34 Drugs Commonly Used for Nerve Blocking

34A Pharmacology of Local Anesthetics

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Regional anesthesia is the placement of local anesthetics at various sites along the neural axis to produce surgical anesthesia, postoperative analgesia, or analgesia for acute and chronic pain management. Drugs may be used alone or in conjunction with other adjuvant drugs in order to alter speed of onset, duration of action, or intensity of anesthesia or analgesia. Subsequent sections of this chapter describe the pharmacology of these drugs and indicate some of the factors that the clinician can modify when selecting a local anesthetic drug to achieve a specific therapeutic purpose. In addition, this chapter also describes the desirable and undesirable pharmacologic responses produced by these drugs.

CHEMICAL AND PHYSICAL PROPERTIES

The chemical structure and the physical properties of local anesthetic drugs are illustrated in Fig. 34A-1 and Table 34A-1. The physical properties of lipid solubility, pK_a (ionization), and protein binding can be directly related to local anesthetic potency, onset of action, and duration of action, respectively; whereas the chemical structure determines the metabolism and elimination of these drugs in the body. In addition, some of these drugs also have chiral forms (chemical isomers) and, when present, are indicated in Fig. 34A-1. Differences in activity and toxicity of the chiral forms of these drugs are discussed in a subsequent section.

Lipid solubility

The aromatic group (benzene ring) present at one end of the local anesthetic molecule is the major determinant of the lipid solubility of these drugs. Lipid solubility is measured by evaluating the solubility of the uncharged base form of the drug in an organic solvent. The significance of this property is based on the finding that the uncharged base form is soluble in and can pass through the lipid-containing nerve membrane to reach the local anesthetic site of action. Lipid solubility is associated in a nonlinear manner with the potency of the local anesthetics:[1] the more lipid-soluble drugs are the more potent local anesthetic drugs.

Clinically, local anesthetic potency appears to increase until a lipid partition coefficient of four is achieved. Additional increases above four are not associated with any increase in potency that can be measured by a change in anesthetic concentration required to produce equivalent blockade[1] (see Table 34A-1). This, in part, might be the result of

Table 34A-1 Physical properties and equipotent concentrations of local anesthetics

	Procaine	Lidocaine	Mepivacaine	Bupivacaine	Etidocaine	Ropivacaine
Molecular weight	236	234	246	288	276	274
pK_a	8.9	7.7	7.6	8.1	7.7	8.0
Lipidsolubility	1	4	1	30	140	2.8
Partition coefficient	0.02	2.9	0.8	28	141	9*
Protein binding	5	65	75	95	95	90-95
Equipotent conc %		2.0	1.5	0.5	1.0	0.75

*Estimated from data by Rosenberg PH, Kytta J, Alila A, et al, Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into N-heptane, rat sciatic nerve, and human extradural and subcutaneous fat, *Br J Anaesth* 58:310-314, 1986.

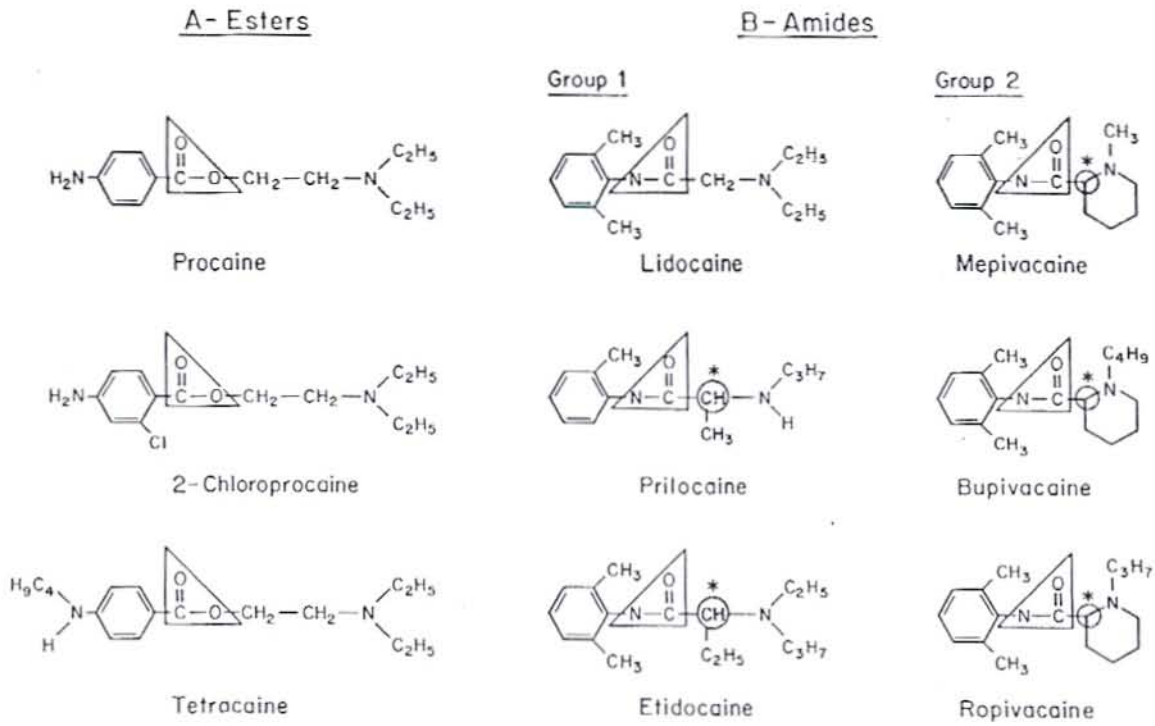

Fig. 34A-1 Local anesthetic structures with the ester and amide link shown within the superimposed triangle. When present, the asymmetric carbon is circled, shaded and marked with an "*."

increased uptake of local anesthetics with very high lipid solubilities into nonneural structures, such as fat and blood vessels in the area adjacent to the target nerves.[2] This uptake can be a major factor when large amounts of fat and blood vessels are present, such as in the epidural space. This effectively decreases the total amount of local anesthetic available for penetration into the nerve roots and, hence, limits further increases in potency with increases in lipid solubility. However, the conclusion remains that, over a wide range, the potency of each local anesthetic is directly related to its lipid solubility.

Ionization

At the end opposite the benzene ring, the local anesthetic molecules contain an amino group, and this group determines the hydrophilic activity and ionization of the molecule. This amino group can have from one to four alkyl substitutions; for local anesthetic molecules, three substitutions is the most common configuration (i.e., a tertiary amine). This amino group is capable of accepting a hydrogen ion (H^+), and in so doing converts the unionized base form of the drug into the cationic form of the drug (Fig. 34A-2). The proportion of each form (unionized base and cation) present is determined by the pK_a of the drug and the pH of the solution. The pK_a is defined as the pH at which 50% of the drug is ionized, and 50% is present as the free base. For a local anesthetic, the pK_a falls within a narrow range, 7.6 to 8.9. This relationship between pH, pK_a and concentration of the cation and base forms of the local anesthetic is described by the Henderson-Hasselbach equation:

$$pK_a = pH + \log [\text{cation/base}]$$

In local anesthetics, the coexistence of the two drug forms, the charged cation and the uncharged base form, is important: it is believed that the unionized (base) form penetrates the nerve membrane and the ionized (cation) form produces blockade of sodium ion movement through the sodium channel. Since local anesthetics have a pK_a greater than 7.6, at equilibrium these drugs exist predominantly in the cationic form at normal body pH. The closer the pK_a is to body pH, the greater is the fraction of drug present in its base form when it equilibrates with body fluids, thereby increasing the concentration of the membrane-crossing form surrounding the nerve.

With many local anesthetics the speed of onset

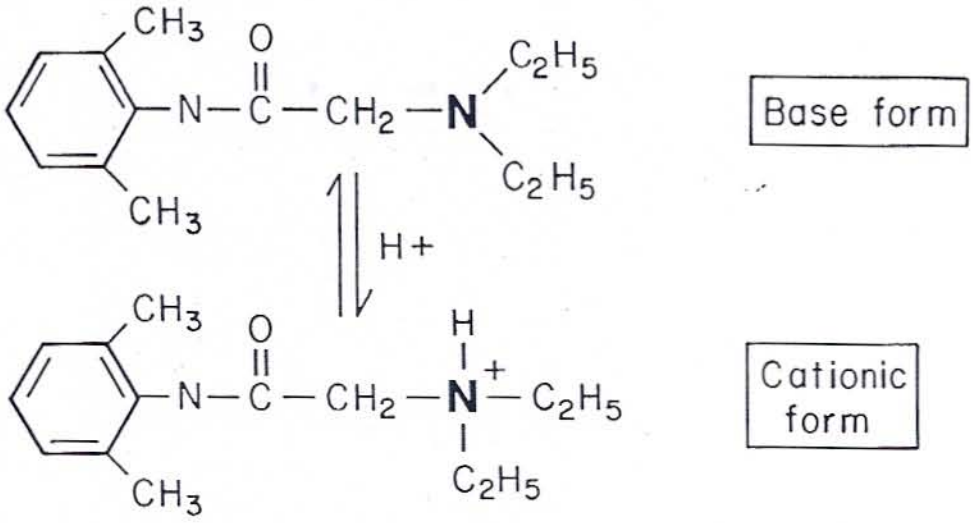

Fig. 34A-2 Equilibration of lidocaine into base and cationic forms.

can be related to the degree of difference between the pK_a of the drug and normal body pH. Additionally, since the pH of the solution injected dictates the amount of base form injected before buffering by the body, the pH can be a major factor affecting onset of action. Commercial preparations of local anesthetics are all considerably acidic in order to enhance solubility and stability.[3] The addition of bicarbonate to acidic local anesthetic solutions increases the pH of the solution injected to a value closer to that of body fluids. The use of bicarbonate represents an attempt to use knowledge of the physiochemistry of these agents to improve their efficacy—elevation of the pH shifts the equilibrium towards the unionized form that is necessary for nerve membrane penetration and thus shortens the onset time for anesthesia. Because the local anesthetic base has very little aqueous solubility, however, an excess amount of bicarbonate causes precipitation of the local anesthetic from solution. The clinical use of this pH adjustment is discussed further in a subsequent section.

As a general rule for chemically similar drugs, the lower the pK_a of the local anesthetic (i.e., the closer the pK_a is to body pH) the shorter the onset time for induction of anesthesia with the local anesthetic. As a corollary, the closer the pH of the solution injected is to body pH, the shorter the onset time.

Protein binding

Most local anesthetics exist in the body, most predominantly bound to proteins. These include plasma proteins as well as tissue proteins. It is important to note that anesthetics are not pharmacologically active while in their bound form, and thus the degree of protein binding has implications for the activity, toxicity, and metabolism of these drugs.

For local anesthetics the important binding proteins in plasma are albumin and $alpha_1$-acid glycoprotein. The binding to $alpha_1$-acid glycoprotein is characterized as a high-affinity, low-capacity binding, while the binding to albumin is characterized as a low-affinity, high-capacity binding.[4] Accordingly, local anesthetic binding to $alpha_1$-acid glycoprotein occurs preferentially compared to albumin, yet $alpha_1$-acid glycoprotein is easily saturated with clinically achieved blood levels of local anesthetics. As the plasma concentration of a local anesthetic increases, additional binding is to albumin. In contrast to the binding to $alpha_1$-acid glycoprotein, the binding capacity of albumin for local anesthetics is very large, and albumin is able to bind these drugs without saturation at plasma levels that are an order of magnitude greater than usually achieved clinically. Additionally, the binding of local anesthetics to proteins is concentration dependent and decreases in a curvilinear manner as the local anesthetic concentration in plasma increases[5] (Fig. 34A-3).

The clinical importance of this finding is that the potential for toxicity increases disproportionately with increases in plasma concentration. For example, the plasma level of lidocaine in adults following a typical epidural results in a plasma concentration of 2 to 3 mcg/ml. In general, the reported concentrations of local anesthetics represent the total amount of drug in plasma and include both bound and unbound drug. At 2 to 3 mcg/ml, lidocaine is 65% bound to protein, leaving a free (unbound) fraction of 35%. At serum

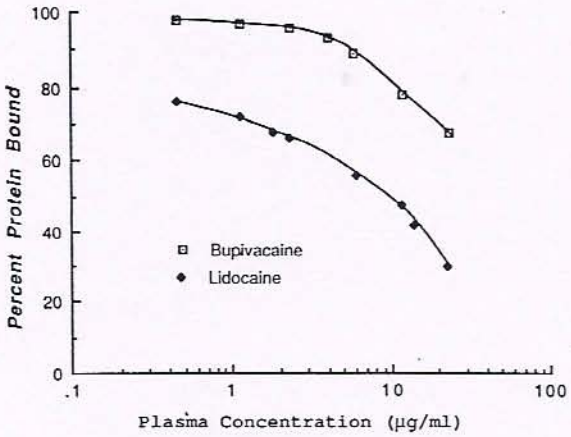

Fig. 34A-3 Protein binding of lidocaine and bupivacaine with increasing concentration of each drug in human plasma. (Adapted from the data of Tucker et al.[5])

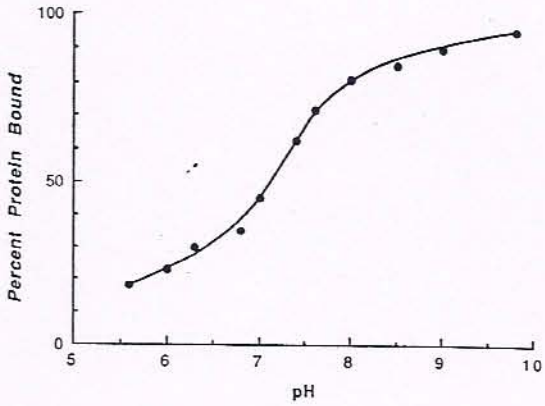

Fig. 34A-4 Protein binding of lidocaine as a function of pH in adult plasma.

levels of 20 mcg/ml, a level that might be achieved following a major intravascular injection, the bound fraction decreases to 30% and the free fraction increases to 70%. In the above example, the amount of free, biologically active lidocaine at a serum concentration of 3 mcg/ml is approximately 1 mcg/ml; while at 20 mcg/ml, the amount of free, biologically active lidocaine increases to 14 mcg/ml. Thus, a sixfold to sevenfold increase in the total plasma lidocaine concentration results in a 14-fold increase in the active form of the drug in the plasma. Therefore, when speaking of protein binding of a particular local anesthetic, the clinician needs to specify the plasma concentration at which the binding was measured.

Protein binding of local anesthetics is also influenced by the pH of the plasma in that the percentage of bound drug decreases as pH decreases. The practical importance of this is that, with the development of acidosis, the amount of free drug increases (Fig. 34A-4). For example, in the adult, lidocaine at pH 7.4 at a concentration of 5 to 10 mcg/ml is 50% bound. However, with a decrease in plasma pH to 7.0, the drug is 35% bound; so that while the total drug concentration in plasma remains the same, the free, active drug concentration increases almost 50% with this change in pH.[6,7] Acidosis, therefore, should be regarded as potentiating the toxicity of local anesthetics by increasing the fraction of the active form of the drug in the circulation and at the active site.

Protein binding of local anesthetics is decreased in newborns and pregnant women,[8,9,10] primarily because of changes in plasma alpha$_1$-acid glycoprotein levels that are age and pregnancy related. For instance, premature infants have approximately one half of the alpha$_1$-acid glycoprotein present in newborns; newborn levels of alpha$_1$-acid glycoprotein increase three to four times by adulthood. Pregnant patients at term have approximately one half of the alpha$_1$-acid glycoprotein levels seen in nonpregnant controls and, therefore, pregnancy results in an increase in the free fraction of local anesthetic. Likewise, in the elderly, alpha$_1$-acid glycoprotein has been found to be decreased, a situation that may thus increase susceptibility to the toxicity of local anesthetics.

Aside from affecting toxicity, the fraction of drug bound to protein in plasma also correlates with duration of local anesthetic activity. Therefore, bupivacaine and etidocaine (95% bound) are longer lasting than ropivacaine (90% to 95% bound), which in turn is longer lasting than mepivacaine (75% bound), which is longer than lidocaine (65% bound), which in turn is longer acting than procaine and 2-chloroprocaine (5% bound). One might thus speculate on a possible similarity between the binding of the local anesthetic molecule to plasma proteins and binding to the receptor protein in the sodium channel.

Chiral forms

An area of newfound importance for anesthesiologists is in the identification of the *stereoisomers* of the drugs in clinical use. Stereoisomers of the local anesthetics etidocaine, mepivacaine, bupivacaine, prilocaine, and ropivacaine have been recognized; and some evaluation of the potency and toxicity of these drugs has been completed. For stereoisomerism to be present, an asymmetric carbon atom must be present in the molecule. In the local anesthetics described above, the asymmetric carbons are indicated in Fig. 34A-1. In

Table 34A-2 Anesthetic duration and toxicity of local anesthetic isomers

Drug	Duration	Toxicity
Etidocaine	S = R	S = R
Mepivacaine	S > R	S = R
Bupivacaine	S > R	S < R
Ropivacaine	S > R	S < R

the older literature, the isomers were described as *"L"* and *"D"* on the basis of chemical configurations and a *(+)* or *(−)* on the basis of optical rotation i.e., *L(+)* or *L(−)* and *D(+)* and *D(−)*. More recent literature describes these isomers as "R" and "S," and the optical rotation is still included in the parentheses. The *R* and *S* correspond respectively to *D* and *L* in the older nomenclature. The observations on the activity and toxicity of the chiral forms are summarized in Table 34A-2. For etidocaine, little difference in activity or toxicity has been observed for the two respective isomers; while for mepivacaine a longer duration of infiltration anesthesia was produced with the *S* isomer than with the *R* isomer, and little difference in toxicity between the isomers was observed. With bupivacaine, infiltration anesthesia was also of longer duration with the *S* isomer; yet, in contrast with mepivacaine, the *S* isomer had lower systemic toxicity when compared to the *R* isomer.[11,12] The mean convulsant dose of *R* bupivacaine was 57% that of *S* bupivacaine. When the isomers of ropivacaine were evaluated, the *S* isomer of the drug was found to have a longer duration of blockade with similar doses of drug and yet to have lower toxicity than its *R* form.[13] Additionally, in animal studies, when cardiac electrophysiologic toxicity was evaluated, ropivacaine, which is the *S* form of drug, at equipotent nerve blocking doses appears to have a safety margin that is almost twice that of commercial bupivacaine, which is a mixture of *R* and *S* isomers.

As a general rule, when differences between the isomers are present for the local anesthetics evaluated, the *S* form is less toxic and has a longer duration of anesthesia.

HOW AND WHERE OF LOCAL ANESTHETIC ACTION

Stimulation of a nerve results in a propagated impulse that passes along the course of the nerve from the peripheral site of stimulation to the central nervous system (CNS), where perception of the stimulus takes place. The electrical signal in excitable nerve tissue is the result of propagated ionic currents that are created by a transient alteration in the concentration gradient across the nerve cell membrane for several ionic species. The ionic concentration of sodium (Na+) is large extracellularly and low intracellularly, while that of potassium (K+) is large intracellularly and low extracellularly. The resting potential for the nerve is about −90 mV and is largely the result of a steady leak of potassium ions from the cell (potassium conductance), which at rest is much larger than the leak of sodium into the cell (sodium conductance). This ionic gradient of sodium and potassium across the cell membrane is maintained by an ion-translocating, sodium-potassium, ATP pump mechanism within the nerve.

Using voltage clamp studies, the initial upswing of an action potential associated with a nerve impulse was found to be caused by an increase in permeability of the nerve membrane to sodium ions, with the resultant inward movement of sodium ions through specific channels in the cell membrane. The initial stimulus that leads to an action potential causes a voltage-dependent sodium channel to open in the membrane, allows sodium ions to move intracellularly, and results in depolarization of the nerve in the area of the open channels as the negative intracellular charge is reversed by the entry of positively charged sodium ions. Several investigators have postulated that the action potential causes a confirmational change in the nerve membrane lipoprotein, and this change results in the actual opening of the sodium channel gate, which consists of two proteins designated as the *"m"* and *"h"* gating proteins. The sodium channel, because of size and charge, is in large part ion specific. The suprathreshold action potential of an impulse ends with the closure of the sodium channel. The depolarization spreads to adjacent membrane areas that, in turn, reach threshold voltage and propagate the action potential. Potassium ion outflow in the area of depolarization commences slower and later and peaks after the inward movement of sodium ions subsides; both ions are subsequently restored to their initial intra- and extracellular concentrations by the sodium-potassium, ATP-dependent pump mechanisms (Fig. 34A-5).

The local anesthetic drugs prevent the development of the action potential in a nerve by preventing sodium ions from moving intracellularly through the sodium channels. The anesthesia that results has been referred to as *membrane stabilization*, because the resting membrane potential is unaffected by further nerve stimulation.

For commonly used local anesthetic drugs, the ester- and amide-type local anesthetics, drug binding occurs *within* the sodium channel after

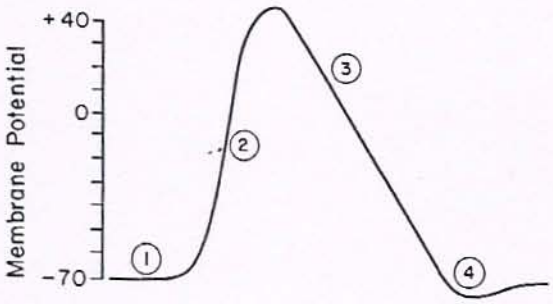

Fig. 34A-5 Nerve membrane action potential and associated sodium and potassium ionic events in relation to sodium channels changes. The numbered times include (1) resting membrane; (2) depolarization (sodium channel open); (3) repolarization (sodium channel closed); (4) reequilibration of sodium and potassium.

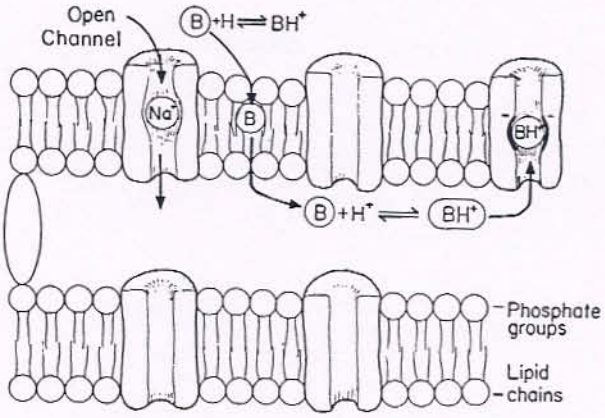

Fig. 34A-6 Local anesthetic movement and equilibration of local anesthetic forms across the nerve membrane and into the sodium channel. B, base; cation, BH^+.

the drug enters the channel from the axoplasmic (intracellular) side of the nerve membrane (Fig. 34A-6). These local anesthetics are believed to penetrate the lipid bilayer structure of the cell membrane in their lipid-soluble, uncharged free base form and to then reequilibrate in the axoplasm of the nerve into the charged cationic and uncharged, free base forms in accordance with the drug pK_a and the pH of the axoplasm. The cationic form of the drug then enters the sodium channel from the intracellular side of the nerve membrane, binds to an anionic site within the sodium channel, and physically or ionically blocks sodium ion movements. Hille has referred to this as the hydrophilic pathway for the action of local anesthetics.[14]

LOCAL ANESTHETIC BLOOD LEVELS AND TOXICITY

After administration for neural blockade, local anesthetics either enter the nerve, are absorbed into the systemic circulation, or enter into fat surrounding the nerves. The resulting blood levels for these drugs at any particular time is the summation of factors including: (1) the dose of the drug administered; (2) the absorption of the drug from the site injected, which depends on the chemical properties of the drug, site vascularity, vasoactivity of the local anesthetic, and whether a vasoconstrictor has been added to the administered anesthetic solution; and (3) the biotransformation and elimination of the drug from the circulation.

Local anesthetics develop a peak blood level that is directly related to the dose administered at a given site. Doubling of the dose approximately doubles the blood level achieved. Administration of a given dose of drug, however, at different sites of injection results in different peak blood levels. As previously noted these differences in blood levels are the result of differences in the vascularity of the site injected and the vasoactivity of various concentrations of the local anesthetic used. As a general rule of thumb, using lidocaine as an example, a 1-mg/kg dose given as an epidural or caudal results in approximately a 1-μg/ml peak blood level. When this dose (1 mg/kg) is used in less vascular areas, such as for a brachial plexus block using an axillary approach, or when the drug is administered for subcutaneous infiltration, a peak blood level of approximately 0.5 μg/ml occurs. In contrast, when lidocaine (1 mg/kg) is injected into a highly vascular area, such as for an intercostal block, a 1.5 μg/ml peak blood level occurs (Fig. 34A-7). Peak blood lev-

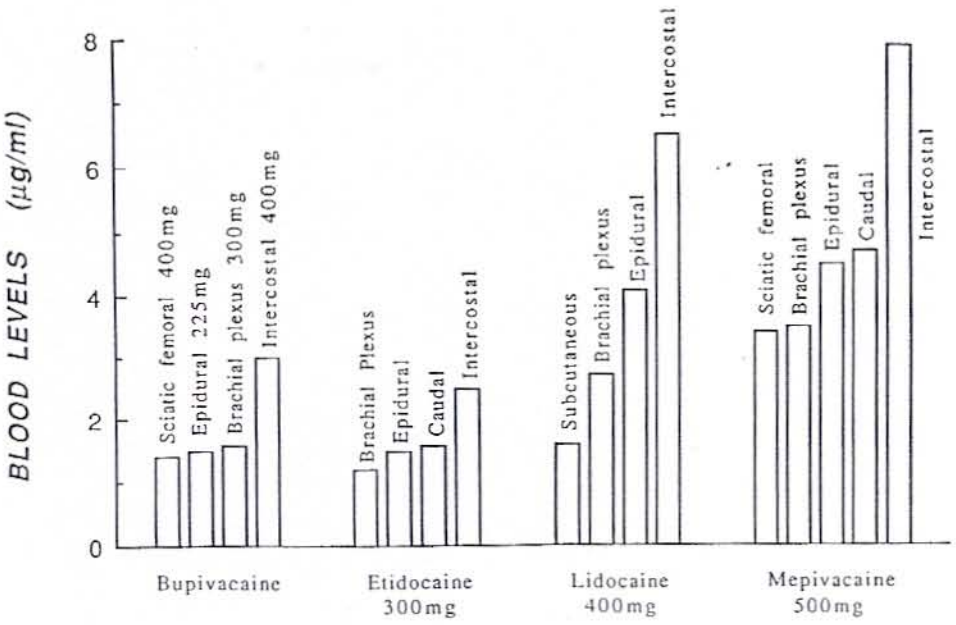

Fig. 34A-7 Peak local anesthetic blood levels seen with various blocks and doses of drug.

els following injection into extravascular sites, such as the brachial plexus, epidural space, and intercostal region, may occur from 10 to 30 minutes after administration.

Peak blood levels of the drug achieved are also affected by the rate at which the local anesthetic drug undergoes biotransformation and elimination. For the amide local anesthetics such as lidocaine, this effect is small. While 70% of lidocaine presented to the liver undergoes hepatic extraction, this is limited by hepatic blood flow and the relatively low concentration in plasma. For example, after an epidural anesthetic in which 300 mg of lidocaine is administered, peak blood levels of approximately 3 mcg/ml in a total blood volume of 5L result in 15 mg of lidocaine in the intravascular compartment. Thus, since only a fraction of the cardiac output goes to the liver, one can estimate that 3 mg of lidocaine are presented to the liver each minute, and 2 mg of this are extracted and metabolized. Thus, in 90 minutes, the elimination half-life of lidocaine, one could expect that a maximum of 180 mg would be metabolized. However, since the blood levels decline as metabolism occurs, less and less lidocaine is presented to the liver during subsequent time periods, so this is an overestimation. Of the 300 mg of lidocaine initially deposited in the epidural space, only a small fraction is taken up by nerve tissue. The fate of the majority of the lidocaine is absorption into the bloodstream and then redistribution to other tissue (brain, muscle, heart, etc.) and, for that portion going to the liver, biotransformation and, ultimately, elimination of metabolites by the kidney. Renal excretion of lidocaine contributes little to the overall removal of unchanged lidocaine, with only 3% to 5% of the injected dose of drug being excreted by the kidney in a 24-hour period.

By contrast, for very actively metabolized drugs such as 2-chloroprocaine, which has a plasma half-life of approximately 45 seconds, biotransformation is the primary determinant of the very low plasma levels that occur. The distribution and elimination half-life, along with other important pharmacokinetic values for the local anesthetics, are shown in Table 34A-3. As a general rule, the blood levels seen with lidocaine in the previous example for a 1-mg/kg dose represent the highest values achieved for the amide local anesthetics. Using the same rule of thumb for the other amide local anesthetics results in an approximation that consistently overestimates the plasma drug concentration (see Fig. 34A-7).

Knowledge of expected local anesthetic blood levels following various routes of administration is important, since systemic toxicity is correlated with blood levels. For lidocaine, blood levels of 1 to 5 μg/ml are considered therapeutic in the treatment of cardiac arrhythmias and as a supplement to general anesthesia. With blood levels of 3 to 5 μg/ml, systemic symptoms include circumoral numbness and buzzing or ringing in the ears. The effects of lidocaine on the brain are paradoxical:

Table 34A-3 Pharmacokinetic parameters of local anesthetics in adults

	Elimination half-life ($T_{1/2b}$) (min)	Volume distribution $(V_D)_{ss}$ (liters)	Clearance (Cl) (liters/min)	Hepatic extraction
Lidocaine	96	91	1.0	0.7
Bupivacaine	162	73	0.6	0.4
Mepivacaine	114	84	0.8	0.5
Etidocaine	162	73	1.1	0.4

at these low blood levels it is an anticonvulsant, whereas at elevated blood levels the drug produces seizures. In humans, blood levels of lidocaine associated with seizures appear to be in the 10- to 12-μg/ml range. At these blood levels, inhibitory pathways in the brain are selectively blocked, which in turn allows facilitory neurons to function unopposed. The seizures that result appear to originate in the amygdala and the hippocampus.[15] With lidocaine, the signs and symptoms that appear before the onset of seizures usually include slow speech, jerky movements, tremors, and hallucinations. While these symptoms are helpful as a prodrome in identifying lidocaine CNS toxicity, these findings are less frequently seen when other local anesthetics approach their seizure threshold. As the peak blood level of the local anesthetic is further increased, cardiac toxicity from these drugs becomes a concern. Lidocaine levels above 20 to 25 μg/ml are necessary for cardiac toxicity. By contrast, for bupivacaine, blood levels of approximately 4 μg/ml result in seizures; blood levels of approximately 6 μg/ml are associated with cardiac toxicity.

Treatment of local anesthetic seizures consists primarily of preventing the detrimental effects of hypoxia. Therefore, the primary concern should be adequate ventilation with 100% oxygen. Secondarily, suppression of seizures can be achieved by raising the seizure threshold of the CNS with an intravenous (IV) dose of either thiopental (50 to 100 mg) or a benzodiazepine such as midazolam (1 to 2 mg) or diazepam (5 to 10 mg).[16] Cardiac output and cerebral blood flow are increased during seizure activity; hence, high brain levels of local anesthetics will rapidly dissipate with redistribution of the drug to other tissue compartments. However, if local anesthetic levels are high enough to cause significant cardiotoxicity, then cardiac output is greatly diminished and redistribution delayed. The use of thiopental in this situation is of concern, since it may further depress myocardial function and should be administered judiciously, if at all. Patients with severe toxicity warrant tracheal intubation, and succinylcholine can be used primarily to facilitate intubation. An additional benefit of muscle paralysis with succinylcholine is that termination of the tonic clonic muscle activity associated with a seizure will prevent further contribution to any acidosis from increased muscle activity. Failure to stop the seizure activity at the earliest possible moment leads to progressive acidosis that, in turn, can further potentiate toxicity of the local anesthetic by decreasing the fraction of the drug bound to protein and thus creating more unbound (free), active drug.

For all of the local anesthetics, CNS toxicity in the form of seizures occurs at a lower blood level than cardiac toxicity consisting of ventricular arrhythmias and possibly circulatory collapse. Concern by anesthesiologists about the cardiac toxicity of the long-acting local anesthetic drugs such as bupivacaine and etidocaine followed a number of reports of maternal cardiac arrest with difficult and often unsuccessful resuscitations.[17] In all cases, the patients apparently had excessively high blood levels of local anesthetic from an unintended intravascular injection of a large amount of drug during administration of epidural anesthesia. In other cases not involving parturients, cardiac toxicity has been preceded by the premature release of a tourniquet during IV regional anesthesia.

Numerous animal studies have subsequently provided an insight into the cardiotoxicity of the different local anesthetic agents. All local anesthetics have been observed to cause a dose-dependent depression of contractility of cardiac muscle. This cardiodepressant effect on contractility parallels the anesthetic potency of the local anesthetic in blocking peripheral nerves. Therefore, bupivacaine, which is four times more potent than lidocaine in blocking peripheral nerves, is also four times more cardiodepressant with respect to contractility.[18] However, cases of death with bupivacaine overdoses have been characterized by a progressive prolongation of ventricular conduction, evidenced by a widened QRS complex, which is followed by the sudden onset of ventricular fibrillation. It has been theorized that the delay in ventricular conduction predisposes to reen-

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trant phenomena leading to ventricular dysrhythmias. Experimental studies have shown that all local anesthetics produce a dose-dependent depression of conduction velocity in cardiac tissue, including intraatrial, A-V nodal, His-Purkinje, and intraventricular pathways. When the potential for producing this electrophysiologic toxicity has been evaluated, bupivacaine has been shown to be approximately 16 times more toxic than lidocaine.[19] Therefore, this effect is out of proportion to the anesthetic potency of the drug in blocking peripheral nerve conduction. In a recent study evaluating the new local anesthetic ropivacaine, bupivacaine was found to be approximately two times more toxic than ropivacaine, while bupivacaine's nerve blocking potential was essentially the same as ropivacaine.[20]

In vitro studies have demonstrated that local anesthetics block cardiac sodium channels as well as cardiac calcium channels and that the blockade of these channels is better tolerated for lidocaine than for bupivacaine. The best current explanation for the differences in toxicity of these agents has been given by Clarkson and Hondegham,[21] who demonstrated that with depolarization, lidocaine rapidly enters and leaves the open cardiac channels and thus has little cardiac blocking effect at slow or normal heart rates. This is described as a fast-in, fast-out effect. In contrast, bupivacaine also rapidly enters the channel but, because of differences in binding, is slow to leave and has been classified as a fast-in, slow-out local anesthetic. Thus, bupivacaine strongly blocks inactivated open cardiac channels, while not allowing for recovery during diastole. This leads to susceptibility to reentrant dysrhythmias and possible ventricular fibrillation.

Some investigators have also speculated that cardiac dysrhythmias may be mediated by local anesthetic effects on the CNS.[22,23] This is based on animal studies in which the local anesthetic was infused directly into the ventricles of the brain, and cardiac arrhythmias occurred. This was observed to be more common when bupivacaine rather than lidocaine was used. While the CNS effects cannot be excluded, these effects are not likely to be the primary event in the production of arrhythmias. In a separate study using an animal model in which the local anesthetic was injected directly into the left anterior descending coronary artery (LAD), the direct effects of various drugs upon the left ventricle were evaluated. Independent of the CNS effects, local anesthetics administered in the LAD caused slowing of ventricular conduction and, with sufficient doses, produced ventricular fibrillation.[24]

Increases in cardiac toxicity of local anesthetics can also be further enhanced by the presence of acidosis, hypoxia, hypercarbia, or hyperkalemia. The administration of bupivacaine in these situations causes a marked depression of cardiac function.[25-27] Acidosis contributes to increased toxicity by affecting both ionization and protein binding of the local anesthetic. As discussed previously, acidosis decreases the protein binding of local anesthetic, which in turn increases the free (active) fraction of the drug. Acidosis also shifts the equilibrium towards the ionized form, which has a dual effect on toxicity. In the case of an accidental intravascular injection, a rapid rise in the blood concentration occurs, which leads to rapid movement of the local anesthetic into neural and cardiac cells. When the brain levels are sufficiently high, seizures occur. Secondarily, a resultant combined metabolic and respiratory acidosis results and leads to a rapid decrease in pH; changes from normal to a pH below 7.0 in less than 2 minutes have been described.[28] The fall in intracellular pH increases the intracellular concentration of the ionized, active form at the expense of the free base form of the drug initially present, thus producing a greater effect at the intracellular receptor site. An additional effect of the acidosis is that transmembrane passage is impaired and intracellular levels tend to remain higher. In addition to effects on protein binding and ionization, acidosis may have direct membrane effects and thus alter cell permeability to various ions.

With major overdoses of bupivacaine, a clinical picture of cardiovascular collapse may result in which drug-induced myocardial depression is accompanied by systemic vasodilatation and extreme hypotension. It is unlikely that this vasodilatation is the result of the circulating local anesthetic, since in animal studies these agents have been shown to produce vasoconstriction at the concentrations associated with clinical toxicity; vasodilatation did not occur until the concentrations used were several orders of magnitude higher.[29] It is more likely that the peripheral vasodilatation is caused by severe hypoxia and acidosis, making it all the more important to take action to reverse these physiological derangements as rapidly as possible, which includes adequate ventilation, seizure termination, fluid support, vasopressor therapy, antiarrhythmia therapy (i.e., with bretylium[29a] or magnesium sulfate [29b]), and inotropic support of the myocardium in extreme cases.

Cardiotoxicity of the long-acting agents may also be increased in the pregnant patient. Significantly lower doses of bupivacaine are required to produce cardiovascular collapse in pregnant, compared to nonpregnant, sheep. This may be the result of a reduced fraction of bupivacaine that is

protein bound during pregnancy. Approximately 50% of bupivacaine is bound to proteins in pregnant sheep at serum concentrations associated with cardiovascular collapse, compared to a bound fraction of 66% in nonpregnant animals at this same concentration. This results in a mean dose required to produce cardiotoxicity that is significantly lower (5.1 mg/kg) in pregnant animals compared to nonpregnant animals (8.9 mg/kg).[30] Despite the difference in dose, tissue levels of bupivicaine were essentially the same in both groups at the point of circulating collapse. It can be speculated that the increased toxicity may be a function of a decrease in protein binding with an increased fraction of free drug during pregnancy, as previously discussed. In addition, hormonally induced alterations in neural sensitivity,[31] membrane permeability,[32] or cardiac sensitivity may contribute to the increased risk for toxicity in pregnant patients.[33]

BIOTRANSFORMATION AND ELIMINATION

An ester or amide linkage is present between the lipophilic (benzene ring) and the hydrophilic (amide) ends of the drug molecule. The type of link present (ester or amide) determines the site of metabolic inactivation of the drug (see Fig. 34A-1). The ester-linked local anesthetics are inactivated predominantly in plasma, while the amide-linked drugs undergo inactivation in the liver.

Ester-linked local anesthetics are hydrolyzed at the ester link in plasma by plasma pseudocholinesterase. This plasma enzyme also hydrolyzes natural choline esters and succinylcholine. The rate of hydrolysis of ester-linked local anesthetics depends on the type and location of the substitutions present in the aromatic ring structure, with 2-chloroprocaine being hydrolyzed about four times faster than procaine, which in turn is hydrolyzed about four times faster than tetracaine. In the case of 2-chloroprocaine, the half-life in the normal adult is approximately 45 seconds. In individuals with atypical plasma pseudocholinesterase, the rate of hydrolysis of the ester-linked local anesthetics is markedly decreased, and a prolonged half-life of these drugs results. Therefore, while the potential for toxicity from accumulation of the ester-linked local anesthetics such as 2-chloroprocaine in plasma is extremely remote in normal individuals, this likelihood should be considered in the administration of large or repeated doses of this drug to individuals with atypical pseudocholinesterase enzyme.[34] The hydrolysis of all ester-linked local anesthetics leads to the formation of para-amino benzoic acid (PABA) or a substituted PABA. PABA and its derivatives are associated with a low but real potential for an allergic reaction.

The amide-linked local anesthetics, however, need to be transported by the circulation to the liver before biotransformation can occur. The two major factors controlling the clearance of amide-linked local anesthetics by the liver are hepatic blood flow (delivery of drug to the liver) and hepatic function (drug extraction by the liver). Factors that decrease hepatic blood flow or hepatic drug extraction result in an increased elimination half-life. Drugs such as general anesthetics, norepinephrine, cimetidine, propranalol, and calcium channel blockers (e.g., diltiazem) all can decrease hepatic blood flow and increase the elimination half-life of amide local anesthetics. In a similar manner, decreases in hepatic function caused by a lowering of body temperature, immaturity of the hepatic enzyme system, or liver damage, such as in cirrhosis, lead to a decrease in the rate of hepatic metabolism of amide local anesthetics. The hepatic extraction ratio, clearance, and elimination half-life for these local anesthetics for the normal adult are presented in Table 34A-3.

Renal clearance of unchanged lidocaine in the adult is small (3% to 5% of the total dose administered). For bupivacaine, the renal excretion of unchanged drug may approach 16% of the administered dose.

Once taken up from the circulation by the liver, the primary biotransformation step for lidocaine is a dealkalization reaction in which an ethyl group is cleaved from the tertiary amino group. For bupivacaine, dealkalization removes a butyl group from this amino terminus. Subsequent metabolic reactions include hydrolysis of the amide linkage and/or oxidation of the benzene ring. The metabolites formed are cleared by the kidney as unchanged or conjugated compounds.

CLINICAL APPLICATIONS TO IMPROVE SAFETY

Systemic toxicity is directly related to blood levels of local anesthetics. The potential for producing systemic toxicity can be markedly reduced in the clinical situation by careful attention to the following details:

1. Select a dose that should be associated with clinically safe blood levels based on the site of injection. As a general rule, the maximum drug dose administered should be selected so that the peak blood concentration that is achieved does not exceed one half to two thirds of the convulsant blood level. Suggested maximum doses are indicated in Table 34A-4.

Table 34A-4 Comparable safe doses of local anesthetics (mg/kg)*

Drugs	Areas Injected			
	Peripheral blocks‡	Central blocks‡		Intercostal blocks§ with Epi 1:200,000
		Plain	With Epi 1:200,000	
2-Chloroprocaine	—	20	25	—
Procaine	—	14	18	—
Lidocaine	20	7	9	6
Mepivacaine	20	7	9	6
Bupivacaine	5	2	2	2
Tetracaine	—	2	2	—

*Estimated to produce peak plasma levels that are less than half the plasma levels at which seizures could occur.
†Areas of moderate vascularity (i.e., caudal epidural blocks).
‡Areas of low vascularity (i.e., axillary blocks using local anesthetic solutions containing 1:200,000 epinephrine).
§Areas of high vascularity (i.e., intercostal blocks using local anesthetic solutions containing 1:200,000 epinephrine).

2. Administer the dose of drug in a manner that identifies an unintended intravascular injection while minimizing the volume of drug injected. This is achieved by adhering to the practice of *fractionating* the dose of local anesthetic, aspirating frequently during injection, and maintaining verbal contact with the patient. The latter is essential in order to identify early subjective sensations, such as circumoral tingling and ringing in the ears, which are the first manifestations associated with an unintentional intravascular injection of local anesthetic. The addition of epinephrine in a 1:200,000 concentration to a small test dose also has been advocated to allow for the more rapid recognition of intravascular injections. An alternative agent that has been proposed is isoproterenol. The potential advantage it offers, compared to epinephrine is that it has a greater specific chronotropic (Beta 1) effect without the alpha-adrenergic activity of epinephrine. Another suggested method for detecting intravascular entry is injection of a tiny aliquot of air coupled with a precordial Doppler device.[33a]

SELECTION OF LOCAL ANESTHETICS

Choosing a specific local anesthetic for a given regional block ultimately depends on identifying the following factors:

1. Duration of anesthesia needed
2. The need for motor blockade
3. Onset of action

The drugs from which the anesthesiologist can choose include the ester-derived drugs such as procaine, 2-chloroprocaine, and tetracaine or the amide-derived drugs such as lidocaine, bupivacaine, etidocaine, and mepivacaine. In the near future, ropivacaine will probably be added to this list. The following describes some characteristics of the individual drugs that influence this decision.

Procaine

This agent was the first synthetic local anesthetic developed. Procaine has a slow onset and short duration of action and is described as being a relatively low-potency local anesthetic. Clinical observation of this drug has shown that it penetrates tissue barriers poorly, and thus results in a high incidence of unsuccessful blocks. In general, the low potency and rapid metabolism of this drug lead to the conclusion that procaine has low systemic toxicity.

The metabolism of procaine produces as an intermediary hydrolytic product, PABA, which has significant allergenic potential and is felt to contribute to the allergic response to procaine. At present, the drug is infrequently used. It does produce a differential spinal block and has been used for diagnostic purposes in pain centers.

2-Chloroprocaine

This drug is the 2-chloro derivative of procaine and has been noted to have a rapid onset of action and a short duration of activity (30 to 60 minutes). This drug is rapidly metabolized in plasma, with a half-life of approximately 45 seconds, and because of this extremely rapid breakdown has a low potential for systemic toxicity. On this basis, it is particularly attractive to obstetric anesthesiologists whose patients have a greater risk for toxicity and the additional complication of a fetus who is dependent upon maternal well-being. This

drug is also used for peripheral blocks in an ambulatory surgery setting, where anesthesia for only 30 to 60 minutes is needed, and rapid recovery is highly desirous.

The epidural use of this drug, however, has been limited in the past because of reports of prolonged and profound motor and sensory deficits that occurred with the unintentional subarachnoid injection of the 2-chloroprocaine commercial preparation containing the preservative bisulfite. Extensive classic work by Gissen demonstrated that bisulfite in the presence of a highly acidic solution releases SO_2, which in turn can form the neurotoxic sulfurous acid.[35] Gissen postulated that injection of the acidic commercial 2-chloroprocaine solution into the spinal sac resulted in a prolonged exposure to sulfurous acid. More recently, a new preparation has been released in which the bisulfite is removed and EDTA substituted. This change has not been totally satisfactory, as there appears to be an infrequent occurrence of spasm of the back muscles following epidural application of this new preparation, which may relate to the EDTA binding calcium in the paraspinous muscles.[36]

Tetracaine

This drug is the butyl amino benzoic acid derivative of procaine. Tetracaine is a potent, long-acting local anesthetic and has been used mainly for spinal anesthesia in a dose of 6 to 15 mg. The drug produces a high degree of motor-blockade that may outlast the sensory blockade. Although tetracaine has been used as a 0.2% to 0.5% solution for epidural anesthesia, it is not considered adequate for this purpose because of its slow onset of action and the tendency to produce a sensory anesthetic pattern that is spotty.

Lidocaine

Lidocaine was the first of the amide-derived local anesthetics to be clinically introduced. This drug is probably the most versatile local anesthetic available and as such is the most commonly used. Lidocaine has excellent tissue penetration and produces a rapid onset of anesthesia that is of intermediate duration (1 to 2 hours). The addition of epinephrine has been shown to improve the quality of the block and to decrease the absorption of lidocaine from the site injected. In addition, the duration of anesthesia at most sites can be markedly prolonged by the addition of epinephrine. For instance, an 80% to 90% increase in the duration of brachial blockade and epidural blockade has been observed when epinephrine is added. The drug has fair to poor motor-sensory separation, which means that sensory anesthesia cannot reliably be produced without significant motor blockade. In contrast to some other local anesthetics, lidocaine is also efficacious as a topical anesthetic when applied to mucous membranes and is used in 4% and 10% concentrations, particularly in the upper airway.

Mepivacaine

This drug is very similar to lidocaine in anesthetic activity and toxicity in that it has a rapid onset of action and produces anesthesia of intermediate duration. The duration of action of mepivacaine is somewhat longer than lidocaine without epinephrine. The addition of epinephrine will also prolong the duration of action of mepivacaine by 75% to 85% when used for brachial plexus blockade or for epidural anesthesia. This drug is poorly metabolized in the liver by the fetus, which can result in prolonged blood levels in the neonate for several days following maternal regional anesthesia with mepivacaine. It, therefore, is infrequently used for obstetrical anesthesia. As a further contrast to lidocaine, mepivacaine is not effective topically.

Bupivacaine

This drug was developed from mepivacaine, and the structural similarities with mepivacaine are readily apparent from Fig. 34A-1. Bupivacaine has made a contribution to regional anesthesia second in importance only to lidocaine; it is one of the first clinically used drugs that provides good separation of motor and sensory anesthesia following its application. The onset of anesthesia is slow, but the duration of action is long and can be further prolonged by the addition of epinephrine. A 50% increase in duration of brachial plexus blockade following the addition of epinephrine to the bupivacaine solution has been noted, although an occasional patient has been noted to have a significantly longer blockade. In contrast, only a 10% to 15% increase in the duration of epidural anesthesia results from the addition of epinephrine to epidural bupivacaine solutions.

The major use of bupivacaine in this country has been in obstetrical anesthesia, where analgesia without significant motor blockade is highly desirable. Similarly, the drug is being increasingly used for postoperative analgesia because of this motor-sensory separation. The hepatic enzyme systems for the metabolism of bupivacaine are present in the fetus, and active biotransformation is present, although at a somewhat slower rate than in adults. Bupivacaine has been noted to produce a higher incidence of cardiotoxic effects and has been noted to have a poorer therapeutic

index than lidocaine in producing electrophysiologic toxicity of the heart, as previously discussed.

Bupivacaine is now also being extensively used for subarachnoid anesthesia. In this context, it produces very reliable onset of anesthesia within 5 minutes and a duration of anesthesia that is approximately 3 hours. In many ways, it is similar to tetracaine, and the dose relationship is such that 10 mg of tetracaine is approximately equal to 12 to 15 mg of bupivacaine. The onset of sympathetic blockade following spinal anesthesia appears to be more gradual with bupivacaine than with tetracaine. Also, the sensory blockade produced by bupivacaine lasts longer than the motor blockade, in contrast to tetracaine. The drug can be used for subarachnoid anesthesia in either a glucose-containing hyperbaric solution (0.75%) or in an isobaric solution (the drug packaged for epidural use) in a 0.5% concentration.

Etidocaine

This drug is structurally similar to lidocaine (Fig. 34A-1) and has been observed to have a very rapid onset of action, while producing prolonged duration of anesthesia. Etidocaine produces profound motor and sensory blockade with the clinically used concentrations of the drug, thus making etidocaine unacceptable for obstetrical analgesia where motor blockade is undesirable. In addition, motor blockade has been observed in many instances to far outlast sensory blockade and may contribute to postoperative patient anxiety. Some practitioners, in longer cases, have taken advantage of the rapid onset associated with etidocaine by using it to induce epidural anesthesia, and then using bupivacaine or lidocaine for subsequent doses to maintain an adequate sensory level without undue prolongation of the motor block. The addition of epinephrine to etidocaine solutions produces a 50% increase in duration of brachial plexus blockade, while producing only a 10% to 15% increase in epidural duration.

LOCAL ANESTHETIC ALLERGY

A common problem faced by the clinician is the report by patients that they are allergic to local anesthetics. Unfortunately, most of these patients are then subjected to a lifetime of inconvenience because this diagnosis more likely than not was incorrectly established. It is estimated that less than 1% of all adverse reactions to local anesthetics are actually due to true allergic reactions, and the balance more likely had one of the previously described pharmacologic responses to circulating local anesthetics or epinephrine.

Allergic reactions to ester-linked local anesthetics and to the metabolic products of ester-linked drugs, namely PABA, are known and need to be carefully considered.[37] Additionally, any multidose vial of drug including amide-linked local anesthetics very likely contains PABA as a preservative, and thus presents a risk of producing an allergic reaction. True allergic reactions to amide-linked local anesthetics in preservative-free vials are extremely rare, to the point of being essentially nonexistent.[38] Furthermore, no evidence is available to suggest that cross-sensitivity between local anesthetics in similar or different chemical families occurs. Therefore, patients allergic to ester local anesthetics could receive amide local anesthetics; however, careful attention to the use of a preservative-free solution is essential.

MODIFICATION OF LOCAL ANESTHETIC ONSET OF ACTION

One of the primary concerns of the clinician administering a local anesthetic for neural blockade is the production of an anesthetic effect in an acceptable period of time. In order to achieve this goal, various approaches have been used to facilitate onset of action. Most of these involve manipulating the physiochemical factors involved in producing anesthesia of the nerves with local anesthetics. Local anesthetic drugs, as previously described, pass through the nerve membrane in the unionized lipid-soluble base form and then, once within the nerve axoplasm, reequilibrate into an ionic form that is active within the sodium channel (see Fig. 34A-6). The rate-limiting step in this cascade is penetration through the nerve membrane, since all of the commercially available local anesthetic solutions contain very little drug in the unionized lipid-soluble form. The fraction of the unionized form, as well as the cationic form present, is determined from the pK_a of the drug and the pH of the drug solution (pK_a = pH + log [cation/base]). In the commercially available solutions that are acidic, the cationic form predominates and is desired because it is more soluble and more stable than the base form. However, the cationic form does not cross biological membranes readily. Thus, to increase the amount of drug in the base form, the clinician can either alter the pH or the pK_a of the solution or of the drug being injected.

Adjustment of the pH is an old technique, first reported in 1910, and more recently repopularized.[39,40] Reports of marked decreases in onset time have been achieved with major pH changes in the local anesthetic solution being injected. These major changes occur most frequently when commercially available local anesthetic solutions containing epinephrine are pH adjusted, since the epinephrine in the local anesthetic solutions re-

quires a very acidic environment for stability. DiFazio et al[39] demonstrated that a greater than 50% decrease in onset time for epidural anesthesia occurred when the pH of commercially available lidocaine with epinephrine was raised from a pH of 4.5 to a pH-adjusted level of 7.2 by the addition of bicarbonate. Similarly, Hilgier[41] reported a marked improvement in onset time for brachial plexus anesthesia when bupivacaine with epinephrine (pH 3.9) was alkalinized to pH 6.4 before injection. These relatively large changes in pH resulted in major increases in the amount of free base available in solution for nerve penetration and resulted in a marked improvement in the onset time for anesthesia. When only small changes in pH can be achieved by the addition of bicarbonate, only small decreases in onset time can be expected to occur. For example, adjusting the pH of plain bupivacaine from 5.5 to the maximal level permitted by its solubility produces small changes in the free base fraction and, hence, the decreases in onset time are modest at best.[42]

As an alternate approach, epinephrine can be freshly added to the plain local anesthetic solution resulting, in the case of lidocaine, in a solution with a pH of 6.5, in contrast to the pH of 4.5 seen in the commercially available lidocaine with epinephrine solutions. By using the higher pH plain local anesthetic solution with freshly added epinephrine, the onset time can be decreased approximately 20%, as compared to using the commercially available lidocaine with epinephrine.[39]

Increases in the amount of free base in solution achieved by increases in pH are limited by the solubility of the free base in solution. For each local anesthetic, there is a pH at which the amount of free base in solution is maximal (a saturated solution). Further increases in pH results in precipitation of the drug. Attempts to further increase the pH of the local anesthetic solution beyond the saturation point does not result in a decrease in the onset time of blockade when such solutions are applied.

Another approach to shortening onset time for producing surgical anesthesia has been through the use of carbonated local anesthetic solutions in which the local anesthetic salt is the carbonate (i.e., lidocaine carbonate rather than lidocaine hydrochloride), and CO_2 is added to maintain a high concentration of the carbonate anion. Carbonated local anesthetics are not currently available in the United States. In two past clinical studies, Bromage[43,44] found that the spread of anesthesia was more extensive and a better quality of neural blockade occurred when the carbonated rather than the uncarbonated lidocaine solution was used. Numerous animal studies using carbonated lidocaine have also shown shortened onset time and improved neural blockade. A recent study by Sukhani and Winnie[45] similarly observed that, when using a carbonated lidocaine with epinephrine solution, more rapid and more complete brachial plexus anesthesia occurred than when a comparable uncarbonated solution was used. Several explanations have been put forth to define the role of carbonation: (1) carbon dioxide may cause some degree of direct neural blockade, and (2) the increased CO_2 that results in the axoplasm can cause an increase in ion trapping of the local anesthetic in the axoplasm. A further contribution may be the result of a pH change that occurs after opening the containers. Solutions of carbonated lidocaine have a pH of 6.5, with a PCO_2 of 700 mmHg. As CO_2 is lost on opening the vial, the pH of the solution increases to about 7, and thus modestly increases the fraction of free base available for nerve penetration. Studies using carbonated bupivacaine epidurally, however, have failed to consistently demonstrate improvements in onset time.[46] It would appear that improvement in the efficacy of neural blockade with carbonation of local anesthetic solutions is most pronounced when lidocaine is the local anesthetic agent used.

The addition of bicarbonate to the local anesthetic solution, along with pH adjustment, also produces an increase in PCO_2 in the local anesthetic solution to a level of approximately 100 mm Hg. This contrasts to the level of 700 mm Hg seen with carbonation. However, this modest increase in PCO_2 may further contribute to the decrease in onset time of the local anesthetic by one of the mechanisms described above for carbonation.

Yet another technique demonstrated to modify latency is the warming of the local anesthetic solution.[47] Although the exact mechanism of this result is not entirely clear, it would appear that a major portion of it is due to the increase in the pK_a of the local anesthetic that occurs with increases in temperature (Table 34A-5). Again, referring to the Henderson-Hasselbach equation, an

Table 34A-5 Relationships between temperature and pK_a[2]

	10°C	25°C	38°C
Lidocaine	8.24	7.91	7.57
Bupivacaine	8.49	8.16	7.92
Mepivacaine	8.02	7.76	7.55
Chloroprocaine	9.37	8.97	8.77
Procaine	9.38	9.05	8.66

increase in pK_a at a constant pH results in an increase in the fraction of the free base available in solution. A consistently faster onset of action was seen in women having vaginal deliveries and cesarean sections when bupivacaine was warmed to 37.7°C before epidural injection. The duration of anesthesia was noted to be unchanged, as was the degree of motor blockade produced.[47]

OPIATE–LOCAL ANESTHETIC COMBINATIONS

Recently, there has been a great deal of interest in the combined use of the local anesthetics and opiates to improve the quality and duration of regional anesthesia. The original observations by Justins et al[48] and subsequent investigators[49,50] noted that the onset is more rapid and anesthesia more complete and more prolonged when fentanyl is added to bupivacaine solutions for epidural use. Subsequent studies have shown that very dilute solutions of local anesthetic combined with an opiate produce anesthesia that is comparable to that produced by a more concentrated solution of the same local anesthetic alone.[51] Use of dilute solutions of local anesthetic results in less motor blockade. Chestnut,[52] for example, demonstrated that using a 0.06% bupivacaine solution combined with fentanyl produced good analgesia with minimal motor blockade during labor.

At present, labor analgesia with local anesthetic alone is being replaced in many institutions with dilute local anesthetic-opiate combinations. In addition, these dilute local anesthetic-opiate combinations have similarly been used for postoperative analgesia to achieve patient comfort without inhibiting the motor activity necessary for the production of an adequate cough and patient movement. Pharmacologically, opiates do not have local anesthetic activity in the concentrations administered clinically, with the exception of meperidine and methadone. The action of the opiates at receptors mediating pain in the dorsal horn of the spinal cord has been well-demonstrated in the past. It would appear that the interaction of opiates and local anesthetics is the result of a synergistic action of the drugs administered epidurally at two or more sites to decrease or obtund sensory input. The local anesthetics act at the dorsal root ganglion while the opiates act at the next synaptic region in the pathway for neural pain transmission, the dorsal horn of the spinal cord. Further investigations into the use of these combinations, as well as additional agents such as the alpha-2 drugs, are expected to produce better quality analgesia with less risk of systemic toxicity and other undesirable side effects.

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