PART C

Pharmacology

CHAPTER 8

Local Anesthetic Pharmacology*

Rudolph H. de Jong, M.D.

PART ONE Fundamentals

Local anesthetics are sodium channel–blocking drugs that halt impulse conduction in excitable tissues such as peripheral nerves and spinal roots. The conduction block is reversible, dissipating with time as drug is released from channel receptors. Applied to an accessible neural structure, local anesthetics dull sensation in the innervated part distal to the block without altering sensation in other body parts or depressing consciousness. Local anesthetics are conceptually and technically different from general anesthetics, depressant drugs that dull sensation and allow invasive therapy anywhere.

History

The mouth-numbing properties of cocaine, an extract from the leaves of the coca shrub grown in the Andean foothills, have been known for centuries. In 1855, Gaedicke extracted the alkaloid erythroxyline from coca leaves. Albert Niemann isolated cocaine from the erythroxyline extract in 1860 and sagely observed that the bitter crystals numbed his tongue.

Sigmund Freud, the founder of psychoanalysis, became intrigued by the new drug's medicinal properties and shared his insights with Carl Koller, a fellow intern. Koller realized that anesthesia of the eye might become a reality. The first report of such anesthesia was in 1884. News of the discovery spread like wildfire through the medical world, and cocaine soon was tested on the upper airway for ear, nose, and throat surgery. Although his contribution to ophthalmology is uncontested, Koller failed to receive the coveted Assistantship to the Vienna Eye Clinic. He died in 1944, a bitter man.[1]

Erdtman from Sweden, testing the alkaloid gramine in the 1940s, noticed that the substance numbed the tongue. The potential for local anesthesia was apparent from the similarities to the history of cocaine. Löfgren, his assistant, synthesized lidocaine from a series of aniline derivatives in 1943. Lidocaine, a potent and stable local anesthetic, combines high tissue penetrance with acceptably low toxicity. To this day, Sweden remains the birthplace of many new local anesthetics (e.g., long-acting bupivacaine and ropivacaine).

*Reprinted in part from de Jong RH: Local Anesthetics. St. Louis, Mosby–Year Book, 1994.

Pharmacodynamics

As detailed in Chapter 5 (see also reviews[2] or texts[3]), the key to local anesthetic action is locked in the lipoprotein membrane that separates a nerve's internal stable axoplasm from the more turbulent extraneural environment; the membrane functions like the casing of a sausage. Traversing the nerve membrane are sparsely distributed, protein-lined, ion-conducting channels. A nerve's resting potential is generated by the potassium ion concentration gradient, and the action potential is generated by the sodium ion concentration gradient. The metabolically fueled sodium-potassium pump restores and maintains these cross-membrane ionic gradients by continuously pumping sodium out and potassium in.

Local Anesthetic Action

Deactivation of the sodium channel is the heart of local anesthetic blockade. Local anesthetics stop impulse generation and halt signal propagation by preventing initiation of an action potential. This is brought about by rendering transmembrane sodium channels, which normally provide conducting pathways, impermeable to the inward surge of sodium ions during depolarization. The resting potential is unaffected, and the blocked nerve remains polarized. Local anesthetic blockade is a nondepolarizing (i.e., stabilizing) type of block, somewhat comparable to neuromuscular block by curare.

The sodium channel has a polar local anesthetic binding site that becomes accessible during voltage-induced conformational changes of the channel protein configuration. Electrostatic binding, probably to charged fatty acid tails, locks the movement of helical protein subunits that normally open and close (i.e., gate) the channel to transmembrane sodium ion traffic. The channel binding site is accessible to the local anesthetic cation only through the inner (i.e., axoplasmic) pore, requiring initial passage by the lipophilic local anesthetic base through the lipid nerve membrane (Fig. 8–1).

The uncharged local anesthetic base also contributes to the sodium channel block. The local anesthetic base is lipid soluble and serves as the carrier vehicle that traverses the nerve membrane. On emergence at the inner surface of the membrane, the base dissociates, and the cation locks the sodium channel. The local anesthetic base also diffuses laterally through the membrane to reach the sodium channel binding site by means of the membrane-channel interface. This route does not require pore transit and functions independently of the channel state.

Minimum Blocking Concentration

Bupivacaine is severalfold more potent than lidocaine, which is severalfold more potent than procaine. To offer a measure of relative potency, the minimum blocking concentration (C_m) of local anesthetic is defined as the drug concentration that just halts impulse traffic; this is the concentration that blocks the nerve and provides regional anesthesia.

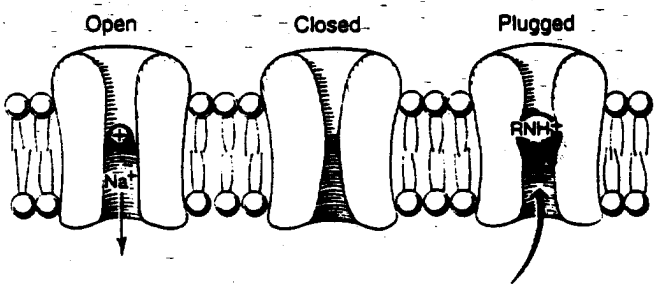


Figure 8–1 Channel entry. On the left is an open channel, inward permeant to sodium ions. The center channel is in the resting closed configuration; although impermeant to sodium ions here, the channel remains voltage responsive. The channel on the right, although in open configuration, is impermeant to sodium ions because it has a local anesthetic cation (RNH^+) bound to the gating receptor site. Notice that the local anesthetic enters the sodium channel from the axoplasmic (lower) side; the channel filter precludes direct entry through the external mouth. Because the local anesthetic renders the membrane impermeant to sodium ions and therefore inexcitable to local action currents, the nerve is blocked. (Modified from de Jong RH: Local Anesthetics, p 49. St. Louis, Mosby–Year Book, 1994.)

However, in myelinated axons, the electrical impulse can skip over one, two, or even three solidly blocked nodes of Ranvier. At the C_m of a local anesthetic, propagation of a single impulse is halted by bathing three successive nodes of a myelinated axon or the same length (5 to 6 mm) of a nonmyelinated fiber. For the sake of standardization and convenience, the C_m commonly is expressed for a 10-mm length of nerve.

In contrast with previously held beliefs, the experimental C_m appears to be independent of fiber diameter at steady-state conditions and at slow rates of nerve stimulation. The C_m represents a dynamic equilibrium between channel-bound and channel-released drug, such that the net sodium current is decreased below the firing threshold level. Clinically, variables such as nerve length, rate of impulse traffic, speed of drug diffusion, and concentration and volume of local anesthetic solution considerably complicate idealized laboratory situations.

Frequency-Dependent Nerve Block

Local anesthetic preferentially binds to sodium channels in the open state, but it is released faster than it is bound by channels in the resting state. The receptor accessibility status of the channel state (i.e., open, inactivated, closed, or resting) itself affects the quality or depth of the block. This membrane polarity-dependent variability in the quality of the block is called a state-dependent block.

When the frequency of stimulation is increased, membrane ion channels are open and exposed to local anesthetic more frequently. Accordingly, opportunities are enhanced for sodium channel drug binding and

reduced for drug release, and a frequency-dependent (i.e., use-dependent or phasic) nerve block ensues. The faster the nerve is made to fire, the more profound is the block that develops. State and frequency dependence are useful concepts for understanding the cardiotoxicities of local anesthetics such as lidocaine and bupivacaine.

Critical Blocking Length

Nerve impulses can skip over one, two, or even three blocked nodes. Anatomically, the thicker a nerve fiber, the longer is the distance between one node and the next; the internodal interval is much greater in large-diameter motor fibers than in small, thin pain-conducting fibers. Each nerve fiber has a critical blocking length (CBL), which is proportional to the diameter, spanning three nodes that must be coated by local anesthetic to ensure a complete impulse block.

Differential Nerve Block

As explained in Chapters 3 and 5, the CBL of a large-diameter nerve fiber is several times that of a small-diameter nerve fiber. A large A-alpha motor fiber may remain functional, but pain-related barrages in thin A-delta and C fibers are halted. During such a differential nerve block, the patient, although pain free, can still perceive touch and pressure and contract muscles (Fig. 8–2).

The CBL of spinal B fibers (i.e., preganglionic autonomic axons) approximates that of the smallest sensory (i.e., cold) fibers. The sympathetic block that inevitably accompanies spinal or epidural anesthesia extends several segments higher and lingers longer than analgesia; it can be approximated by testing for cold sensation. Similar considerations of low C_m and small CBL apply to postganglionic fibers in the sympathetic chains.

Because an impulse can skip over two blocked inexcitable nodes, at least 5 mm (preferably 8 mm or more) of nerve length must be bathed in local anesthetic solution to ensure a dense block of even the thickest nerve fibers. Because the internodal distance increases with the diameter of the axon, uneven longitudinal diffusion further contributes to erratic drug distribution, leading to a differential block of small and large myelinated fibers. Obstructed radial penetration toward, and erratic axial spread through, the core of a major nerve trunk are additional causes for incomplete anesthesia, a differential block of sensory and motor fibers, or both.

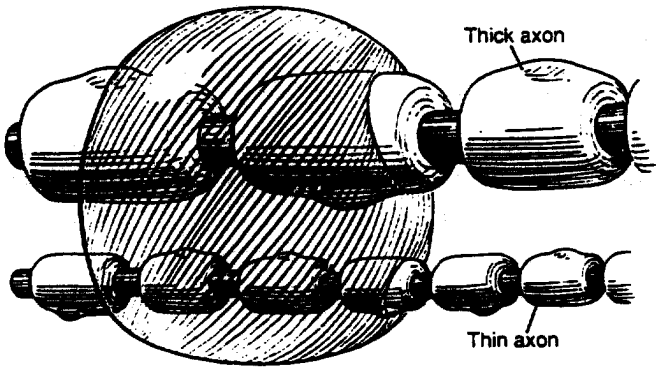


Figure 8–2 Nodal interval longitudinal (length-dependent) blockade. Two side-by-side axons—one thin, one thick—are bathed in a puddle of local anesthetic at the minimum blocking concentration (C_m): the internode (i.e., internodal interval) of the thick fiber is twice that of the thin one. The local anesthetic solution covers three successive nodes of the thin axon *(bottom)* but only one node of the thick axon *(top)*. Impulses can skip easily over one and even two inexcitable nodes, enabling conduction along the thick axon to continue uninterrupted. In the thin axon, with its three nodes covered by local anesthetic, impulse conduction is halted. Sufficient volume should be injected to coat at least three successive nodes (~1 cm) of even the thickest axon. A longitudinal block is the main operand in a threshold differential block of thin nerve bundles (e.g., spinal roots). (Modified from de Jong RH: Local Anesthetics, p 68. St. Louis, Mosby–Year Book, 1994.)

Physicochemical Considerations

Local anesthetics are organic amines, with an intermediary ester or amide linkage separating the lipophilic ring-linked head from the hydrophilic hydrocarbon tail. The weakly basic local anesthetic amine is lipid soluble but water insoluble and unstable. Crystalline salts of the local anesthetic base, conversely, are water soluble and stable but lipid insoluble.

When dissolved in water, the salt crystals ionize to yield local anesthetic cations and chloride or other acid anions. The local anesthetic cation (i.e., positively charged quaternary amine) is in dissociation equilibrium with the local anesthetic base (i.e., uncharged amine). The proportions of cation and base are governed by the drug's fixed pK_a and the variable ambient pH. The more acid the solution, the greater is the proportion of cation and the lesser that of local anesthetic base, according to the equation

$$\log\left(\frac{[\text{cation}]}{[\text{base}]}\right) = pK_a - pH$$

in which [cation] and [base] denote the concentration of local anesthetic cation and base, respectively.

Drug Dissociation

The lipid-soluble uncharged local anesthetic base species diffuses from the extraneural injection site through the nerve sheath toward individual nerve fibers, and it eventually penetrates the neural membrane. Once through the axonal membrane, the local anesthetic base reverts to a cation that interacts with sodium channel binding sites to barricade sodium ion traffic and block impulse conduction. The cation to base ratio, as determined from the previous equation, is critical to a successful nerve conduction block. If too little base and too few local anesthetic molecules reach the neural target, too few cations are available for binding and too few sodium channels close to ion

Table 8–1 Dissociation Constants

LOCAL ANESTHETIC	pK_a*
Benzocaine	3.5
Mepivacaine	7.7
Lidocaine	7.8
Etidocaine	7.9
Prilocaine	7.9
Ropivacaine	8.1
Bupivacaine	8.1
MEGX (monoethylglycine xylidide)	8.1
Tetracaine	8.4
Pipecolyl xylidide	8.6
Cocaine	8.6
Dibucaine	8.8
Procaine	8.9
Chloroprocaine	9.1
Hexylcaine	9.3
Procainamide	9.3
Piperocaine	9.8

*The dissociation constants are rounded.
From de Jong RH: Local Anesthetics. p 109. St. Louis. Mosby–Year Book. 1994.

traffic. The dissociation constants of local anesthetics are shown in Table 8–1.

The tissue acidosis accompanying infection or the limited buffering capacity of mucous membrane hampers base dissociation, yielding incomplete anesthesia. A local anesthetic with low pK_a (e.g., benzocaine), conversely, is virtually undissociated at physiologic pH and provides excellent mucosal penetrance. However, because of an ultra-low pK_a, few cations dissociate to consummate the block, and a high concentration of benzocaine (10% to 20%) is needed to numb the submucosal nerve endings.

Pharmacokinetics

Absorption diverts local anesthetic into the bloodstream, which distributes it throughout the organism. A portion of the blood-borne local anesthetic is bound to plasma albumin and globulin fractions (mainly α_1-acid glycoprotein) that limit the amount of freely diffusible unbound drug. Most organs have greater affinity and larger storage volume for local anesthetic than plasma compartments and represent a vast static reservoir that buffers the blood level. During continuous local anesthetic infusion, these buffers eventually become saturated (about 2 days in the case of bupivacaine), sharply raising the drug's blood level and the risk of drug toxicity.

The plasma concentration–time profile provides a snapshot of the shifting balance among local anesthetic absorption from the injection site, interim uptake by tissue reservoirs, drug biotransformation, and ultimate excretion. Pharmacokinetic equations are derived from sequential plasma drug concentrations, permitting construction of drug disposition models. The terminology is a bit arcane, but what follows are explanations applicable to clinical practice.

The combined volume of organ reservoirs represents the apparent volume of drug distribution. Clearance expresses the rate at which local anesthetic is removed from this reservoir. Half-time is a convenient composite measure describing how quickly or slowly the local anesthetic plasma concentration is halved. After four or five half-times, the drug is cleared from storage sites for all practical purposes.

Absorption

The rate of local anesthetic absorption depends on the vascularity of the injection site. The more vascular the tissue, the faster the absorption, the higher the blood level, and the sooner the blood level peaks. For any given site, absorption depends on drug dose delivered and on tissue perfusion; absorption is essentially concentration independent. Local vasoconstriction, as with epinephrine, slows absorption, and more local anesthetic is retained for a longer time at the target site, generating a more profound and prolonged impulse block.

Disposition

Local anesthetic disposition in humans is approximated by a two-compartment model: one phase of rapid dilution into blood and well-perfused organs (e.g., brain), followed by a slower steady phase of distribution into the capacious buffer of less-perfused organs (e.g., muscle). Two half-times are defined: one (alpha) for the rapid initial dilution phase and a second (beta) for the slow but steady distribution phase. The second (or beta) phase parameters have greater clinical application because they represent steady-state conditions. Rapid lowering of blood level (i.e., short half-time) is a desirable trait, because it shortens the duration of a toxic reaction.

Amino amide local anesthetics rely on hepatic blood flow for clearance. Incompletely protein-bound drugs such as lidocaine or mepivacaine have a major free plasma fraction; their disposition is hepatic and flow dependent. Drugs that are bound strongly to plasma protein such as bupivacaine or ropivacaine have little free (unbound) drug to donate to hepatic clearance; their elimination rate depends on the concentration of the free fraction. Urinary and fecal elimination are minor routes for intact local anesthetic; the drug metabolites and conjugates are largely excreted renally.

Diffusion

To reach the neural target site, local anesthetic must diffuse through tissue barriers. In a peripheral nerve, the main diffusion barrier is the perineurium. In transmeningeal diffusion, the arachnoid mater is the principal barrier.[4] Intravenous regional anesthesia results from reverse diffusion of local anesthetic across the blood-nerve barrier. The blocking agent reaches nerve trunks and terminal nerve branches. The threshold local anesthetic block so attained is bolstered by an ischemic conduction block.[5]

Tachyphylaxis to local anesthetics turns out to be a mechanical rather than a pharmacodynamic phenome-

non: it is seen only with staggered injections. In contrast, continuous infusion enhances local anesthetic potency by raising the nerve to a supra-C_m steady state level. Over time, the quantity of local anesthetic required for a continuous infusion block decreases as drug absorption matches drug disposition. A gradual decrease of the concentration of infused local anesthetic to the near-C_m range can maintain adequate analgesia for days with little or no motor block and without risking spillover from saturated tissue buffers.

Molecular Configuration

Local anesthetics form a remarkably homogeneous class of drugs with respect to their biologic properties and molecular structure. Other than chemical variations on a common structural theme, three distinguishing features individualize local anesthetics. One is the drug's linkage (i.e., ester or amide), which separates the aromatic lipophilic head from the hydrophilic tail. Second is the drug's binding to lipids and proteins, which controls spread, penetration, duration, and toxicity. Third is the drug's pK_a (see Table 8–1), which governs the proportions of local anesthetic base and cation at any given pH.

Most injectable local anesthetics in common use are weakly basic tertiary amines; prilocaine (a partner with lidocaine in a eutectic mixture of local anesthetics [EMLA] cream) and articaine are secondary amines. Conceptually, a tertiary amine is derived from ammonia (NH_3), with each of the three hydrogen atoms replaced by organic substitutes. The general configuration of local anesthetic amines (Fig. 8–3) comprises two key structural components: a lipophilic aromatic head and a hydrophilic aminoalkyl tail. The two are joined by an intermediate carboxy linkage, which is an ester or an amide configuration.

The bulky aromatic head commonly is derived from benzoic acid (i.e., ester family) or aniline (i.e., aminoacyl family). The hydrophilic hydrocarbon tail, containing dissociable nitrogen, is less easily characterized: amino derivatives of ethyl alcohol, acetic acid, or ringed piperidine are common. Compounds lacking the hydrophilic tail are almost insoluble in water (e.g., 1 part benzocaine dissolves in 2500 parts water) and are unsuitable for injection, although quite satisfactory for topical application to mucosal surfaces.

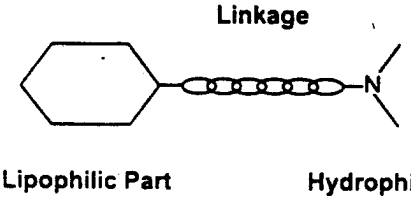


Figure 8–3 Basic assembly of a local anesthetic molecule, with aromatic and amino fractions joined by an amino ester or amino amide "linkage." (From de Jong RH: Local Anesthetics, p 99. St. Louis, Mosby-Year Book, 1994.)

Ester and Amide Linkages

The 0.6- to 0.9-nm separation of the lipophilic and hydrophilic fractions by an intermediate chain of four or five atoms has proved to be critical in providing proper planar orientation for the molecule's characteristic binding to sodium channel receptors. Other compounds, such as antihistaminic and anticholinergic drugs, share this general structure (except for linkage composition) but exhibit weak local anesthetic effects at best. The linkage also determines the course of biotransformation, an important feature underscored by the classification of local anesthetics as ester-linked or amide-linked compounds.

Ester-linked local anesthetics, as characterized by procaine, are readily hydrolyzed by appropriate plasma esterases. Amide-linked local anesthetics, as characterized by lidocaine, generally require prior enzymatic dismantling to ready them for eventual hepatic hydrolysis. Consequently, amino amides more often are excreted partially or almost intact.

The linkage's reactive carbonyl group (C=O), common to ester and amide local anesthetics, is essentially planar, because it is stabilized by considerable resonance energy. The linkage also keeps the head and tail of the molecule stretched apart while retaining the spatially flexible orientation that allows molding to the ion channel receptors.

Structural Characteristics

Of the hundreds of local anesthetics synthesized, few have survived outside the pharmaceutical laboratory and even fewer have survived clinical trials. Some initially promising drugs proved to be highly toxic systemically or irritating to tissues; others were too insoluble in water or too unstable in solution. The proper balance among high potency, low toxicity, and adequate solubility in water and lipids seems to be attained with intermediate linkages of one to three carbon atoms.

Lengthening the para-amino chain of the aromatic ring makes the compound more resistant to hydrolysis, offering a longer duration of action but greater toxicity, as for tetracaine. Substitution elsewhere along the aromatic ring alters the three-dimensional configuration of the molecule and imparts new features. The methyl groups occupying the two ortho positions of the xylidine ring convey great stability to the molecule (e.g., lidocaine, bupivacaine). Their bulk also shields the amide linkage, rendering it resistant to enzymatic hydrolysis.

When the four valences of a carbon atom each are linked to a different atom or group, the carbon atom is said to be asymmetric or chiral, because the molecule can be configured around the chiral carbon in two three-dimensional mirror images. The resultant stereoisomers have different physicochemical and often different biologic properties, including rotation of the axis of polarization of a light beam in a counterclockwise (left) or clockwise (right) direction.

The two structural variants are designated as *S* (sinis-

ter or left) and *R* (rectus or right) enantiomers, with the axis of light rotation shown as (−) for counterclockwise and (+) for clockwise deflection. Notice that the optical axis does not necessarily follow the steric configuration: *S*(+)-mepivacaine compares with *S*(−)-ropivacaine.

Many local anesthetics (e.g., bupivacaine, prilocaine) contain a chiral carbon and both have *S* and *R* configurations. During synthesis, equal proportions of the two enantiomers are generated, and the mixture is said to be racemic because the effects of opposite light-polarizing axes cancel each other. Cocaine, the naturally derived original local anesthetic, is a pure levorotatory enantiomer, designated as β-cocaine; a dextrorotatory cocaine, named α-cocaine or pseudococaine, was said in the 1920s to be twice as potent, more thermostable, and less toxic than naturally occurring cocaine.

The stereospecificity of local anesthetics was not seriously explored until bupivacaine cardiotoxicity was investigated. *R*(+)-bupivacaine has a much longer dwell time in cardiac sodium channels than the *S*(−) form, accounting for the considerably greater cardiotoxicity of *R*(+)-bupivacaine.[9] Of additional significance is the more potent depressant effect on brain-stem cardiorespiratory neurons of *R*(+)-bupivacaine compared with its *S*(−) enantiomer.[10]

Metabolism

The intramolecular linkage determines a drug's cardinal properties, which include direction and rapidity of the first stage of metabolism. Ester-linked local anesthetics (e.g., procaine, tetracaine) are readily hydrolyzed in plasma to the parent aromatic acid and amino alcohol, but amide-linked tertiary amines (e.g., lidocaine) resist direct plasma hydrolysis and require one or more preliminary degradation steps before eventual hepatic hydrolysis. Other amino amides with a nonlinear cyclic amino tail (e.g., mepivacaine, bupivacaine) are eliminated as intermediaries with the amide linkage still intact, defying any attempt at hydrolytic cleavage.

The resistance of the amide bond to nonenzymatic hydrolysis is shown by the ability of amino amide local anesthetics to withstand considerable physicochemical abuse; they can be autoclaved with supersaturated steam without a significant loss of potency. Procaine, conversely, tolerates autoclaving only briefly, and poorly at that, before becoming biologically inert; its shelf life too is less than that of lidocaine. Tetracaine, probably because it is hydrolyzed much more slowly than procaine, can be autoclaved repeatedly with little loss of potency.

The cardiotherapeutic use of lidocaine given systemically permitted biochemical mapping of its fate in humans, which was not feasible in studies using volunteers. Study of bupivacaine disposition in humans has been spurred by long-term infusion in the control of postoperative and chronic pain. As a result, differences between biotransformation in laboratory animals and in humans have become apparent.

PART TWO Clinical Pharmacology

Amino Ester Local Anesthetics

One major class of local anesthetics (Fig. 8–4) has an ester linkage to benzoic acid or its derivatives in common. Because cocaine, the first local anesthetic, is a benzoic acid ester, subsequent synthetic local anesthetics (e.g., procaine) all were developed from that mold. Not until about 60 years later was a whole new class of local anesthetics—the amide-linked (amino amide) group—introduced.

Ester-linked local anesthetics are cleaved by hydrolysis at the ester linkage, but the rates of the reaction vary considerably among amino esters. Tetracaine, for example, is hydrolyzed four or five times more slowly than procaine in human plasma, and other amino esters are affected more by hepatic than by plasma enzymes. As a rule, esters of para-aminobenzoic acid or its derivatives (e.g., procaine, tetracaine) are more readily hydrolyzed by plasma enzymes than by liver enzymes compared with local anesthetic esters of other aromatic acids (e.g., piperocaine), which are hydrolyzed more readily in the liver than in plasma. Cocaine, a double ester, straddles the divide and requires both plasma and liver cholinesterases for disposition.

Procaine

Procaine, the first in the synthetic para-aminobenzoic acid ester family, was synonymous with local anesthesia for a long time. Its relatively low toxicity permitted extensive regional block procedures, with up to 1000 mg being considered an acceptable dose. It has long since been replaced by more potent, longer-acting, and more readily diffusible ester- and amide-linked local anesthetics.

The primary step in human procaine metabolism is hydrolysis by plasma enzymes to form para-aminobenzoic acid and diethylaminoethanol. Procainesterase is indistinguishable from serum pseudocholinesterase, which also hydrolyzes succinylcholine; patients with low plasma pseudocholinesterase levels could suffer protracted procaine toxicity. If this deficiency is a possibility, a nonhydrolyzable local anesthetic such as lidocaine may be the better choice.

Chloroprocaine

Rather trivial alterations of the procaine molecule can introduce major changes in biologic activity. To illustrate, chloroprocaine (2-chloroprocaine; see Fig. 8–4) is hydrolyzed some four times faster than procaine in human plasma; it is less toxic after intravenous injection than procaine. In obstetric analgesia, in particular, fetal metabolism of chloroprocaine (although half as fast as in maternal plasma) still ensures fast clearance with minimal residual effect. However, nag-

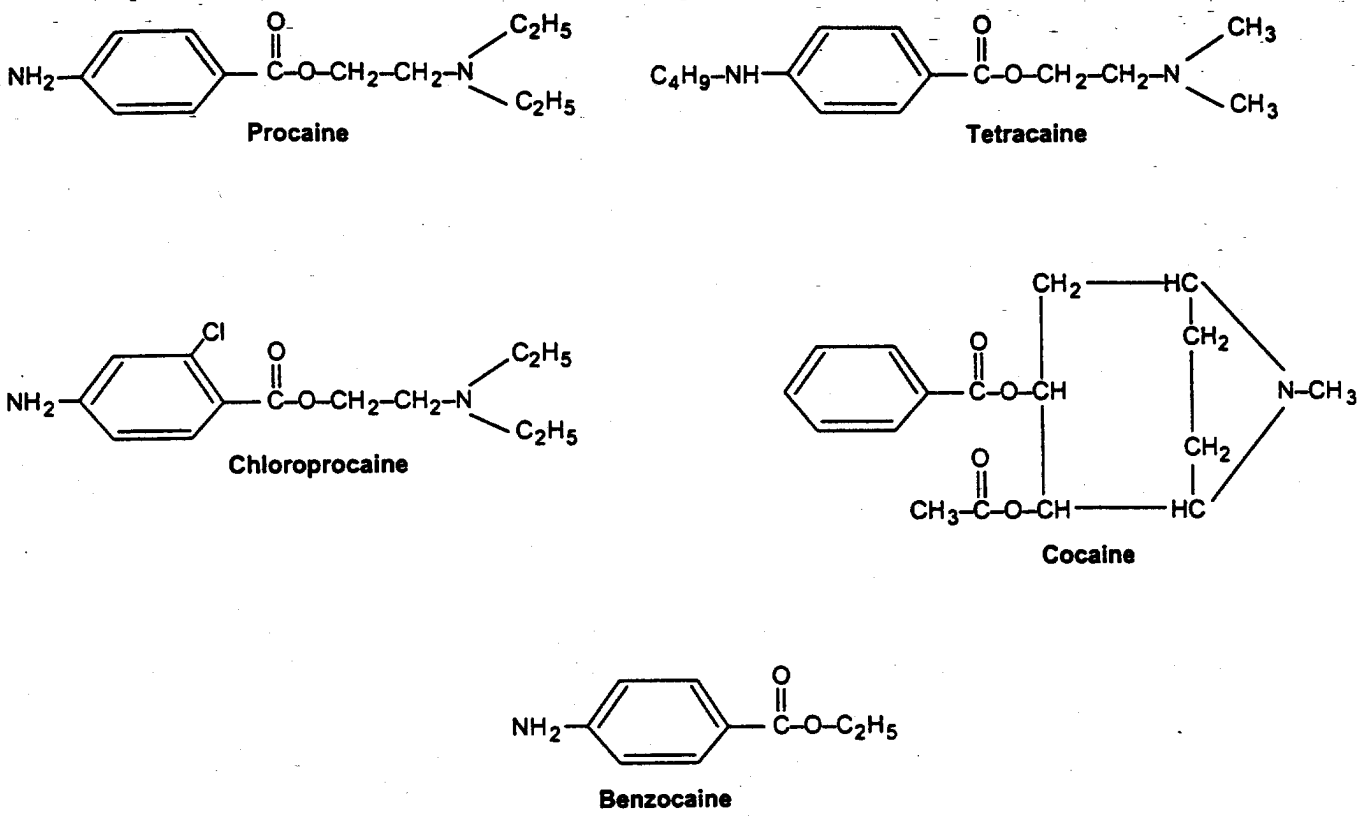


Figure 8–4 Representative ester-linked local anesthetics. (From de Jong RH: Local Anesthetics, p 178. St. Louis, Mosby–Year Book, 1994.)

ging issues about potential myelotoxicity and neurotoxicity caused chloroprocaine to yield ground again to bupivacaine.

The Chloroprocaine Riddle

When word spread in the 1970s that intrathecally delivered chloroprocaine solution might be neurotoxic, attention focused on what was previously considered an innocuous drug of low toxicity. The formulation of Nesacaine was unusual in that it contained an acid stabilizer (i.e., sodium metabisulfite) that prevented oxidation and ensured a stable shelf life. In vivo experiments soon showed that the chloroprocaine formulation caused neural damage, whereas lidocaine, bupivacaine, and saline proved innocuous.[8] The prevailing opinion was that the local anesthetic was benign but the stabilizer was not.[9, 10]

Because strong demand continued for a local anesthetic that rapidly hydrolyzed in the fetal circulation, the product was reformulated by substituting ethylenediaminetetraacetic acid (EDTA) as a stabilizer antioxidant. Soon after the switch from bisulfite to EDTA stabilizer, reports appeared in the 1980s of severe lumbar muscle spasm after uneventful epidural analgesia with chloroprocaine, probably secondary to the calcium-chelating action of EDTA.[11] Table 8–2 shows that large (>40 mL) volumes of EDTA-containing solution greatly increase the incidence of lumbar back pain but that chloroprocaine alone contributes to a lesser extent.

Table 8–2 Lumbar Back Pain After Epidural Chloroprocaine Injection

LOCAL ANESTHETIC	VOLUME, mL	EDTA	pH	NO PAIN (INCIDENCE)	NEEDLE TRACK PAIN (INCIDENCE)*	LUMBAR PAIN (INCIDENCE)*
2% Lidocaine	≥40	No	6.3	14/20	6/20	0/20
3% Chloroprocaine	≥20	Yes	3.3	13/20	6/20	1/20
3% Chloroprocaine	≥40	Yes	3.3	6/20	2/20	12/20
3% Chloroprocaine	≥40	No	2.9	10/20	7/20	3/20
3% Chloroprocaine	≥40	Yes	7.3	8/20	6/20	6/20

*Localized needle track pain versus general lumbar ache, 1 day after epidural injection.
EDTA, ethylenediaminetetraacetic acid.
Adapted from Stevens RA, Urmey WF, Urquhart BL, et al: Back pain after epidural anesthesia with chloroprocaine. Anesthesiology 1993; 78: 492–497; in de Jong RH: Local Anesthetics, p 362. St. Louis, Mosby–Year Book, 1994.

Lidocaine, even in a large volume (>40 mL), caused, at most, needle track discomfort but no lumbar muscle spasm pain.

Premature Obituary?

If the dual obstacles of an innocuous stabilizer and high acidity could be resolved, chloroprocaine might well emerge again as a clinically relevant local anesthetic. Potential advantages are its favorable blocking potency, high diffusibility, fast onset, and extremely rapid metabolism that limits toxicity. Further setting it apart from currently favored amino amide local anesthetics is its rapid disposition by fetus and newborn, offering all the makings of a potentially ideal obstetric analgesic.

Tetracaine

Substituting a butylamino radical for the para-amino group on procaine's aromatic ring and shortening the alkylamino tail yields tetracaine. This rather simple modification (see Fig. 8–4) spawns a totally different local anesthetic that is 10 times more potent and hydrolyzed three to four times more slowly than procaine. However, it also is about 10 times more toxic systemically. Nevertheless, the therapeutic advantages of tetracaine over procaine are considerably longer duration of action and more intense neural blockade; it remains a staple for subarachnoid anesthesia because of a proven track record of safety, predictable duration of action, and rapid onset.

As a spinal anesthetic, 10 to 15 mg of tetracaine offers a solid block to midthoracic dermatomes, lasting 2 to 3 hours. The duration of action can be prolonged by about 50% with the addition of epinephrine. Doses for vaginal or abdominal delivery should be decreased by one third or more to avoid excessively high spread. Bupivacaine is a solid contender for drug of choice in spinal anesthesia, with approximately equal duration of action. Its unique advantage is a long duration of nerve block without resorting to a vasoconstrictor, a potentially important consideration in selected patients.

Tetracaine is hydrolyzed completely by cleavage at the ester linkage; hydrolysis products appear first in the bile and then, after reabsorption from the intestinal tract, in the urine. Although the speed of tetracaine hydrolysis is four times slower than that of procaine, it still is fast compared with amino amide local anesthetics. The hydrolysis products are para-butylaminobenzoic acid and dimethylaminoethanol, neither of which is thought to be toxic. Whether these metabolites are excreted as such, conjugated, or further modified is unknown.

Benzocaine

The ethyl ester of para-aminobenzoic acid (see Fig. 8–4) differs from injectable amino esters in that it lacks the characteristic hydrophilic amine tail. Even so, it possesses the essential anesthesiophoric configuration. As a weak base (pK_a = 3.5), benzocaine exists almost entirely as the uncharged (i.e., neutral) free base species at physiologic pH. Accordingly, it is barely soluble in water (1 part in 2500) and causes tissue irritation when injected. Benzocaine is used extensively as a wound-dusting powder or as a topical anesthetic in products like burn nostrums, hemorrhoid salves, or throat lozenges. The probable metabolic pathway is hydrolysis to para-aminobenzoic acid and ethanol, but whether this takes place and to what extent remain uncertain.

Benzocaine is used in upper airway manipulation to anesthetize the trachea with products such as Hurricaine or Cetacaine. It was noticed serendipitously that spraying the tracheal stoma of goats with benzocaine caused pronounced methemoglobinemia (up to 32%).[12] Further analysis of clinical reports suggested a direct toxic drug (or metabolite) action, rather than an idiosyncratic reaction, as ruled earlier by an expert panel from the Food and Drug Administration. Neonates may be particularly susceptible because fetal hemoglobin is more readily oxidized than the adult form.

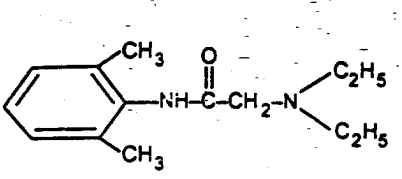
Amino Amide Local Anesthetics

The amide-linked local anesthetics (Fig. 8–5) are much more resistant to hydrolysis at the linkage joint than their ester-linked cousins; their longer duration of action is an immediate benefit. In most instances, a tertiary amino amide must be converted first to a simpler, secondary amine form before the linkage can be cleaved. A common first step is dealkylation of the amino nitrogen, transforming a tertiary to a secondary amine: for example, lidocaine to monoethyl-glycine xylidide (MEGX). A secondary amine such as prilocaine is more readily hydrolyzed by amidases than are tertiary amines.

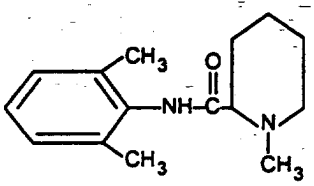
Subclassification

The two different ways by which an amide linkage is pieced together influence the resultant amino amide's metabolism and its duration of action. The amide linkage is formed by fusing an aromatic amine with an alkyl-amino acid or, the other way around, by joining an aromatic acid to an alkyl-amino alcohol compound (Fig. 8–6). The former approach yields an aminoacyl amide, typified by lidocaine and mepivacaine; the latter yields an aminoalkyl amide, represented by dibucaine and procainamide. Differences in rate and route of biotransformation between the aminoacyl and aminoalkyl amides are that the aminoacyl local anesthetics are metabolized faster and more completely than the aminoalkyl local anesthetics.

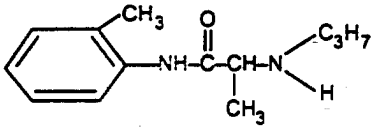
Within the dominant aminoacyl class there is a further distinction based on whether the hydrophilic amino tail is a straight carbon chain (e.g., lidocaine) or the amino nitrogen is captured within a ringed struc-



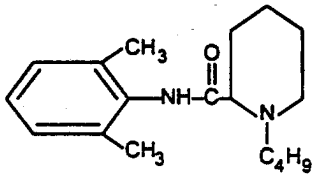
Lidocaine



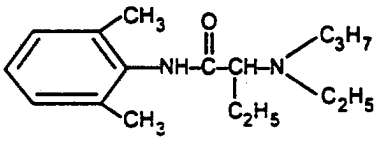
Mepivacaine



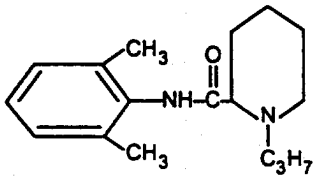
Prilocaine



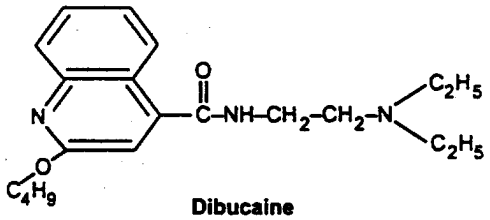
Bupivacaine



Etidocaine



Ropivacaine (S-)



Dibucaine

Figure 8–5 Representative amide-linked local anesthetics. (From de Jong RH: Local Anesthetics, p 186. St. Louis, Mosby–Year Book, 1994.)

ture (e.g., mepivacaine). The lipophilic aromatic head is a ringed carbon product.

The pipecolyl xylidide ringed local anesthetics (e.g., mepivacaine) differ from the aminoalkyl xylidide class (e.g., lidocaine) by being even more strongly resistant to hydrolytic cleavage of the amide linkage. The massive piperidine ring evidently shields them from enzymatic access.[13] The resistance to amide linkage cleavage of pipecolyl xylidides presents a particular problem for local anesthetic disposition in neonates.

Aminoacyl Amides

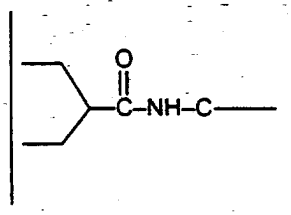
Because the bulk of the local anesthetic molecule remains essentially intact during initial metabolic steps, questions remain about the biologic activity and toxicity of complex intermediary products. Lidocaine and bupivacaine metabolism are singled out, because these local anesthetics commonly are given as a continuous infusion spanning days or longer periods. Efficient disposition of the infused drug is desirable because, if it is not cleared, the parent drug or metabolites may accumulate, causing unwanted and perhaps unexpected toxic side effects.

Aminoalkyl Xylidides: The Lidocaine Family

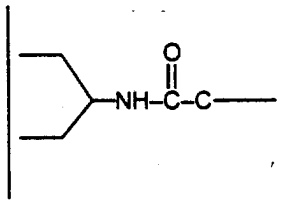
Lidocaine. In the half century since its discovery, lidocaine has supplanted procaine as the standard local anesthetic. Although its activity to toxicity ratio is not much different from that of procaine, lidocaine diffuses farther and faster, yields a more solid and longer-lasting block, and seldom raises concern about allergy.

Widespread use and varied applications (e.g., antiarrhythmic, anticonvulsant) of lidocaine led to a detailed study, and more is known about its fate in humans than that of any other local anesthetic. Its duration of action is several hours, which is a desirable attribute for rapid recovery (e.g., ambulatory surgery) but less desirable when prolonged anesthesia or pain relief is needed. One approach is to slow drug absorption with a vasoconstrictor; another is repeated injection or continuous catheter infusion.

Vasoconstrictor. The addition of a vasoconstrictor to the local anesthetic solution theoretically decreases blood flow in the target region, slowing drug absorption. If the drug stays longer on target, this prolongs the duration of the nerve block by as much as 50% (in the case of lidocaine). There are other advantages as well. Because more drug molecules are available, with less dilution by tissue fluid, the nerve block is more intense. It is possible to obtain the same depth of block



Aminoalkyl Amide



Aminoacyl Amide

Figure 8–6 The amide linkage of local anesthetics is expressed in two varieties. Dibucaine and procainamide are aminoalkyl amides, and lidocaine and bupivacaine are aminoacyl amides. (From de Jong RH: Local Anesthetics. p 187. St. Louis, Mosby–Year Book, 1994.)

with a lower drug concentration, decreasing the total drug dose; alternatively, a larger volume of more dilute drug can be used to achieve a wider spread of analgesia, as in epidural anesthesia.

By analogous reasoning, systemic toxicity is decreased because less drug is absorbed per unit time, and the total absorptive process is slowed. The net result is a lower peak blood level (compared with the same dose of plain lidocaine) that occurs later. The enhanced margin of safety is shown by manufacturer-suggested recommended maximum drug doses: for plain lidocaine, 5 mg/kg body weight, compared with 7 mg/kg for lidocaine with epinephrine (Table 8–3).

Although numerous vasoconstrictors and adrenergic agents have been tested (e.g., phenylephrine, octapressin, clonidine), epinephrine has remained the first choice. The usual amount of epinephrine is 5 μg/mL (also expressed as 1:200,000). More epinephrine (i.e., 10 μg/mL) provides little or no extended duration of action and raises the possibility of side effects from epinephrine injection.

Therapeutic Uses. Lidocaine has found other therapeutic uses, especially the suppression of ventricular arrhythmias. Lidocaine is a fast-acting, sodium channel–blocking class Ib agent, widely used to treat postmyocardial infarction ventricular dysrhythmias. Rapid unbinding from the cardiac sodium channel during diastole places lidocaine in the fast-in, fast-out category, quite unlike the persistent conduction-blocking effect of bupivacaine. An intriguing laboratory finding is paradoxic agonism, in which lidocaine displaces bupivacaine from cardiac sodium channel binding sites.[14] If confirmed, this may help explain the unexpected observation that lidocaine reverses bupivacaine-induced cardiac arrhythmias.[15, 16]

There appears to be solid, albeit old evidence that a moderate systemic dose of lidocaine decreases intensity and duration of experimentally induced and clinically manifested seizures. Anticonvulsant therapy with lidocaine remains an option in Scandinavia: it has proved effective, even for conventional, therapy-resistant newborn convulsions.[17]

Intravenous Regional Anesthesia. Intravenous regional anesthesia, filling the venous tree of a vascularly isolated limb with dilute local anesthetic solution, differs from conventional nerve block in that it generates a core-to-mantle diffusion gradient in nerve trunks. Superimposed on that action is direct local anesthetic access to nerve terminals and small cutaneous nerve filaments,[18] combined with ischemic conduction block of large-diameter motor nerves that, with time, supplements local anesthetic block.[5]

Lidocaine has resumed its drug-of-choice status for intravenous regional anesthesia in North America because other contenders have not fared as well. Prilocaine would be an ideal choice, because of near-equal potency yet lower systemic toxicity, were it not for hemotoxic metabolites that cause delayed onset methemoglobinemia. Bupivacaine, because it is more strongly tissue bound, also looked promising initially. Analgesia remained after tourniquet deflation, but systemic cardiotoxicity removed bupivacaine from consideration. Perhaps ropivacaine will fare better.

Systemic Analgesia. A fascinating application, with growth potential in management of central pain, is lidocaine-induced systemic analgesia. Lidocaine is an effective, albeit short-duration suppressant of the cough reflex during tracheal intubation,[19] suggesting an effect on peripheral nociceptors and on central impulse conduction. Infusion of lidocaine (5 mg/kg body weight) over a 30-minute span relieved the burning foot pain of diabetic neuropathy for 3 to 21 days in 11 of 15 patients.[20]

Lidocaine given orally has poor bioavailability because of pronounced hepatic first-pass extraction. More resistant derivatives were developed for antiarrhythmic therapy, and these are finding niche application in pain management. Diabetic neuropathy, for instance, responds to mexiletine given orally. A commonly used dose of mexiletine is 750 mg/d, with considerable comfort produced at an average blood level of 3.4 μmol/L.[21] A similar mexiletine dose of 10 mg/kg/d relieved various neuropathic pain syndromes, including amputation stump pain and chemotherapeutic and postirradiation neuralgias.[22] Holding out hope for therapy-resistant central pain syndromes is a report[23] of relief from thalamic pain syndrome in eight of nine patients treated with mexiletine at a dose of 10 mg/kg/d.

Metabolism. Lidocaine is metabolized in the liver by microsomal mixed-function oxidases and amidases. The oxidative pathway requires cytochrome P-450, which is present even in neonatal liver.[24] The liver is the chief (probably the sole) organ for lidocaine biotransformation; lidocaine metabolism is limited by hepatic blood flow. With lidocaine's high extraction ratio, only advanced hepatic disease hampers its metabolism, causing the blood level to increase.[25]

Species- and route-dependent pathways of lidocaine

biotransformation have been postulated (Fig. 8–7). In humans, direct hydrolysis of the amide linkage can be considered minor at best.[26] However, oxidative metabolism of the various intermediary products of lidocaine is brisk. Almost 80% of a single dose of lidocaine can be accounted for as hydroxylated products in human urine.

Biotransformation of lidocaine starts with oxidative de-ethylation of the amino nitrogen to an intermediary secondary amine. De-ethylation of diethylglycine xylidide (i.e., lidocaine) yields MEGX and acetaldehyde (see Fig. 8–7). MEGX, which is much more readily hydrolyzed than lidocaine, yields ethylglycine and ortho-xylidine. MEGX is then further dismantled by shearing the remaining ethyl radical from the amino nitrogen. Two-step de-ethylation of lidocaine eventually yields glycine xylidide, a primary amine, that makes a late appearance in human plasma and urine. The plasma half-life of glycine xylidide is quite long (i.e., traces can still be detected 2 days after a lidocaine bolus), and once formed, glycine xylidide continues to be excreted long after lidocaine and MEGX have faded away. The potential for glycine xylidide accumulation during continuous lidocaine infusion is quite real.[27]

MEGX is excreted renally, and the kidney seems amply capable of keeping up with the metabolite load during infusion; decreased renal function raises neither lidocaine nor MEGX blood levels.[25] Only frank renal failure could present the hazard of drug and primary metabolite accumulation. Surprisingly, given its simpler chemical structure, renal capacity for glycine xylidide elimination is much more marginal than for MEGX. Glycine xylidide accumulates slowly during continuous lidocaine infusion, because it is much closer to renal transport saturation; reduction in renal function that is well short of frank renal failure leads to further glycine xylidide accumulation.[25] Glycine xylidide accumulation is of some clinical concern because it, like lidocaine, blocks cardiac sodium channels and competes with the parent drug for channel occupancy.[24]

MEGX retains much of lidocaine's cardiovascular activity and is comparable to lidocaine in its potential to

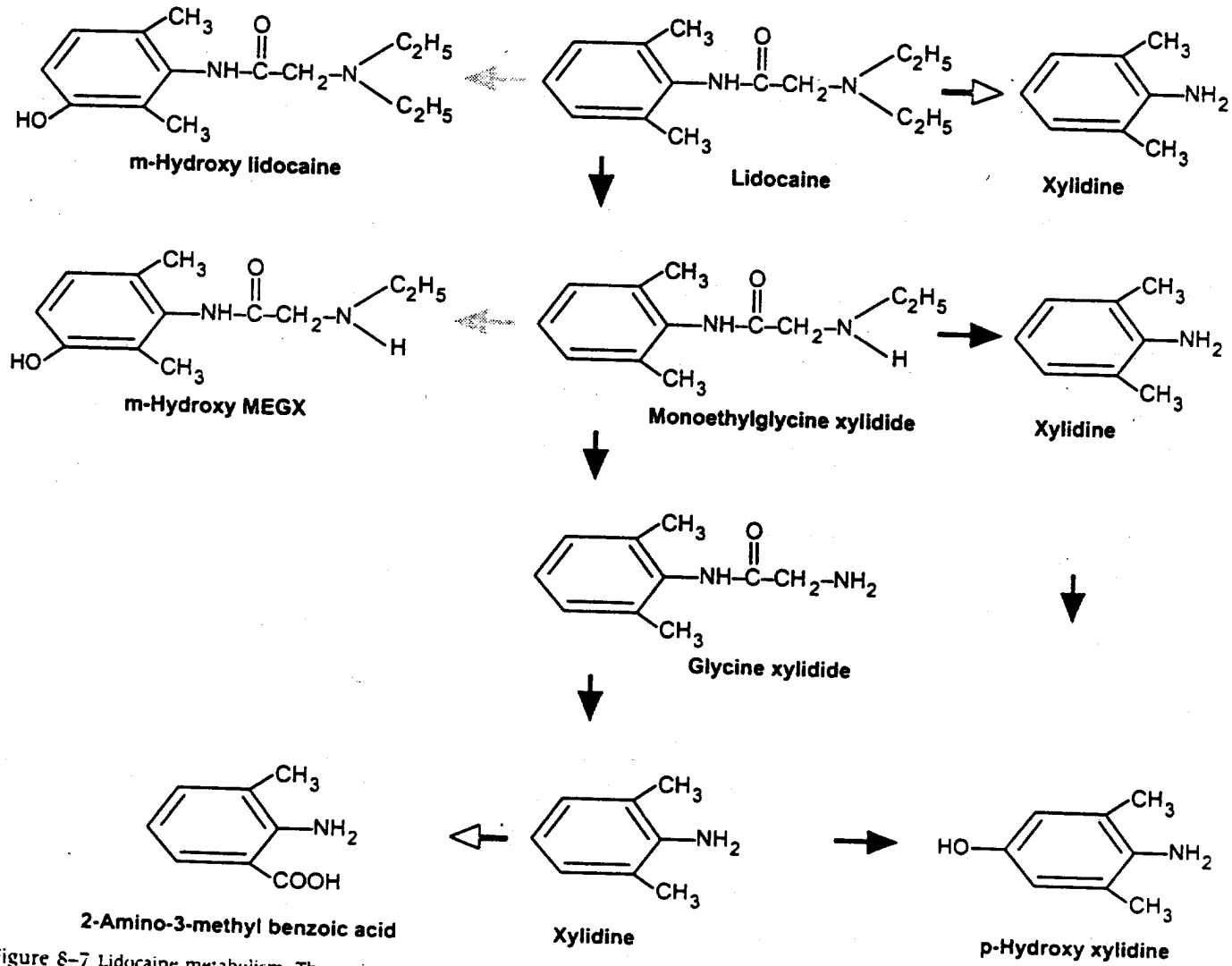


Figure 8–7 Lidocaine metabolism. The major metabolic pathways for lidocaine in humans are shown with solid arrows; the minor routes are indicated with stippled arrows. Unfilled arrows point to products in nonhuman species. MEGX, monoethyl-glycine xylidide. (From de Jong RH: Local Anesthetics. p 189. St. Louis, Mosby–Year Book, 1994.)

induce convulsions at increased blood levels. Although glycine xylidide alone does not induce convulsions, it does retain the latent convulsant potential of its lidocaine precursor. When glycine xylidide coexists with lidocaine or MEGX, it potentiates the convulsant property of the other two. Signs of central nervous system toxicity could occur—even if the lidocaine blood level is subconvulsant—when substantial quantities of MEGX or glycine xylidide, or both, accumulate.[27]

Because lidocaine readily crosses the placenta, consideration of drug disposition in the newborn is germane to selecting an obstetric anesthetic. Because of near-adult cytochrome P-450 levels, oxidative dealkylation and hydroxylation of lidocaine proceed together, with MEGX as the first step, although proportions could vary.[26] The newborn can dispose adequately of lidocaine. Mepivacaine, however, fares less well; it is cleared three times slower than lidocaine from the fetal circulation. Unlike lidocaine, mepivacaine is metabolized very little by the immature liver; its disposition instead relies mainly on renal excretion of intact drug.

Prilocaine. Prilocaine, a lidocaine homologue (see Fig. 8–5), is a secondary amine local anesthetic. When first introduced, prilocaine received considerable notice because it is approximately as potent as lidocaine yet has remarkably lower intravenous toxicity. Because the fetus tolerates prilocaine better than lidocaine, prilocaine was viewed as the replacement for lidocaine in obstetric anesthesia. Aromatic hydroxylation is accomplished by microsomal oxidation, a pathway that involves cytochrome P-450 and is present in neonates, suggesting rapid prilocaine disposition after birth.[26]

Biotransformation proved to be problematic for prilocaine, because its aminophenol metabolites oxidize hemoglobin to methemoglobin. Although minor degrees of methemoglobinemia occasionally follow the use of lidocaine or benzocaine, prilocaine consistently decreases the blood's oxygen-carrying capacity, sometimes sufficiently to cause visible cyanosis. Despite its undeniable advantages, prilocaine is infrequently used for regional anesthesia because of its metabolites.

Prilocaine has made a comeback because of another physicochemical attribute: miscibility. When mixed in equal proportions, lidocaine and prilocaine crystals form an oily substance with a melting point lower than either of its parents. This EMLA is picked up by the transdermal transport system to anesthetize terminal afferent nerve fibers. The resultant dermal analgesia allows painless venipuncture in children and other superficial dermal procedures. The main drawback is slow absorption; dermal analgesia requires 1 hour's application under an occluded skin dressing.

Because of its impulse-generation blocking action on subdermal nerve endings, application to spontaneously discharging neurons seems a logical therapeutic extension. In early informal clinical trials, we and others have used EMLA cream with encouraging results in the treatment of postherpetic allodynia, superficial scar neuromas, and atypical facial pain. Although encouraging, the uncertainties of prolonged aminophenol metabolite exposure must first be dispelled before long-term treatment can be recommended.

Articaine. Articaine was introduced in the 1970s as a low-toxicity replacement for lidocaine. It has found favor as a regional anesthetic in dentistry, but dependence on epinephrine addition (without it, an articaine block can be unpredictable) negated evanescent advantages in regional anesthesia of other body parts. The efficacy, safety, kinetic properties, and physicochemical attributes are close to those of lidocaine in a peripheral or epidural nerve block.[28] Overall, articaine with epinephrine has little to distinguish it from lidocaine or mepivacaine, whose proven track records give them the advantage.

Articaine is an aminoacyl amide-linked local anesthetic that is unique in two ways. First, it is a secondary amine, like prilocaine. Second, unlike the prevalent 6-member xylidine aromatic ring in other aminoacyls, it has a 5-member sulfur-containing thiophene ring. Also different is its metabolism, which oxidizes the thiophene ring rather than the secondary amino nitrogen tail. Articaine's cardiotoxicity is on the order of that of lidocaine but with less frequency dependence.[29] The drug seems to have found a comfortable niche in dentistry, where the addition of epinephrine is an advantage.

Etidocaine. Etidocaine, derived from lidocaine (see Fig. 8–5), initially seemed promising because of its long duration of action (i.e., on the order of bupivacaine), short latency (i.e., similar to lidocaine), and intense motor blockade. However, like bupivacaine, etidocaine was cursed with early cardiotoxicity.[30] Worse yet, etidocaine selectively blocked motor fibers more intensely than sensory fibers, giving rise to the anomalous situation of a weak patient with unsatisfactory analgesia, especially undesirable in patients in labor.

Etidocaine's great lipid solubility and near-total plasma protein binding theoretically give it strong advantages of long duration, low toxicity, and minor placental transfer. However, the clinical impression negated any potential advantages, and the drug is little used in North America. A niche market remains in regional anesthesia for surgery of the eye, in which profound cycloplegia is a distinct asset.[31] Metabolic information, because of etidocaine's rare use, is sketchy.

Pipecolyl Xylidides: the Mepivacaine Family

The pipecolyl xylidide family, like the aminoalkyl xylidide family, traces its roots to Sweden in the 1950s. Although structurally different in tail assembly, the common amide linkage conveys clinical qualities comparable to mepivacaine and lidocaine for surgical anesthesia. Differences arise from the more complex and bulky nitrogen-containing piperidine ring compared with the simpler straight-chained aminoalkyl portion.

The metabolism is more circuitous and less complete because of extensive shielding of the amide linkage by a ringed structure at either end (see Fig. 8–5). This becomes evident in neonates, whose immature hepatic enzyme system may be overwhelmed by mepivacaine, clearing it much more slowly than lidocaine. The second difference is that the carbon atom connecting the piperidine ring to the amide linkage is chiral, and

pipecolyl xylidides exist in two structural configurations: *R* and *S*. Experimentally, the *S* enantiomer is less cardiotoxic than the *R* antipode.

Mepivacaine. Although it has a cyclic piperidine rather than a linear alkyl-amino hydrophilic tail (see Fig. 8–5), mepivacaine resembles lidocaine in many clinical respects, such as impulse blocking potency and toxicity. Mepivacaine's duration of action may be slightly longer than that of lidocaine, although the difference is not sufficiently pronounced to often warrant selection of one agent over the other. The 1.5% solution of mepivacaine has become a popular choice for major nerve blocks (e.g., brachial plexus) because of rapid onset of analgesia, predictable diffusion, adequate motor block, and duration of action sufficient for ambulatory surgery, yet not so long as to require prolonged recovery room stay.

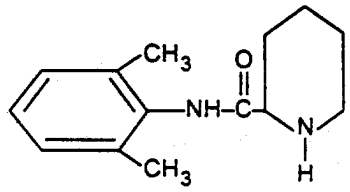
Although marketing claims for intrinsic vasoconstriction have been made, in practice, epinephrine (5 μg/mL) commonly is added to decrease absorption and to prolong duration. Mepivacaine also lends itself well to mixture with a long-acting agent such as bupivacaine. The resultant "supercaine" theoretically combines the best features of both drugs to provide rapid onset with long duration of block for postsurgical pain relief. The toxicity of "supercaine" is approximately the sum of its local anesthetic constituents.

Mepivacaine has not fared as well as lidocaine in obstetric anesthesia because of poor hepatic handling of the complex double-ringed structure. Otherwise, few significant differences between mepivacaine and lidocaine appear in clinical studies, and the selection of one over the other for regional anesthesia is more a matter of personal experience and price negotiation than of major pharmacologic distinction. The commercial product is the racemic, optically neutral, balanced mixture of *R* and *S* enantiomers.

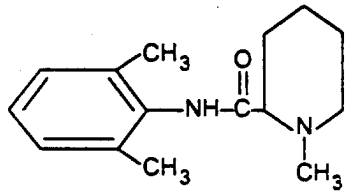
R-mepivacaine has threefold greater affinity for, and fourfold slower diastolic release from, the cardiac sodium channel than *S*-mepivacaine.[32] The former is the more cardiotoxic fast-in, slow-out component of racemic (*R-S*) mepivacaine; in humans, mepivacaine cardiotoxicity has not been as troublesome as with bupivacaine. Metabolism also may be stereoselective.

Mepivacaine's bicyclic structure, like that of bupivacaine and ropivacaine, guides it down a metabolic trail that differs from lidocaine. The chief or sole metabolic activity resides in the liver, with metabolites appearing as such and as conjugates with glucuronic acid in the bile. The greater portion of metabolites excreted in the bile subsequently is reabsorbed from the intestinal tract to be renally eliminated. Only a tiny fraction of the original mepivacaine input ultimately is recoverable from feces.

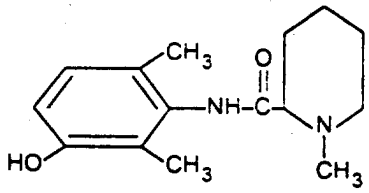
A major product of mepivacaine metabolism (Fig. 8–8) in adult humans is obtained by *N*-demethylation of the piperidine nucleus to pipecolyl xylidide (i.e., desmethyl mepivacaine), which has proved remarkably



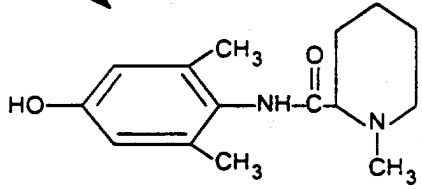
Pipecolyl xylidide



Mepivacaine



m-Hydroxy mepivacaine



p-Hydroxy mepivacaine

Figure 8–8 Metabolic pathways for mepivacaine in humans. Aromatic ring hydroxylation at the meta and para positions occurs in about equal proportions. The stippled arrow indicates a minor route. (From de Jong RH: Local Anesthetics. p 197. St. Louis, Mosby-Year Book, 1994.)

resistant to further degradation.[3] An alternative route, more productive with mepivacaine than with bupivacaine, is ring hydroxylation to meta- and para-hydroxy mepivacaine. Because *R*-mepivacaine and *S*-mepivacaine clear at different rates, hepatic meta- and para-hydroxylation may be site specific, the racemic commercial product yielding equal amounts of each.[32]

Mepivacaine illustrates the metabolic attempts at lowering local anesthetic toxicity. Although desmethyl mepivacaine is about two thirds as toxic as mepivacaine, para-hydroxy mepivacaine is only one third as toxic. And subsequent breakdown or conjugation, or both, further lower the toxicity of mepivacaine fragments. Because mepivacaine resists attempts at degradation beyond *N*-dealkylation, conjugation to water-soluble renally excreted nontoxic glucuronides clearly is the detoxification avenue of choice.

Bupivacaine. Bupivacaine is representative of a second-generation of longer-acting local anesthetics. It is closely related to mepivacaine (see Fig. 8–5), as is ropivacaine. Lengthening the methyl tail of mepivacaine's piperidine ring to a four-carbon butyl chain imparts longer duration of action and enhances potency, albeit with greater toxicity as the trade-off. Bupivacaine analgesia lasts two to three times longer than that provided by lidocaine or mepivacaine. Repeated administration or continuous infusion may cause drug and by-product accumulation as a result of saturation of storage reservoirs; blood levels increase. The local anesthetic is quite lipid soluble, is extensively bound to plasma proteins, and has a favorable maternal-to-fetal gradient.

By all appearances, bupivacaine was well on the way to even wider use, until an editorial linked hitherto scattered clinical and anecdotal reports of sudden cardiac arrest after regional anesthesia with long-lasting agents; worse yet, most of the adverse outcomes occurred in term-pregnant women.[33] Eventually, 0.75% bupivacaine was withdrawn from obstetric use. The potent 0.75% solution remains available for nonobstetric use; it is a preferred local anesthetic for ophthalmic blocks, because it combines solid analgesia with profound relaxation of orbital and periorbital muscles.[31]

The 0.25% and 0.5% solutions of bupivacaine are used most often in regional anesthesia. The latter is used when muscle relaxation and analgesia are required (e.g., brachial plexus block for shoulder operation or fracture repair); 0.25% solution is used for routine analgesia techniques or in the elderly. Regardless of concentration, it is the total mass of bupivacaine used that sets the limit on dosing: the manufacturer recommends 1 to 2 mg/kg body weight or 150 to 200 mg for a fit adult. As highlighted later in the chapter, these dosing recommendations may need to be tailored to individual circumstances. For example, the upper limit of bupivacaine dose used during epidural anesthesia should be less than that used during combined femoral and sciatic nerve block. A cautious approach is simple to implement: the injection is fractionated while the patient's voice is monitored for early warning signs of slurred speech.

Although bupivacaine is well absorbed from the injection site, strong tissue binding ensures buffering from too-rapid peaks and long duration of action. Used for perineural analgesia, a bupivacaine block may last from 4 to 6 or more hours. The duration of action in the epidural space is about 2 to 3 hours; a longer duration of analgesia requires catheter placement for infusion. Epinephrine has not significantly reduced blood levels of absorbed bupivacaine or notably prolonged analgesia. Mostly, epinephrine side effects are produced without benefit of longer duration of action. Experimentally, epinephrine could aggravate bupivacaine cardiotoxicity.[34] However, epinephrine may be beneficial as a marker of intravascular injection and has been added to bupivacaine used during regional block, despite minimal prolongation of the block or reduction in bupivacaine blood levels after regional block.

Bupivacaine has become widely used—perhaps as drug of choice in North America—for extended labor or postoperative analgesia by continuous catheter infusion. After a period of "soaking" with concentrated solution, the infusate can be diluted gradually to 0.1% or less. For extended relief of pain, the synergistic analgesic action of opioid with local anesthetic is particularly useful because it permits pain relief without significant muscle weakness. Tachyphylaxis in response to local anesthetics (i.e., the drug becomes increasingly less effective, mandating more frequent injection of ever larger volumes) has become a curiosity of the past, because intermittent injection was replaced by continuous infusion. With continuous infusion, the opposite of tachyphylaxis is seen, and clinical local anesthetic concentrations eventually approach the experimental C_m.

Bupivacaine's amide linkage, well sheltered by piperidine at one end and by xylidine at the other end, is virtually hydrolysis resistant in humans.[13] The initial metabolic process instead turns to dealkylation of the piperidine nitrogen to yield pipecolyl xylidide (i.e., desmethyl mepivacaine), which is also the dealkylation product of mepivacaine and ropivacaine metabolism; similarities between the fate of the three local anesthetics may be noticed. Debutylation (Fig. 8–9) is a genuine detoxification process: pipecolyl xylidide is only one eighth as lethal as the bupivacaine parent.

Because bupivacaine is widely used for prolonged epidural or peripheral infusion, metabolites not previously encountered with administration of a single dose have been uncovered. Of these, para-hydroxy (4-OH) bupivacaine is best characterized. Pipecolyl xylidide and para-hydroxy bupivacaine accumulate slowly when bupivacaine is infused at a rate sufficient to provide pain relief. As with the parent drug, buffer reservoir saturation may take 1 to 2 days, after which blood levels are a function of clearance rates.[35] Although bupivacaine levels during infusion can rise quite high (>5 μg/mL), signs of overt toxicity are rare.[36] Because in the central nervous system of humans the acute toxic level of bupivacaine is on the order of 2 μg/mL, it appears that it is not so much the absolute bupivacaine blood level as it is the rate of change in plasma concentration that provokes signs of toxicity.[3]

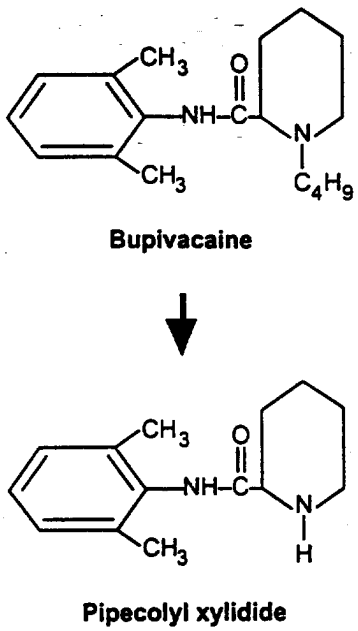


Figure 8–9 Bupivacaine biotransformation. (From de Jong RH: Local Anesthetics. p 199. St. Louis, Mosby-Year Book, 1994.)

Like mepivacaine and ropivacaine, bupivacaine has an asymmetric chiral carbon atom. The concepts of chirality and stereospecificity are clarified by an everyday example. The right hand (Fig. 8–10)—one member of a left-right pair—slides into only a right glove to conform to a specific fit. The right foot, conversely, nonselectively fits either one of a pair of socks.

Stereospecificity of the cardiac sodium channel has been especially well studied, demonstrating a threefold tighter affinity for *R*(−)- than for *S*(−)-bupivacaine.[37] The *R*(+)-bupivacaine enantiomer appears to be the fast-in, slow-out partner of the racemic bupivacaine isomer pair, and the *S*(−) enantiomer is the less cardiotoxic of the two. The issue is more complex, because in comparing the effects of bupivacaine enantiomers on medullary control neurons, *R*-bupivacaine had severalfold greater cardiorespiratory depressant effects than the *S* enantiomer.[7] Bupivacaine cardiotoxicity is precipitated by a direct myocardial and an indirect central component. The net result of these two actions remains a lively issue that may help resolve the puzzling cardiac sensitivity to bupivacaine at term pregnancy.

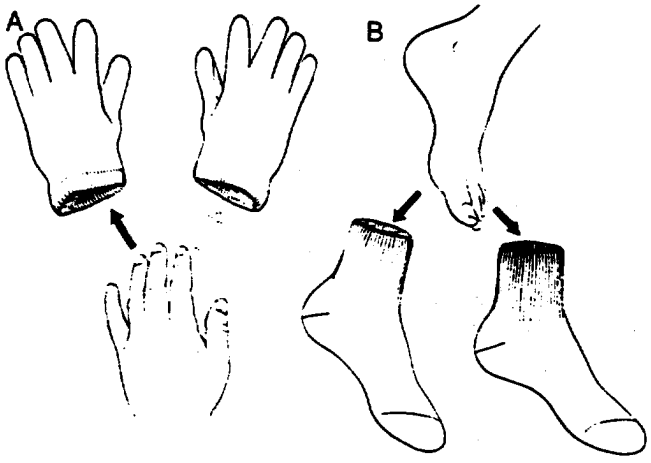


Figure 8–10 Stereospecificity. *A*, A stereoselective receptor accepts only the matching *R*- or *S*-configuration enantiomer, much like a left-hand glove fits only the left hand. The right-hand glove does not match at all with ("rejects") the left hand. *B*, A nonselective receptor accepts either of the two steric antipodes, much like the left foot fits either one of a pair of socks.

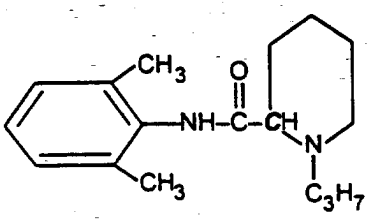
These stereoselective findings culminated in the introduction of ropivacaine, the *S*(−) enantiomer of the propyl homologue of mepivacaine and bupivacaine. Ropivacaine's channel association and dissociation constants may not be quite those of lidocaine, but they are a considerable step forward compared with those of racemic bupivacaine.[38] Theory and in vitro analysis aside, ropivacaine is a remarkable advance in decreasing in vivo cardiotoxicity.

Ropivacaine. The newest member of the pipecolyl xylidide amino amide family is ropivacaine, the propyl (C_3H_7) derivative of pipecolyl xylidide (see Fig. 8–5). Its pharmacologic properties lie between those of bupivacaine and mepivacaine, leaning closer to the former than the latter. Like its cousins, ropivacaine has an asymmetric chiral carbon atom where the carboxyamide linkage joins the piperidine ring. The chiral carbon allows for two mirror-imaged steric twins of the molecule: one is the left-rotating *S*(−) enantiomer, and the other is the right-rotating *R*(+) enantiomer (Fig. 8–11). Although mepivacaine and bupivacaine are dispensed as the optically inactive (i.e., left-rotation nullifies right-rotation) racemic *R*-*S* mixture, ropivacaine is the optically active (left-rotating) pure *S*(−) isomer.

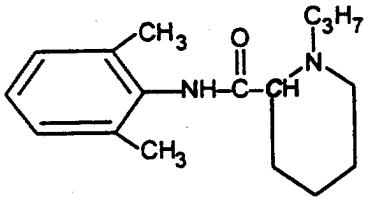
Far from being a me-too drug, ropivacaine takes unique advantage of the high-potency, low-toxicity profile of the left-rotary form compared with the right-rotary enantiomer. In vitro studies comparing *S*(−)- with *R*(+)-ropivacaine show the former to be severalfold less arrhythmogenic than the latter. The lethality of *S*(−) is also less than that of *R*(+)-ropivacaine but nerve impulse blocking potency and duration of action compare favorably with racemic bupivacaine. Some unknowns, such as myotoxicity relative to bupivacaine, remain to be determined. Even so, obstetric regional anesthesia practice should reap immediate benefits in labor and delivery applications.

Clinically meaningful vasoconstriction appears to accompany ropivacaine injection, unlike mepivacaine. Blanching and decreased cutaneous blood flow are observed with ropivacaine infiltration, making it a good candidate for surgical field blocks.[39] Epidural blood flow and drug uptake are decreased by ropivacaine.[40] By the same token, vasoconstriction begs the question of uterine blood flow and placental circulation. Reassuringly, ropivacaine blood levels as high as 2.5 μg/mL did not affect ovine placental blood flow, fetal outcome, or maternal or fetal toxic responses.[41]

Pipecolyl xylidide appears to be the primary metabolic product of hepatic dealkylation, with toxicity about one-eighth that of the parent compound (see Fig. 8–9). Renal excretion of unchanged ropivacaine is



S-Ropivacaine



R-Ropivacaine

Figure 8–11 Ropivacaine is the propylpipecolyl xylidide homologue of mepivacaine (methylpipecolyl xylidide) and bupivacaine (butylpipecolyl xylidide). All three have a chiral asymmetric carbon atom (dense C in figure) where the aminoacyl linkage joins the piperidine ring. Two mirror-image optical isomers coexist: *S*-ropivacaine (sinister: *top*) and *R*-ropivacaine (rectus: *bottom*). Unlike its cousin homologues, formulated as the racemic [*RS*(±); optically neutral] mixture, only the *S*(−) enantiomer of ropivacaine is used clinically; the *R*(+) enantiomer proved more cardiotoxic than the *S*(−) form. (From de Jong RH: Local Anesthetics, p 385. St. Louis, Mosby–Year Book, 1994.)

a small percentage of parent drug, but that of pipecolyl xylidide, although about 50%, appears to be rate limited; metabolite accumulation is possible during extended ropivacaine infusion.[13] From the metabolism of mepivacaine and bupivacaine, hydroxylated ropivacaine, pipecolyl xylidide, or both may be expected, as well as conjugation products. Limited studies in human subjects confirm the rapid disposition and low systemic toxicity of ropivacaine.[42]

Aminoalkyl Amides

Of the two better-known aminoalkyl amides, only procainamide has been studied in detail. Dibucaine, the first aminoalkyl amide local anesthetic to be synthesized, has found only limited use, mostly as a spinal or topical anesthetic.

Procainamide

Procainamide is a weak local anesthetic and irritating on injection; it has found no application in regional anesthesia. Conversely, it is widely used by cardiologists in the oral prophylaxis and therapy of cardiac arrhythmias. More than one half of the procainamide administered orally is excreted unchanged in human urine; concern over metabolic accumulation has not been as intense as in the case of lidocaine. Procainamide is hydrolyzed spontaneously in human plasma; the blood level slowly declines by 10% to 15% per hour.

Dibucaine

The biodegradation of dibucaine is sluggish compared with that of other amide-linked local anesthetics. Limited use, high toxicity, and a complex heterocyclic molecule have stifled investment in the sensitive analytic methodology needed to trace its fate in humans. Whatever the by-products, dibucaine metabolism is slow and incomplete, and the dominant excretory product is unchanged local anesthetic in the urine.[3]

Adverse Effects

Untoward responses to local anesthetics are systemic or localized. Systemic reactions occur when organ systems distant to the injection site respond to bloodborne drug. Localized reactions occur when the drug injures the structures it contacts directly. Because local anesthetic is injected perineurally in concentrations severalfold greater than the theoretical minimum to offset gross inefficiency of the delivery system, cells or tissues in direct contact with this strong solution can be harmed.

Systemic Toxicity

Systemic reactions, except allergy, are dose dependent: the higher the local anesthetic concentration in the blood, the more pronounced the response. Measures aimed at lowering the local anesthetic blood level, such as using the lowest dose in the weakest solution plus minimizing absorption with a vasoconstrictor, go a long way toward decreasing the incidence of systemic reactions in the patient population. A special concern is that local anesthetic absorbed into the maternal bloodstream may harm the fetus or depress the newborn infant.

Between localized and systemic responses are global reactions that can be precipitated by minute quantities of drug in previously sensitized or genetically atopic individuals. Although local anesthetics enjoy an enviable record of safety, familiarity with the various manifestations of toxicity provides early warning that something may be amiss, thereby minimizing the more unpleasant complications.

Overdosage

The higher the plasma level and the faster it increases, the more likely that an adverse systemic response is about to happen. Most toxic reactions are straightforward time- and dose-dependent phenomena. The more molecules attached to a receptor configuration, the more pronounced is the response.

Some field-proven guidelines are provided in Table 8–3, but physicians should heed the term "suggested"

Table 8–3 Manufacturers' Suggested Perineural Local Anesthetic Doses*

LOCAL ANESTHETIC	DOSE BY BODY WEIGHT, mg/kg	AVERAGE ADULT DOSE, mg
Procaine (Novocain)	14	1000
Prilocaine (Citanest)	10	600
Lidocaine (Xylocaine)	7†	500†
Mepivacaine (Carbocaine)	7†	500†
Tetracaine (Pontocaine)	1.5	100
Ropivacaine (tentative)	1–2	150–200
Bupivacaine (Marcaine, Sensorcaine)	1–2	150

*Manufacturer-suggested dose limits for perineural (extravascular and extrathecal) use. This table in no way implies that these dosages are safe or absolute maxima. Systemic reactions can be encountered with much smaller doses, but much larger doses, used judiciously, have been administered without ill effects.
†With 5 μg/mL of 1:200,000 epinephrine.
Adapted from Moore DC, Bridenbaugh LD, Thompson GE, et al: Factors determining dosages of amide-type local anesthetic drugs. Anesthesiology 1977; 47: 263–268; in de Jong RH: Local Anesthetics, p 353. St. Louis, Mosby–Year Book, 1994.

in the table. The values are estimates for reasonably fit patients; they may be too high for the elderly or infirm or too low for the healthy. The data reflect the implicit assumption of perineural placement; unintended intravascular or intrathecal injection of so large a dose has the potential for grave adverse effects on heart, brain, and circulation.

Most so-called drug-related reactions are not related to the drug. In this category are the needle-shy patients who respond with hyperventilation, sweating, or vasovagal reaction. Common too are reactions related to the additive rather than the local anesthetic. Sodium bisulfite is a frequent culprit, as are preservatives of the paraben (para-aminobenzoic acid) family, such as methylparaben or propylparaben.

Allergy

Allergy to a given drug is an exception to the rule relating toxicity with drug mass. Allergy is defined as an adverse reaction to a substance after previous sensitization to that same compound or to a closely related one. After the individual is sensitized, minute quantities of the offending drug (i.e., antigen) can trigger a massive allergic response when the person encounters the immunoglobulin antibody. The mating of antigen and antibody initiates a cascading sequence of reactions. An immediate (i.e., systemic, anaphylactic) reaction occurs when humoral antibodies have been synthesized. If the antibody is formed by tissue-resident lymphoid cells, a delayed (i.e., localized) reaction develops, with skin a prominent target.

The causative mechanism of an allergic reaction affects the speed of onset and severity of reaction. The type I immunoglobulin E–mediated antibody response is swiftly progressive and severe; it is true anaphylaxis. Circulating bioamines, released by mast cell degranulation, trigger a massive systemic defense reaction: airway edema, bronchospasm, and hypotension are particularly pernicious. The slower-onset type IV allergic reaction follows non–immunoglobin E–mediated release of histamine and other reactive products from sensitized lymphocytes. Depending on the amount of mediator released, severity of reaction can vary from rapid anaphylactoid shock to slowly progressive contact dermatitis.

Although true allergy to amino amides (e.g., lidocaine, bupivacaine) is exceedingly rare, the anesthesiologist cannot ignore the warning, and testing is needed. There is little doubt that cross sensitivity between amino esters (e.g., procaine, benzocaine, tetracaine) exists and extends to other para-aminobenzoic acid esters, such as sunscreen lotions or preservatives of the paraben (e.g., methylparaben, propylparaben) family. Whether amino amide local anesthetics cross-react within the group is far less certain. Most so-called allergies to local anesthetic represent adverse reactions to preservatives and additives.

Convulsions

Convulsions occur when focal excitation of a subcortical limbic site (possibly amygdala) propagates beyond its bounds to spread globally. As local anesthetic blood levels increase, limbic discharges fan out through the brain, precipitating synchronous epileptiform bursts characteristic of a grand mal seizure. Paradoxically, local anesthetics are used as anticonvulsants at lower blood levels.

A short-acting neuromuscular blocking agent such as succinylcholine has been advocated to stop the convulsive muscle spasms of a seizure.[43] The paralyzing agent does not stop the brain's electrical seizure discharges; it merely stops their external muscular manifestations. The primary indication for a paralyzing agent is an inability to adequately ventilate a convulsing patient; its use meets the increased oxygen demand of the convulsing brain and contracting muscles, and it lowers the arterial carbon dioxide tension, raising the brain's seizure threshold to local anesthetics.

Benzodiazepines have proved to be specific and effective in subcortical seizure management. They play a prime role in preventing and in treating local anesthetic-induced convulsions in humans. Benzodiazepines, by decreasing limbic excitability, preclude activation of the focal seizure generator and may be useful in preventing central local anesthetic toxicity.[3] When contemplating the use of high doses of local anesthetic

close to presumed toxic limits, as in a brachial plexus block, benzodiazepine premedication may be advisable.

Neurotoxicity

In the laboratory, local anesthetics are effective sodium current blockers and destructive neurotoxins, at concentrations severalfold lower than those used clinically. This may seem worrisome, but there is a comfortable 50-fold margin between the median blocking and toxic concentrations.[44] This is a considerably more generous therapeutic window than that available for most other drugs. It appears that the optimal conditions of the laboratory environment are miniature models of more rugged clinical conditions. A more concentrated local anesthetic solution is needed for regional block in humans, but the neurotoxic concentration is commensurately higher.

Perhaps the one clinical situation equivalent to an isolated nerve stretched in a test chamber is spinal anesthesia. Bare spinal rootlets float in an enclosed sac of fluid and may be more readily blocked and more readily injured. Chloroprocaine or its stabilizers, or both, were implicated in the past. Attention in the 1990s has focused on spinal anesthesia with concentrated (5%) lidocaine made hyperbaric with syrup (7.5% dextrose). Although neural injury was initially thought to result from mechanical stasis from fine-bore spinal catheters, the drug combination now is coming under scrutiny, and the device has been recast in the lesser role of accessory.[45]

Cardiotoxicity

As in nerve, local anesthetics decrease the cardiac action potential by limiting the inward flow of sodium current. Cardiac tissue is rendered less excitable and more frequency dependent, such that impulse propagation can be slowed; lidocaine and congeners such as mexiletine are widely used antiarrhythmics. Lidocaine is a fast-in, fast-out sodium channel blocker that reaches steady-state blockade in one or two beats. Bupivacaine is a fast-in but slow-out local anesthetic whose blocking action increases with successive beats and with faster rates; this sets the stage for malignant reentrant cardiac arrhythmias. For reasons yet unclear, the heart is further sensitized to bupivacaine at term pregnancy.

Local anesthetics with an asymmetric chiral carbon atom (e.g., mepivacaine, bupivacaine) show stereoselectivity for the cardiac sodium channel binding site. The *R* enantiomer has greater receptor affinity than the *S* isopode. Ropivacaine, a pure *S*(−) enantiomer, is considerably less cardiotoxic than racemic bupivacaine.

Cardiovascular effects of local anesthetics arise, in part, with a magnitude yet unknown, from central action on medullary autonomic control sites. Arrhythmias and blood pressure changes are produced by intracerebral injection of minute amounts of bupivacaine; medullary cardiorespiratory control sites also show stereoselectivity. That arrhythmias in unanesthetized humans or animals often precede convulsions further points to a centrally mediated component. Prior medication with a known central nervous system suppressant, such as a benzodiazepine, is suggested; a dilemma is the risk-benefit balance between maternal and fetal welfare.

Because experimental work with induction, prevention, modification, or treatment of bupivacaine-induced arrhythmias has been done mostly in isolated hearts or in surgically anesthetized animals, the clinical impact is far from clear. First, experiments on isolated hearts may point the way but need to be refined in the intact organism. Second, because regional anesthesia is practiced on awake patients, experiments need to be conducted on previously instrumented awake animals. Until these standards are met, no specific drug therapy for bupivacaine cardiotoxicity can be recommended.

Expectations are high that ropivacaine will circumvent the curse of racemic bupivacaine cardiotoxicity; whether ropivacaine will prove as hardy a local anesthetic still is unanswered. The *S*(−)-bupivacaine enantiomer bears watching. Its longer butyl side chain, compared with ropivacaine's propyl tail, may make for greater potency and longer staying power. Whether these attributes are outweighed by greater toxicity determines which of the two cousins will be the frontrunner, whether each will fill a practical niche, or whether one will fade from use.

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