentration of drug that produces ½ of the E_{max} response, and γ is the Hill coefficient. When $\gamma > 1$, the PD is said to have positive cooperativity; when $\gamma < 1$, the PD has negative cooperativity; and when $\gamma = 1$, the PD has no cooperativity (see Fig. 1.3 for a comparison of γ).

In the more commonly used model, notice that as "dose" or the x-axis changes, the effect or response instantaneously changes. Another way to view this relationship between "dose" and "response" is to assume that the "dose" or "log (Cp)" has reached steady state or equilibrium before the effect has been measured. The direct model can still be used to simulate drug tolerance by either attenuating E_{max} or increasing EC_{50} as a function of Cp or Ce. The utility of this model cannot be overstated as it has provided many researchers and clinicians with useful pharmacodynamic insights.

Therapeutic Range and Therapeutic Monitoring

Most drugs have established therapeutic ranges. Therapeutic ranges are typically expressed as a range of drug plasma concentrations that achieve an optimal effect while minimizing adverse reactions. However, drugs that require constant monitoring of drug concentrations are ones that have narrow therapeutic ranges, a low threshold for serious adverse reactions, or must reach a minimum plasma concentration to achieve an effect.

Table 1.3 Minimal alveolar concentration of commonly used inhaled anesthetics

	Isoflurane	Sevoflurane	Desflurane	Nitrous oxide
MAC in O_2 in adults	1.15	1.71	6.0	104

In anesthesiology, the minimum alveolar concentration (MAC; Table 1.3) of inhaled anesthetics is used as the target to achieve the necessary therapeutic effect. MAC is the amount of inhaled anesthetic required to inhibit physical movement in response to a noxious stimuli in 50 % of patients [5]. MAC values can also be used to compare the relative potencies between two inhaled anesthetic agents.

The continuous monitoring of plasma concentrations of intravenous anesthetics is not performed due to practicality. The half-lives and durations of action of most intravenous anesthetics are relatively short. It may take several hours for the laboratory to determine anesthetic concentrations. Therefore, anesthetic concentrations do not provide rapid feedback for clinicians to make necessary adjustments to doses during the course of surgery or medical intervention. Thus, monitoring of intravenous anesthetics is reliant on the signs and symptoms of anesthesia for the attainment of therapeutic efficacy and respiratory depression and blood pressure for toxicology.

Table 1.4 summarizes the pharmacokinetic (distribution, metabolism, and renal excretion) and pharmacodynamic properties (onset of action and duration of action) of various anesthetic agents.

Drug Tables (Tables 1.5 and 1.6)

The mechanism of action, indications, contraindications, cautions, pregnancy category, clinical pearls, dosing options, drug interactions, and side effects of commonly-used anesthetic agents are presented in Table 1.5 Lidocaine, with its numerous routes of delivery and dosing options, are presented in Table 1.6.

Table 1.4 Pharmacokinetic and pharmacodynamic properties of anesthetic agents

	Distribution	Metabolism	Renal excretion	Onset of action	Duration of action
Isoflurane	Distributes quickly and extensively to the brain, heart, liver, kidneys, and lungs [6] Does not distribute well into adipose tissue	0.17 % of isoflurane is metabolized by the liver	Rapidly eliminated by lungs	7–10 min [7]	
Sevoflurane	Distributes well to the brain [8] Does not distribute well into adipose tissue	3–5 % hepatic via CYP2E1	Rapidly eliminated by lungs Exhaled gases, up to 3.5 %, excreted renally as inorganic fluoride	1.2 min [9]	4–14 min
Desflurane	Not available	0.02 % [10]	Rapidly eliminated by lungs <0.02 % as metabolite through urine	Single agent, 5–16 min [11] With oxygen, 2–3 min [11] With NO_2, 1.5–2 min [11]	
Nitrous oxide	0.5 blood/gas partition coefficient [12]	<0.004 %	Rapidly eliminated by lungs	2–5 min	
Xenon		Minimum [115]			
Thiopental	Distributes well into adipose tissue; 6–12 times blood	Primarily to inactive metabolites, but pentobarbital (active) is also formed		30–60 s	10–30 min [65]

(continued)

Table 1.4 (continued)

	Distribution	Metabolism	Renal excretion	Onset of action	Duration of action
Methohexital	Distributes quickly into brain, within 30 s; redistribution occurs within 30 min into less vascular areas	Extensive [13]	Less than 1 % excreted unchanged in urine	2–45 s [14]	4–8 min after doses of 45–125 mg [15]
	Does not distribute well into adipose tissue				15–30 min after higher doses of 240–310 mg [15]
Propofol	Rapid distribution: 1–8 min [16]	Rapid and extensive by cytochrome P4502B6 [17]	<0.3 % excreted unchanged; 88 % excreted as metabolite	30 s (10–50 s); onset is infusion rate related [18]	3–10 min
Etomidate	Rapid distribution [116]		2 % excreted unchanged in urine	30–60 s	3–5 min
Ketamine	Rapid distribution into highly perfused tissues [19]	Extensive by cytochrome P450	4 % excreted unchanged in urine	IV: 30 s IM: 3–4 min	IV: 5–10 min IM: 12–25 min
Chloroprocaine	Rapid distribution into highly perfused tissues	Plasma cholinesterases	Undergoes renal excretion	6–12 min	1 h
Procaine	Not available	Rapid by cholinesterase	2 % excreted unchanged in urine		1 h

Lidocaine	1.5 L/kg	90 % by cytochrome P450 1A2 [20]; two active metabolites: monoethylglycinexylidide (MEGX) and glycinexylidide (GX)	10 % excreted unchanged in urine	Dental: <2 min Local: 2–4 min	2 h
Prilocaine	0.7–4.4 L/kg	Undergoes hepatic metabolism [21]	Undergoes renal excretion [21]	2–3 min	1 h
Bupivacaine	2.5 L/kg	Extensive hepatic metabolism	6 % excreted unchanged in urine [22]	5–10 min [23]	1.5–8 h
Ropivacaine	36–60 L	Extensive hepatic metabolism by cytochrome P450 1A2	1 % excreted unchanged in urine	Brachial: 15–30 min Cesarean: 2.5–25 min Epidural: 6–8 min [24]	1.5–8 h
Mepivacaine	Extensively distributes into liver, lung, heart, and brain	Extensive hepatic metabolism by hydroxylation and N-demethylation	5–10 % excreted unchanged in urine	Epidural: 5–15 min Nerve block: 10–20 min	2 h
Articaine	1–2 L/kg	Primarily hepatic by carboxylesterase	2–5 % excreted unchanged in urine [25]	1–6 min	1 h
Tetracaine	Not available	Extensive by plasma esterases		Topical: 30 s Topical, liposomal: 30 min Spinal: 3–5 min	Topical: 2.5 h Topical, liposomal: 2.5 h Spinal: 2–3 h
Levobupivacaine	54–66.9 L [26]	Extensive by hepatic metabolism	Undetectable unchanged drug in urine	Epidural: 8–20 min	Epidural: 7.5–10.5 h
Etidocaine	134 L [27]	Extensive by hepatic metabolism	<10 % excreted unchanged in urine	Infiltration, nerve block, retrobulbar: 2–5 min [28] Epidural: 15–30 min [29]	Infiltration, nerve block: 4–10 h Epidural: 6–10 h

Table 1.5 Drug information of anesthetic agents

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Isoflurane (Florane™, Terrell™) [7, 30]	*Contraindications*: (1) known sensitivity to isoflurane, (2) patients at risk for malignant hyperthermia	Low blood/gas partition coefficient, producing rapid induction and recovery from anesthesia	Induction: 1.5–3 % with O_2 or O_2/nitrous oxide mix; anesthesia obtained within 7–10 min	*Drug interactions* [31]:
MOA: modulation of $GABA_A$ receptors, potentiating inhibitory synaptic transmission [32]	*Caution*: (1) hyperkalemia, (2) malignant hyperthermia	Pungent odor may limit rate of induction	Maintenance: 1–2.5 % with NO; additional 0.5–1 % with O_2 only	clarithromycin, class I and III antiarrhythmics, dolasetron, droperidol, fluconazole, fluoxetine, haloperidol, hydromorphone, ondansetron, oxycodone, quetiapine, risperidone, St. John's wort, telithromycin, tricyclic antidepressants, ziprasidone

Indications: induction and maintenance of anesthesia

Pregnancy category: C

Breast feeding: infant risk has not been ruled out

Good cardiovascular stability; not proarrhythmic

Lower incidence of hepatotoxicity [34]

MAC [7, 33]:

Age	100% O_2	70% NO_2
26±4	1.28	0.56
44±7	1.15	0.50
64±5	1.05	0.37

Concurrent use with neuromuscular-blocking agents (atracurium, cisatracurium, pancuronium) may result in prolongation of neuromuscular-blocking effects

Side effects:

Common: nausea, vomiting, hypotension, cough, excessive salivation, headache

Serious: bradycardia, cardiac arrest, myocardial infarction, hyperkalemia, malignant hyperthermia, decreased liver function, hepatic necrosis, liver failure, seizure, myoglobinuria, renal failure, respiratory depression [7]

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Sevoflurane (Ultane™, Sojourn™) [35, 36]	*Contraindication*: patients at risk for malignant hyperthermia	Low blood/gas partition coefficient, producing rapid induction and recovery from anesthesia	0.5–3 % concentration with or without concomitant use of nitrous oxide [37]	*Drug interactions* [38]: hydromorphone, oxycodone, St. John's wort
MOA: modulation of $GABA_A$ receptors, potentiating inhibitory synaptic transmission [39]	*Caution*: (1) hyperkalemia, (2) malignant hyperthermia	FDA limits its use to 2 MAC hours (1 MAC for 2 h or 2 MACs for 1 h) due to its by-product, compound A, that has caused renal injury in rat models [40]		*Side effects*:
Indication: general anesthesia	*Pregnancy category: B*	Not as pungent as isoflurane or desflurane		*Common*: bradycardia, hypotension, nausea, vomiting, somnolence, agitation, cough, interrupted breathing, shivering
	Breast feeding: infant risk has not been ruled out	Good cardiovascular stability		*Serious*: AV block, hemorrhage, QT prolongation, torsades de pointes, hyperkalemia, malignant hyperthermia, hepatic necrosis, liver failure, hypersensitivity, seizure, laryngeal spasm, respiratory depression

Age (yrs)	With O_2	With 65% NO_2/35% O_2
0-1mo	3.3%	–
1-6mos	3.0%	–
6mos-3yrs	2.8%	2.0%*
3-12	2.5%	–
25	2.6%	1.4%
40	2.1%	1.1%
60	1.7%	0.9%
80	1.4%	0.7%

*60/40% used

Desflurane (Suprane™) [41, 42]

Contraindication: patients at risk for malignant hyperthermia

Low potency

Induction: initiate with 3 % in O_2 or nitrous oxide/O_2 and increase by 0.5–1 % every 2–3 breaths or as tolerated (up to 11 %) until loss of consciousness [41]

MOA: modulation of $GABA_A$ receptors, potentiating inhibitory synaptic transmission [43]

Pregnancy category: B

High cost

Concentrations exceeding 12 % have been reported to be safe [44]

Drug interactions [45]: cisatracurium, hydromorphone, oxycodone, St. John's wort

Indication: general anesthesia

Breast feeding: infant risk has not been ruled out

Low blood/tissue solubility

Maintenance: 2.5–8.5 % with or without concomitant NO_2

MAC [46, 47]

Age	With O_2	With 60% NO_2
18-30	7.25%	4%
31-65	6%	2.8%

Side effects:

Common: hypotension, salivation, nausea, vomiting, cough [48]

Serious: bradycardia, cardiac arrest, heart failure, hypertension, malignant hypertension, shock, sinus arrhythmia, torsades de pointes, hyperkalemia, pancreatitis, hepatic necrosis, liver failure, rhabdomyolysis, nephrotoxicity, interrupted breath, laryngeal spasm

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Nitrous oxide [49, 50]	*Contraindication*: patients receiving nitrous oxide for longer than 24 h	Used primarily in combination with other anesthetics to reduce their dose and therefore side effects; 70 % NO_2 reduces MAC of other anesthetics by 60 % (GG)	Induction: NO_2 with at least 25–30 % O_2; premedicate with narcotic analgesics or barbiturates	
MOA: noncompetitive antagonist activity at the NMDA receptor, potentiating inhibitory synaptic transmission (double-check if it is inhibitory) [51, 52]	*Caution*: patients at risk for gas embolism, pneumothorax, or ileus	Must be administered with at least 25–30 % O_2	Maintenance: 30–70 % NO_2 with O_2	*Drug interactions*: no known significant drug interactions
In addition to anesthesia, also has analgesia and anxiolytic properties	*Pregnancy category*: not established	Less effective in areas of high altitude		*Side effects*: *frequency not defined* [53]: arrhythmias, hypotension, pulmonary hypertension, hypothermia, malignant hyperthermia, abdominal distension, nausea, vomiting, anemia, vitamin B_{12} deficiency, megaloblastic erythropoiesis, methemoglobinemia, myelosuppression, pancytopenia, increased liver enzymes, jaundice, neuropathy, increased intracranial pressure, seizure, spastic paraparesis, spinal cord disease, abnormal vision, psychotic disorder, increased sputum production
Indications: (1) general anesthesia (2) relief of severe pain	*Breast feeding*: infant risk has not been ruled out	Analgesia is produced at concentrations as low as 20 % (GG)		

Xenon	*Contraindication*: hypersensitivity to xenon	Does not potentiate duration of neuromuscular-blocking agents [54]	*Drug interactions* [55]: no known drug interactions
MOA: noncompetitive antagonist activity at the NMDA/glutamate receptor, potentiating inhibitory synaptic transmission [51]	*Caution*: patients at risk for gas embolism, pneumothorax, or ileus [56]	Production costs are high [57]	*Side effects*:
Indication: general anesthesia	*Pregnancy category*: not teratogenic *Breast feeding*: infant risk has not been ruled out	Not detrimental to environment [58] Does not affect renal, hepatic, coagulation, platelet, or immune system function [58, 59] Does not induce malignant hyperthermia [62] Contains analgesic properties [63] More effective than nitrous oxide on cardiovascular function [64]	*Common*: nausea and vomiting (substantial) *Serious*: increased pulmonary resistance [60, 61]

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Intravenous anesthetics				
Thiopental (Pentothal™) [65, 66]	*Contraindications*: acute intermittent porphyria and variegate porphyria	Duration is very short, therefore not recommended in surgical procedures lasting longer than 15 min	Slow induction: 50–75 mg slow IV, single dose at 20–40 s intervals [65]	*Drug interactions* [67]: benzodiazepines, carisoprodol, metaxalone, methocarbamol, opioid analgesics, quetiapine
MOA: $GABA_A$ receptor agonist, opening Cl channels and causing depolarization, resulting in increased inhibitory synaptic transmission [68]	*Caution*: (1) severe cardiovascular shock, (2) hypotension or shock, (3) conditions in which hypnotic effect may be prolonged or potentiated, (4) status asthmaticus, (5) endocrine insufficiency, (6) increased intracranial pressure, (7) ophthalmoplegia, (8) respiratory impairment or obstruction		Rapid induction: 210–280 mg (3–4 mg/kg) IV divided in 2–4 doses	*Side effects*:
Indications: (1) general anesthesia, (2) regional anesthesia; adjunct	Pregnancy category: C Breast feeding: compatible with breast feeding		Maintenance: 25–50 mg IV repeat PRN or continuous IV of 0.2 % or 0.4 % solution Dosing in obese (BMI ≥30) (40) Loading: TBW Maintenance: IBW Renal failure (GFR <10 mL/min): 75 % of usual dose Hepatic insufficiency: no dosing adjustment needed [70]	*Common*: injection site reaction *Serious*: myocardial infarction, hemolytic anemia, anaphylaxis, radial neuropathy, apnea, laryngeal spasm, respiratory depression

Methohexital (Brevital™) [71, 72]	*Contraindication*: latent porphyria	Induction: 50–120 mg (or 1–1.5 mg/kg) in 1 % solution administered at a rate of 1 mL over 5 s [73]	*Drug interactions* [74]: benzodiazepines, carisoprodol, metaxalone, methocarbamol, opioid analgesics, quetiapine
MOA: $GABA_A$ receptor agonist, opening Cl channels and causing depolarization, resulting in increased inhibitory synaptic transmission	*Caution*: (1) anemia, (2) cardiovascular disease, (3) hepatic impairment, (4) obesity, (5) pulmonary disease, (6) renal impairment, (7) seizure disorder	Maintenance: (1) 20–40 mg in 1 % solution administered every 4–7 min, PRN, or (2) 3 mL continuous drip of 0.2 % solution/min (1 drop/s); for longer surgical procedures, gradually reduce rate of administration	*Side effects*:
Indications: (1) general anesthesia prior to other anesthetic agents; (2) adjunct to inhaled anesthetic agents; (3) adjunct with other parenteral agents, typically narcotic analgesics, to supplement less potent inhaled anesthetics; (4) for short procedures and inducing hypnotic state	*Pregnancy category*: C *Breast feeding*: compatible with breast feeding BBW: should only be administered in hospitals or ambulatory care settings with continuous monitoring of respiratory function; resuscitative drugs, age- and size-appropriate intubation equipment, and trained personnel experienced in handling their use should be readily available	Procedural sedation (unlabeled dose): I.V.: 0.75–1 mg/kg; can redose 0.5 mg/kg every 2–5 min as needed [75]	*Common*: hypotension, injection site pain, spasmodic movement, cough, hiccoughs, laryngeal spasm *Serious*: cardiac arrest, shock, thrombophlebitis, anaphylaxis, seizure, cardiorespiratory arrest, respiratory depression

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Propofol (Diprivan™) [76, 77]	*Contraindications*: (1) allergies to eggs, egg products, soybeans, or soy products (Abraxis brand), (2) allergies to soy or peanut (Fresenius Propoven)	Propofol should be administered within 4 h of its removal from sterile packaging due to risk of bacterial growth	*Healthy adults <55* years [76] Induction: 50 mg IV every 10 s until onset (2–2.5 mg/kg); dose adjust according to age and surgery type	*Drug interactions* [78]: bupivacaine, hydromorphone, lidocaine, meclizine, oxycodone, St. John's wort, zolpidem
MOA: $GABA_A$ receptor agonist, opening Cl channels and causing depolarization, resulting in increased inhibitory synaptic transmission [79]	*Caution*: (1) elderly, debilitated, or ASA III/IV patients, (2) seizure history	Patients may still recover rapidly after long duration of use	Maintenance: 100–200 mcg/kg/min IV (6–12 mg/kg/h); dose adjust according to age and surgery type; may administer 20–50 mg IV PRN	*Side effects*:

Indications: (1) general anesthesia, (2) monitored anesthesia care sedation, (3) sedation for mechanically ventilated patient in ICU	*Pregnancy category*: B *Breast feeding*: infant risk has not been ruled out	Less nausea and vomiting than other anesthetic agents (Micromedex) Short half-life allows for flexibility in controlling sedation depth	*Pediatric* Induction (3–16 years): 2.5–3.5 mg/kg IV over 20–30 s Maintenance (2 months–16 years): 125–300 mcg/kg/min IV (7.5–18 mg/kg/h) *Geriatric* Induction: 20 mg IV every 10 s (1–1.5 mg/kg) Maintenance: 50–100 mcg/kg/min (3–6 mg/kg/h) *Debilitated, ASA-PS III–IV patients* Induction: 20 mg IV every 10 s until onset (1–1.5 mg/kg) Maintenance: 50–100 mcg/kg/min (3–6 mg/kg/h) *Cardiac patients* Induction: 20 mg IV every 10 s until onset (0.5–1.5 mg/kg) Maintenance: (1) if propofol is the primary agent, 100–150 mcg/kg/min IV with opioid as adjuvant, or (2) if opioid is the primary agent, propofol 50–100 mcg/kg/min *Neurosurgical patients* Induction: 20 mg IV every 10 s (1–2 mg/kg) Maintenance: 100–200 mcg/kg/min (6–12 mc/kg/h) IV	*Common*: injection site pain, nausea, vomiting, involuntary movement *Serious*: bradycardia, heart failure, hypertension, pancreatitis, anaphylaxis, seizure, acute renal failure, priapism, apnea, respiratory acidosis

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Etomidate (Amidate™) [58, 80, 81]	*Contraindication*: hypersensitivity to etomidate	Rapid recovery with wide therapeutic window	Induction (>10 years): 0.3 mg/kg (0.2–0.6 mg/kg) injected over 30–60 s [52]	*Drug interactions* [82]: St. John's wort
MOA: modulation of $GABA_A$ receptors, potentiating inhibitory synaptic transmission (6281035)	*Caution*: (1) elderly, especially with hypertension, (2) renal impairment	Minimal effects on cardiovascular and respiratory function [83]	Maintenance, adjunct: 0.01–0.02 mg/kg/min IV; dosage must be individualized	*Common*: injection site pain, nausea, vomiting
Indications: (1) general anesthesia, (2) adjunct to subpotent anesthetic agents during maintenance of anesthesia of short procedures	*Pregnancy category*: C *Breast feeding*: infant risk has not been ruled out	Does not cause histamine release [84]	Smaller increments may be administered as adjunct to subpotent anesthetic agents such as nitrous oxide for short procedures	*Serious*: hypotension, myoclonus
Ketamine (Ketalar™) [85, 86]	*Contraindication*: in patients in whom a significant elevation of blood pressure would constitute a serious hazard	Useful in pediatric and uncontrollable patients	Induction: (1) 1–4.5 mg/kg infused over 60 s, (2) 1–2 mg/kg/IV infused at 0.5 mg/kg/min, (3) 6.5–13 mg/kg IM	*Drug interactions* [86]: hydromorphone, oxycodone, St. John's wort, tramadol
MOA: noncompetitive NMDA receptor antagonist, blocking glutamate binding [87]	*Caution*: (1) alcohol intoxication or history of alcohol abuse	Has anesthetic, analgesic, and sedative properties	Additionally, diazepam 2–5 mg administered in separate syringe over 60 s can be used (<15 mg total) [88]	*Side effects*:

Indications: (1) general anesthesia, (2) adjunct to subpotent anesthetic agents during maintenance of anesthesia of short procedures	*Pregnancy category*: A	Diazepam frequently administered as adjunct to prevent psychological manifestations (dreamlike observations, emergence delirium)	Maintenance: increments of 50–100 % of induction dose may be repeated PRN	*Common*: hypertension, tachycardia, psychiatric sign or symptom upon emergence from anesthesia
	Breast feeding: compatible with breast feeding by WHO; infant risk has not been ruled out by Micromedex	Larger doses will require longer recovery times		*Serious*: bradycardia, arrhythmias, hypotension, anaphylaxis, apnea, laryngeal spasm, pulmonary edema, respiratory depression
Local anesthetics				
Chloroprocaine (Nesacaine™) [89, 90]	*Contraindication*: hypersensitivity to chloroprocaine	Effective in labor and delivery due to rapid onset of action and low systemic toxicity	*Procedure* [89] Mandibular: 2–3 mL of 2 % solution (40–60 mg total)	*Drug interactions* [90]: St. John's wort

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: neurological disease, spinal deformities, septicemia, severe hypertension	Not recommended for spinal administration	Infraorbital: 0.5–1 mL of 2 % solution (10–20 mg total)	*Side effects*:
Indication: local anesthesia	*Pregnancy category*: C		Brachial plexus: 30–40 mL of 2 % solution (600–800 mg total)	*Common*: dizziness
	Breast feeding: infant risk has not been ruled out		Digital, without epinephrine: 3–4 mL of 1 % solution (30–40 mg total) Pudendal: 10 mL each side of 2 % solution (400 mg total) Paracervical 3 per each of 4 sites of 1 % solution (up to 120 mg total) *Pediatric* (*>3 years*) Infiltration: 0.5–1 % solution; max 11 mg/kg Nerve block: 1–1.5 % solution; max 11 mg/kg Max dose without epinephrine: 11 mg/kg not to exceed 800 mg total Max dose with epinephrine (1:200,000): 15 mg/kg not to exceed 1,000 mg total	*Serious*: cardiac arrest, negative cardiac inotropic effect, ventricular arrhythmia, anaphylaxis, immune hypersensitivity reaction, chondrolysis of articular cartilage, arachnoiditis, CNS depression, CNS stimulation, loss of consciousness, seizure, hypoventilation, respiratory arrest

Procaine (Novocain™) [91, 92]	*Contraindication*: hypersensitivity to procaine, drugs of a similar chemical structure, or para-aminobenzoic acid (PABA) or its derivatives	Slow onset	Local infiltration: 350–600 mg, administered as diluted solution (140–240 mL of a 0.25 % solution or 70–120 mL of a 0.5 % solution)	*Drug interactions* [92]: St. John's wort
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: (1) severe disturbances of cardiac rhythm, shock, heart block, or hypotension, (2) hepatic disease	Addition of epinephrine as adjunct may be warranted for vasoconstrictive effect	Peripheral nerve block: 0.5 % (up to 200 mL), 1 % (up to 100 mL), or 2 % (up to 50 mL)	*Side effects*:
Indication: production of local or regional analgesia and anesthesia and peripheral nerve block	*Pregnancy category*: C		Epinephrine: 0.5–1 mL of epinephrine 1:1,000 per 100 mL may be added for (1:200,000–1:100,000) during local infiltration and peripheral nerve block	*Common*: nausea, vomiting, nervousness, dizziness, blurred vision
	Breast feeding: infant risk has not been ruled out		Max dose: 1,000 mg/treatment	*Serious*: negative cardiac inotropic effect, hypotension, hypertension, bradycardia, ventricular arrhythmias, cardiac arrest, urticaria, edema, tremors, seizures, respiratory arrest

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Lidocaine (Xylocaine™) [93–96]	*Contraindications*: (1) hypersensitivity to local amide anesthetic, (2) myasthenia gravis, (3) shock, (4) cardiac conduction disease, (5) severe liver disease, (6) severe kidney disease, (7) concurrent systemic use of dronedarone, saquinavir, or dihydroergotamine		See Table 1.6.	*Drug interactions*: amiodarone, amprenavir, arbutamine, atazanavir, class I antiarrhythmics, class III antiarrhythmics, cobicistat, darunavir, delavirdine, dihydroergotamine, dronedarone, etravirine, fosamprenavir, fosphenytoin, lopinavir, metoprolol, nadolol, phenytoin, propofol, propranolol, saquinavir, succinylcholine, St. John's wort
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission [97]	*Caution*: (1) acutely ill and debilitated patients			*Side effects*:
Indication: local anesthesia	*Pregnancy category*: B *Breast feeding*: infant risk is minimal			*Common*: hypotension, nausea *Serious*: cardiac arrest, cardiac arrhythmias, methemoglobinemia, anaphylaxis

Prilocaine (Citanest™) [21, 98]	*Contraindications*: (1) hypersensitivity to prilocaine or local amide anesthetic, (2) congenital or idiopathic methemoglobinemia	No cross-sensitivity in patients allergic to procaine, tetracaine, or benzocaine	*Adults* local anesthetic dental infiltration/local anesthetic nerve block: 1–2 mL (40–80 mg) 4 % solution with or without epinephrine	*Drug interactions* [21]: class I antiarrhythmics, class III antiarrhythmics, propranolol, St. John's wort
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: (1) hepatic disease, (2) impaired cardiovascular function		Max dose calculated based on weight (8 mg/kg) up to 15 mL (600 mg) within a 2-h period	*Side effects*:
Indications: (1) local anesthetic nerve block, (2) local anesthetic dental infiltration	*Pregnancy category*: B		*Pediatrics* local anesthetic dental infiltration/local anesthetic nerve block (age up to 10 years): 1 mL (40 mg) of 4 % solution	*Common*: bradycardia, hypotension, muscle twitch, tremor, confusion, dizziness, lightheadedness, somnolence, blurred vision, diplopia, tinnitus, apprehension, euphoria, feeling nervous, abnormal sensation
	Breast feeding: infant risk has not been ruled out		Max dose calculated based on weight (6.6–8.8 mg/kg)	*Serious*: cardiac arrest, vomiting, methemoglobinemia, anaphylaxis, loss of consciousness, seizure, respiratory arrest
Bupivacaine (Marcaine HCL™, Marcaine Spinal™, Sensorcaine™, Sensorcaine-MPF™) [99, 100]	*Black box warning*: 0.75 % solution not recommended for obstetrical anesthesia	Long-acting useful in local or regional anesthesia for surgical, dental, diagnostic, and obstetrical procedures	Local: 10–30 mL intrapleural bolus of 0.25 %, 0.375 %, or 0.5 % every 4–8 h	*Drug interactions* [100]: propofol, propranolol, St. John's wort, verapamil

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Contraindications*: (1) hypersensitivity to bupivacaine or local amide anesthetic; (2) severe hemorrhage, hypotension, shock, or arrhythmias; (3) local infection at site of proposed lumbar puncture	Analgesic properties of bupivacaine may reduce postoperative analgesic requirements [101]	Local: 0.375 % bupivacaine with epinephrine at 6 mL/h after 20 mL loading dose intrapleural	*Side effects*:
Indications: (1) local anesthesia, (2) regional anesthesia, (3) dental procedure anesthesia, (4) eye procedure anesthesia	*Caution*: (1) history of chondrolysis, (2) concurrent use of monoamine oxidase inhibitors (MAOI) or antidepressants (triptyline or imipramine types), (3) less than 18 years, (4) hepatic disease, (5) impaired cardiovascular function		Regional: 6.25–18.75 mg/h epidural continuous infusion, as a 0.0625–0.125 % solution	*Common*: hypotension

Pregnancy category: C *Breast feeding*: infant risk is minimal	Dental procedure: 1.8–3.6 mL of 0.5 % solution (9–18 mg) with epinephrine; a second dose (9 mg) may be administered; max 90 mg total Procedures on eye: complete motor blockade, 2–4 mL (15–30 mg) of 0.75 % solution Local infiltration: 0.25 % solution up to max doses (max 225 mg with epinephrine or 175 mg without epinephrine) Local sacral epidural: moderate to complete blockade, 15–30 mL of 0.5 % solution (75–150 mg) or 0.25 % solution (37.5–75 mg), repeated once every 3 h PRN Regional epidural: partial to moderate motor blockade, 10–20 mL (25–50 mg) of a 0.25 % solution; moderate to complete motor blockade, 10–20 mL (50–100 mg) as a 0.5 % solution; complete motor blockade, 10–20 mL (75–150 mg) as a 0.75 % solution; repeat once every 3 h PRN	*Serious*: bradycardia, heart block, ventricular arrhythmias, bacterial meningitis, immune hypersensitivity reaction, chondrolysis of articular cartilage, CNS depression, CNS stimulation, cranial nerve disorder paraplegia, seizure, respiratory arrest

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
			Regional (obstetrical) hyperbaric spinal, bupivacaine in dextrose formulation only; normal vaginal delivery, 0.8 mL (6 mg) bupivacaine in dextrose as 0.75 % solution; Cesarean section, 1–1.4 mL (7.5–10.5 mg) bupivacaine in dextrose as 0.75 % solution	
			Regional hyperbaric spinal, bupivacaine in dextrose formulation only; lower extremity and perineal procedures, 1 mL (7.5 mg) bupivacaine in dextrose as 0.75 % solution; lower abdominal procedures, 1.6 mL (12 mg) bupivacaine in dextrose as 0.75 % solution; upper abdominal surgery, 2 mL (15 mg) bupivacaine in dextrose, in horizontal position	
			Regional peripheral nerve block: moderate to complete motor blockade, 5–37.5 mL (25–175 mg) of 0.5 % solution or 5–70 mL (12.5–175 mg) of 0.25 % solution, repeat every 3 h PRN	

			Regional sympathetic nerve block: 20–50 mL (50–125 mg) of 0.25 % solution, repeat once every 3 h PRN	
Ropivacaine (Naropin™) [102, 103]	*Contraindication*: (1) hypersensitivity to ropivacaine or local amide anesthetic	Less cardiotoxic than bupivacaine [104]	Local anesthetic lumbar epidural block for Cesarean section: 20–30 mL of 0.5 % solution (100–150 mg) or 15–20 mL of 0.75 % solution (113–150 mg)	*Drug interactions* [103]: bupivacaine, St. John's wort
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: (1) elderly patients with heart disease, (2) cardiovascular impairment, (3) concurrent use of class I or III antiarrhythmics, (4) hepatic disease, (5) hypotension, hypovolemia, or heart block		Epidural anesthesia for surgical procedure: 15–30 mL (75–150 mg) of 0.5 % solution	*Side effects*:
Indications: (1) local anesthetic lumbar epidural block for Cesarean section, (2) epidural anesthesia for surgical procedure, (3) local anesthetic nerve block for surgical procedure, (4) postoperative pain	*Pregnancy category*: B		Local anesthetic field block for surgical procedure: 1–40 mL of 0.5 % solution (5–200 mg)	*Common*: bradycardia, hypotension, pruritus, nausea, vomiting, backache, headache, paresthesia, fever
	Breast feeding: infant risk has not been ruled out		Local anesthetic nerve block for surgical procedure: 35–50 mL of 0.5 % solution (175–250 mg), 10–40 mL of 0.75 % solution (75–300 mg)	*Serious*: cardiac arrest, chondrolysis of articular cartilage, Horner's syndrome

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Mepivacaine (Carbocaine™, Polocaine™, Polocaine-MPF™, Polocaine Dental™) [105, 106]	*Contraindication*: (1) hypersensitivity to mepivacaine or local amide anesthetic	NOT for use in spinal anesthesia	Cervical, brachial, intercostal, and pudendal nerve block: 5–40 mL (50–400 mg) of 1 % solution or 5–20 mL (100–400 mg) of 2 % solution [105]	*Drug interactions* [106]: propranolol, St. John's wort, verapamil
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: (1) hepatic impairment; (2) renal impairment; (3) cardiovascular impairment; (4) debilitated, elderly, or acutely ill; (5) inflammation or sepsis at site of injection		Transvaginal block (paracervical plus pudendal): up to 30 mL both sides (up to 300 mg both sides) of 1 % solution [105]	*Side effects*:

Indications: (1) local anesthesia; (2) epidural block; (3) anesthetic injection into brachial plexus; (4) anesthetic injection into pudendal nerve; (5) local anesthesia, intercostal nerve block; (6) local anesthesia, cervical region nerve block; (7) paracervical block; (8) regional anesthesia; (9) pain management	*Pregnancy category*: C *Breast feeding*: infant risk has not been ruled out	Paracervical block: up to 20 mg both sides (up to 200 mg both sides) of 1 % solution [105] Caudal and epidural block: 15–30 mL (150–300 mg) of 1 % solution or 10–25 mL (150–375 mL) of 1.5 % solution or 10–20 mL (200–400 mg) of 2 % solution [105] Infiltration: up to 40 mg (up to 400 mL) of 1 % solution [105] Therapeutic block (pain management): 1–5 mL (10–50 mg) of 1 % solution or 1–5 mL (20–100 mg) of 2 % solution [105]	*Common*: anxiety, chills, dizziness, excitation, restlessness, tremors, incontinence, tinnitus, sneezing *Serious*: cardiac arrest, bradycardia, heart block, hypotension, ventricular arrhythmia, bacterial meningitis, immune hypersensitivity reaction, chondrolysis of articular cartilage, cranial nerve disorder, seizure, respiratory arrest

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Articaine and epinephrine (Articadent™, Orabloc™, Septocaine™, with epinephrine) [107, 108]	*Contraindication*: (1) hypersensitivity to articaine or local amide anesthetic	First FDA approval in 30 years of a new local dental anesthetic providing complete pulpal anesthesia for approximately 1 h	Infiltration: 0.5–2.5 mL (20–100 mg) of 4 % solution	*Drug interactions* [108]: bucindolol, carteolol, carvedilol, digoxin, dihydroergotamine, entacapone, halothane, isocarboxazid, labetalol, levobunolol, linezolid, metipranolol, nadolol, penbutolol, phenelzine, pindolol, propranolol, rasagiline, sotalol, tertatolol, timolol, tranylcypromine, tricyclic antidepressants
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: (1) hepatic impairment; (2) renal impairment; (3) cardiovascular impairment; (4) debilitated, elderly, or acutely ill; (5) concomitant use of MAO inhibitors, tricyclic antidepressants, nonselective beta-blockers, phenothiazines, or butyrophenones		Nerve block: 0.5–3.4 mL (20–136 mg) of 4 % solution	*Note*: all drug interactions due to epinephrine in formulation
Indication: (1) local, infiltrative, or conductive anesthesia in both simple and complex dental procedures	*Pregnancy category*: C		Oral surgery: 1–5.1 mL (40–204 mg) of 4 % solution	*Side effects*:
	Breast feeding: infant risk has not been ruled out		Max dosage adults and pediatrics: 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb body weight	*Common*: hypotension, pain *Serious*: cardiac arrest, negative inotrope, syncope, ventricular arrhythmia, injection site necrosis, immune hypersensitivity reaction

Tetracaine (Pontocaine™, [109, 110]	*Contraindication*: (1) hypersensitivity to tetracaine hydrochloride, ester-type local anesthetics, or para-aminobenzoic acid (PABA) or its derivatives	Ophthalmic procedures: 1 drop into the eyes PRN	*Drug interactions* [110]: no known significant drug interactions
Blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: (1) acutely ill, elderly ill, or debilitated patients, (2) cardiac disease, (3) concomitant use of sulfonamides, (4) shock, (5) cardiovascular disease, (6) hyperthyroidism (Lexicomp)	Perineal: 5 mg	*Side effects*:
Indications: (1) for rapid- and short-acting ophthalmic anesthesia, (2) spinal anesthesia	*Pregnancy category*: C	Perineal and lower extremities: 10 mg	*Common*: stinging, burning, and conjunctival redness, hypotension, nausea, vomiting
	Breast feeding: infant risk has not been ruled out	Costal margin: 15 mg; doses up to 20 mg may be given, but are reserved for exceptional cases	*Serious*: allergic corneal reaction, apnea
		Low spinal (saddle block): 2–5 mg	

(continued)

Table 1.5 (continued)

Drug name, mechanism of action, indication	Contraindication, caution, pregnancy category, breast feeding	Clinical pearls	Dosing options	Drug interactions and side effects
Levobupivacaine (Chirocaine™) [111]	*Contraindication*: (1) hypersensitivity to levobupivacaine or local amide anesthetic	Slow onset of action	Local: 60 mL (150 mg) of 0.25 % solution	*Drug interactions* [112]: St. John's wort
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: (1) hepatic impairment		Local, retrobulbar: 5 mL of 0.5 % solution	*Side effects*:
Indications: (1) local anesthesia, (2) regional anesthesia, (3) obstetrical pain, (4) postoperative pain	*Pregnancy category*: C		Regional, peribulbar infiltration: 5–15 mL (37.5–112.5 mg) of 0.75 solution	*Common*: pruritis, nausea, vomiting, dizziness, fever
	Breast feeding: infant risk has not been ruled out		Regional, peripheral block: 30 mL or 0.4 mL/kg of 0.25–0.5 % solution	*Serious*: cardiac arrest, arrhythmias, hypotension, apnea
			Regional, epidural (surgical): 10–20 mL (50–150 mg) of 0.05–0.75 solution	
			Regional, epidural (Cesarean section): 10–20 mL of 0.5 % solution (100–150 mg)—avoid using 0.75 % solution	

Etidocaine (Duranest) [113]	*Contraindication*: (1) hypersensitivity to articaine or local amide anesthetic	First FDA approval in 30 years of a new local dental anesthetic providing complete pulpal anesthesia for approximately 1 h	Infiltration: 0.5–2.5 mL (20–100 mg) of 4 % solution	*Drug interactions* [114]: bucindolol, carteolol, carvedilol, digoxin, dihydroergotamine, entacapone, halothane, isocarboxazid, labetalol, levobunolol, linezolid, metipranolol, nadolol, penbutolol, phenelzine, pindolol, propranolol, rasagiline, sotalol, tertatolol, timolol, tranylcypromine, tricyclic antidepressants
MOA: blocks sodium channels on nerve membranes, decreasing rate of nerve conduction related to pain transmission	*Caution*: (1) hepatic impairment; (2) renal impairment; (3) cardiovascular impairment; (4) debilitated, elderly, or acutely ill; (5) concomitant use of MAO inhibitors, tricyclic antidepressants, nonselective beta-blockers, phenothiazines, or butyrophenones	Contains epinephrine	Nerve block: 0.5–3.4 mL (20–136 mg) of 4 % solution	*Note*: all drug interactions due to epinephrine in formulation
Indication: (1) local, infiltrative, or conductive anesthesia in both simple and complex dental procedures	*Pregnancy category*: C *Breast feeding*: infant risk has not been ruled out		Oral surgery: 1–5.1 mL (40–204 mg) of 4 % solution Max dosage: adults and pediatrics, 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb body weight	*Side effects*: *Common*: hypotension, pain *Serious*: cardiac arrest, negative inotrope, syncope, ventricular arrhythmia, injection site necrosis, immune hypersensitivity reaction

Table 1.6 Dosing options of lidocaine

Adults (>16 years)	Dose
Abdominal	1.5–2 mL (75–100 mg) of 5 % solution with glucose 7.5 %
Brachial block	15–20 mL (225–300 mg) of 1.5 % solution
Cataract surgery	2 % gel applied topically 3–5 times 15–20 min prior to surgery
	2 drops of 4 % solution instilled into both eyes 6 times (i.e., 60, 50, 40, 30, 20, 10 min) prior to surgery
Cervical block	5 mL (50 mg) of 1 % solution
Dental block	1–5 mL of 2 % solution with epinephrine 1:50,000 or 1:100,000 using smallest effective volume; max dose with epinephrine is 7 mg/kg; max dose without epinephrine is 4.5 mg/kg
Eye procedure	2 drops of 3.5 % ophthalmic gel to the eye; reapply as necessary
Intercostal block	3–5 mL (30–50 mg) of 1 % solution
Lumbar epidural block	25–30 mL (250–300 mg) of 1 % solution; test dose of 2–3 mL of 1.5 % solution should be given at least 5 min prior to administering total volume; do not repeat max dose for at least 90 min for continuous epidural
Obstetrical low spinal block	1 mL (50 mg) for normal vaginal delivery of 5 % solution; 1.5 mL (75 mg) for Cesarean section of 5 % solution
Paravertebral block	3–5 mL (30–50 mg) of 1 % solution
Pudendal block	10 mL (100 mg) of 1 % solution; do not repeat for 90 min
Regional block	10–60 mL (50–300 mg) intravenous regional infiltration of 5 % solution; max dose is 4 mg/kg
Percutaneous infiltration	1–60 mL (5–300 mg) of 0.5 or 1 % solution
Retrobulbar infiltration	3–5 mL (120–200 mg) of 4 % solution
Surgical block	1.5–2.0 mL (75–100 mg) of 5 % solution
Topical	Single application not to exceed 5 g of 5 % ointment (250 mg of lidocaine); approximately 6 in. length of ointment from tube; max dose is 17–20 g of ointment (850–1,000 mg of lidocaine) per day
Hepatic impairment	Doses and infusion rates should be reduced

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