Pharmacology of local anesthetics
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Many substances possess local anesthetic properties. The substances to be considered in this article, however, will be limited to those that are in common clinical usage. The scope of the article will be confined to the pharmacology of the local anesthetics, that is, chemistry, pharmacodynamics, pharmacokinetics, systemic pharmacology and toxicology. The broad topic of clinical application, however, will not be presented.

Cocaine, an alkaloid extracted from the leaves of *Erythroxylon coca*, was the first chemical substance used to prevent or treat local pain. Koller, in 1884 described the first clinical use of cocaine when he reported that instillation into the eye produced topical anesthesia. Shortly thereafter Halsted used the agent by injection to produce peripheral nerve blocks. The first major regional block with cocaine, a spinal anesthetic, was described in 1898 by Bier, who had the procedure performed on himself. (Bier was also the first to describe a post-spinal headache.) Cocaine, however, possesses a low therapeutic index (low potency, high systemic toxicity) and addicting properties. Thus, once it was recognized to be a benzoic acid ester, the search was initiated for compounds that incorporated this structure but possessed less toxicity.

Benzocaine was introduced about 1900, but because of poor water solubility, its use parenterally was limited. However, its effectiveness as a topical anesthetic for mucous membranes was recognized, and this use of benzocaine persists today. Procaine, introduced in 1905, was the first agent exhibiting the desired properties of water solubility and an acceptable margin of safety for clinical use. It has been the prototype for the development of numerous similar compounds which make up our local anesthetic armamentarium.

Chemistry

Local anesthetics are weak bases, and most contain three structural components (Figure 1). An aromatic residue (benzene ring) imparts lipophilic (lipid soluble) properties to the compound. Hydrophilic (water soluble) properties are conferred by an amino group, generally a tertiary amine, which is ionizable and accounts for the weak basic characteristic of the drug. An intermediate alkyl chain links the aromatic and amine components. Benzocaine is an exception to this general structure in that it lacks the amino group, which explains its lack of water solubility. Cocaine is also somewhat distinct in that its hydrophilic portion is considerably more complex than the other local anesthetics.

Linkage between the aromatic and alkyl components is either an ester or an amide bond, separating the local anesthetics into two groups with important distinctions: (1) the means of metabolic degradation, and (2) the incidence of allergic reactions (see below). The commonly used ester-linked local anesthetics include benzocaine, procaine, chloroprocaine, and tetracaine. The remain-
ing local anesthetics in common usage, except for cocaine, are amide-linked (lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine and dibucaine). Although cocaine possesses an ester linkage between the aromatic and alkyl groups, it does not share the same method of degradation nor allergic cross-sensitivity with the ester-linked agents. Therefore, it should not be grouped with either the ester-linked or amide-linked local anesthetics.

Pharmacodynamics

The nerve fiber. A nerve fiber, the site of local anesthetic action, is the portion of a neuron through which transmission of a nerve impulse is accomplished. The cell body of the neuron contains a nucleus and other constituents that are present in other types of cells. The fiber, or axon, is a cylinder of axoplasm (the cellular components) surrounded by a membrane (axolemma). Nerve fibers may be surrounded by a myelin sheath (myelinated nerves), which is a lamination of membranes laid down in a continuous spiral around the fiber by a Schwann cell. Unmyelinated nerves, however, are also surrounded by a Schwann cell membrane, with bundles of fibers being enfolded by a single cell. Although all axons are covered, access of the axolemma to the extracellular environment is always present via gaps in the myelin sheath (nodes of Ranvier), or passages in the Schwann cell membrane. This is necessary since the Schwann cell membrane does not play a direct role in the electrophysiology of nerve conduction, that is, there are no ion movements through the membrane during depolarization of the axon.

The axolemma, which is responsible for impulse conduction, is composed predominantly of lipids (approximately 70%) with most of the remainder being protein and only a small amount of carbohydrate. Early concepts of the membrane were that of an inner bimolecular layer of lipids with a hydrophobic core and the hydrophilic lipid heads directed outward, covered by an inner and outer protein layer. Current models utilize proteins as the main organizational element with greater interaction between the lipid and protein components. Although the precise structure is not known, it is the axolemma through which ion movements occur during the electrophysiologic events of the excitation-conduction process.

Electrophysiology. In the resting state an electrical potential of about −70 millivolts exists across the nerve membrane. This potential is accounted for by the different ion compositions of the axoplasm and the extracellular fluid. The intracellular concentration of potassium is high, and that of sodium is low. The opposite situation is present in the extracellular fluid. At rest, the membrane has greater permeability to potassium ions than to sodium ions, thus, there is a net outward diffusion of positively charged ions giving the axon a net negative charge inside (thus the minus in the membrane potential).

When nerve excitation occurs, the electrical potential within the axon becomes less negative due to increased permeability to sodium ions. Once the membrane potential reaches approximately −50 millivolts (the firing level or threshold potential), sodium permeability increases dramatically and rapid depolarization occurs, with the potential reaching approximately +40 millivolts at the peak of the action potential. Repolarization then begins with return of the low permeability state to sodium ions. However, in order to achieve the resting potential, the original balance of sodium and potassium ions must be restored. This is accomplished by active transport of sodium ions from the inside to the outside of the nerve membrane, with transport of potassium ions in the opposite direction.

Conduction of a nerve impulse, however, does not occur by depolarization of the entire axon at
one time. Instead, sequential segments are depolarized, beginning at the cell body and moving toward the end of the axon. The depolarization occurs in adjacent segments of unmyelinated nerves, or at the nodes of Ranvier of myelinated nerves (saltatory conduction) which conduct impulses much more rapidly. The message is then transmitted via a neurotransmitter (for example, acetylcholine) to another nerve cell or to the excitable membrane of the effector cell, for example, a skeletal muscle cell.

Classification of nerve fibers. Classification of nerve fibers is based upon size (diameter), presence or absence of myelination and function (Table I). The A-fibers (myelinated) comprise the somatic nervous system and are subdivided into alpha, beta, gamma and delta fibers. The large rapidly conducting alpha- and beta-fibers subserve somatic motor function and those sensory functions that include touch, pressure, vibration and position. The gamma-fibers are the motor innervation to the muscle spindles and the delta-fibers carry somatic pain ("fast pain") and temperature sensations. Preganglionic autonomic B-fibers are small and myelinated. C-fibers are unmyelinated, thus slow conducting, and consist of visceral sensory ("slow pain") and autonomic postganglionic fibers.

There is a significant difference in the sensitivities of the different types of nerve fibers to blockade by local anesthetics. The most sensitive to neural blockade are the B-fibers. Thus, during performance of spinal or epidural anesthesia, evidence of a sympathetic nervous system (SNS) block precedes that of sensory or motor blockade. The extent of SNS blockade will also be greater (that is, more spinal segments) than the block of other modalities. The A-delta- and C-fibers are equally sensitive to local anesthetics, but less sensitive than B-fibers. Therefore, blockade of pain sensation follows the SNS block. Somatic motor function and the sensory modalities of touch, vibration, pressure and position are the last to be blocked, and the extent of blockade will be less than that of sensory or SNS functions. Return of function follows the reverse order to loss of function, that is, motor function returns followed by sensory and SNS functions.

Local anesthetic mechanism of action. Local anesthetics produce what could be considered to be a nondepolarizing block, that is, they block the electrophysiologic events that lead to axon depolarization and impulse conduction. The primary effect on the nerve membrane is inhibition of the initial rise in sodium permeability which occurs when the nerve is stimulated. Thus, depolarization is insufficient for the membrane potential to reach the firing level, a propagated action potential does not develop, and the membrane returns to the resting state without having transmitted the message it received.

The site of action of local anesthetics appears to be within the axon itself, and likely on the inner aspect of the axolemma at the location of the channels through which the sodium ions pass. The binding of the local anesthetic to its receptor inhibits the movement of sodium ions through the channel. However, in order for the drug to reach its site of action, it must first penetrate the nerve membrane. Since these agents are weak bases, and thus ionizable, it is the lipid-soluble un-ionized form that diffuses inward. Once within the axo-

<table>
<thead>
<tr>
<th>Type</th>
<th>Myelination</th>
<th>Diameter (microns)</th>
<th>Conduction velocity (m/sec)</th>
<th>Functions</th>
<th>Local anesthetic sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-fibers alpha &amp; beta</td>
<td>Yes</td>
<td>8-20</td>
<td>40-120</td>
<td>Somatic Motor, pressure touch, position</td>
<td>Least</td>
</tr>
<tr>
<td>gamma</td>
<td></td>
<td>4-8</td>
<td>15-40</td>
<td>Muscle spindle efferent</td>
<td></td>
</tr>
<tr>
<td>delta</td>
<td></td>
<td>2-4</td>
<td>5-15</td>
<td>Pain, temperature</td>
<td>Intermediate</td>
</tr>
<tr>
<td>B-fibers</td>
<td>Yes</td>
<td>2-3</td>
<td>5-15</td>
<td>Autonomic preganglionic (sympathetic and parasympathetic)</td>
<td>Greatest</td>
</tr>
<tr>
<td>C-fibers</td>
<td>No</td>
<td>0.5-2</td>
<td>0.5-1.5</td>
<td>Autonomic postganglionic, visceral pain</td>
<td>Intermediate</td>
</tr>
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plasm, the un-ionized local anesthetic equilibrates with its positively charged form which binds to the receptor and exerts its action.

Clinical properties of local anesthetics. Considerable variability exists between the local anesthetics with respect to their potency, time to onset of action and duration of action. These characteristics of the drugs are determined by their physiochemical properties (Table II). With respect to onset and duration of action, the discussion to follow will be limited to the clinical aspects of local anesthetic use (that is, what is observed when performing a block), and not to results observed with isolated nerve preparations.

Procaine is the least potent of the commonly used local anesthetics. Agents of intermediate potency (2 to 4 times that of procaine) include chloroprocaine, lidocaine, mepivacaine and prilocaine. High potency (12 to 16 times that of procaine) local anesthetics include tetracaine, bupivacaine, etidocaine and dibucaine. The factors that determine the potency of a local anesthetic are unclear, although there does appear to be some correlation of this property with lipid solubility.

The time to onset of action and duration of action of local anesthetics (Table III) is related to the facility with which they penetrate biological membranes. Drug properties such as degree of ionization and lipid solubility bear some relationship to onset time and duration, although there is no direct correlation. However, agents that readily penetrate biological membranes would be expected to have a rapid onset of action since they reach their site of action quickly. Similarly, a drug with rapid onset time would be expected to have a short duration since it easily diffuses out of the nerve fiber. This relationship appears to hold for regional anesthesia performed with chloroprocaine, which exhibits a rapid onset and short duration of action. Local anesthetics with intermediate onset times, such as lidocaine, mepivacaine and prilocaine, have intermediate durations of action. Surgical anesthesia develops slowly when bupivacaine, tetracaine or dibucaine are used, and the anesthetic duration is long compared to most other agents. A few agents do not follow this general pattern, for example, etidocaine, which exhibits a rapid onset and long duration of action. Its long duration, however, may be explained by its high degree of protein binding (that is, avid binding to membrane proteins).

<table>
<thead>
<tr>
<th>Table III</th>
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<tr>
<td><strong>Clinical characteristics of local anesthetics</strong></td>
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<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset of action</th>
<th>Duration of action</th>
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<tbody>
<tr>
<td>Procaine</td>
<td>Rapid</td>
<td>Short</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>Rapid</td>
<td>Short</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Slow</td>
<td>Long</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Slow</td>
<td>Long</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>Rapid</td>
<td>Long</td>
</tr>
<tr>
<td>Dibucaine</td>
<td>Slow</td>
<td>Long</td>
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</table>

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<thead>
<tr>
<th>Table II</th>
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<tr>
<td><strong>Physicochemical properties of local anesthetics</strong></td>
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</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potency</th>
<th>Lipid solubility</th>
<th>pKa</th>
<th>Plasma protein binding (%)</th>
</tr>
</thead>
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<tr>
<td>Procaine</td>
<td>Low</td>
<td>Low</td>
<td>8.9</td>
<td>6</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>Intermediate</td>
<td>Low</td>
<td>9.0</td>
<td>—</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>7.9</td>
<td>64</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>7.6</td>
<td>77</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>7.9</td>
<td>55</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>High</td>
<td>High</td>
<td>8.1</td>
<td>95</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>High</td>
<td>High</td>
<td>8.2</td>
<td>76</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>High</td>
<td>High</td>
<td>7.7</td>
<td>94</td>
</tr>
<tr>
<td>Dibucaine</td>
<td>High</td>
<td>High</td>
<td>8.8</td>
<td>—</td>
</tr>
</tbody>
</table>
Certain factors or conditions may modify the onset time and duration of action of a local anesthetic. The pH of the environment into which the drug is injected will have a marked influence. If the pH is low, in an area of infection, for example, the proportion of the local anesthetic existing in the protonated (ionized) form will be higher than at physiologic pH (7.4). Since the ionized form does not readily penetrate biological membranes, the effectiveness of the local anesthetic will be substantially reduced. Addition of a vasoconstrictor to the local anesthetic solution will have the opposite effect because of reduced drug absorption from the site of injection. Thus, the local anesthetic will stay in contact with the nerve fibers for a longer period of time allowing for greater penetration. This will result in a more intense block that has a longer duration of action compared to that produced by the local anesthetic alone.

Pharmacokinetics

The duration of local anesthetic action depends upon how readily the agent diffuses out of the nerve fiber and into the blood stream. Metabolism of local anesthetics does not have a bearing upon their duration of action since they are not degraded at the site of injection. However, absorption, distribution to tissues throughout the body and the rate of metabolism do affect the systemic pharmacological actions and toxicity of the local anesthetics. Since local anesthetics (except cocaine, see the following) are almost completely metabolized before they are eliminated from the body, excretion has little bearing upon the pharmacodynamics or toxicity of these drugs.

Absorption. The rate of absorption of a local anesthetic into the bloodstream is determined by the intrinsic ability of the drug to cross biological membranes (that is, the blood vessel wall), the vascularity of the site from which it is absorbed and whether or not a vasoconstrictor has been used. The peak blood level achieved (Figure 2) is a balance between the rate of absorption and the rate of uptake of the drug by tissues to which it is distributed. The anatomic site of local anesthetic injection has a marked influence on drug absorption, with high blood levels being observed after injection into areas with high vascularity (such as the peridural space), and low blood levels occurring after injection into areas of low vascularity (for example, subcutaneous injection). The high blood levels observed after intercostal injection are likely due to multiple injections required for this block. Addition of a vasoconstrictor (such as epinephrine), by reducing the caliber of the blood vessels, delays absorption and reduces the peak blood level.

Distribution. Following absorption into the

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**Figure 2**

Local anesthetic blood levels following regional anesthesia. The values shown are expressed in micrograms per milliliter per 100 mg local anesthetic administered.

- M: Mepivacaine
- L: Lidocaine
- B: Bupivacaine
- E: Etidocaine

- Plain
- Epinephrine

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bloodstream, the local anesthetics are distributed to the various tissues of the body. Uptake by the tissues limits the peak blood level obtained. Distribution of local anesthetics occurs first to those tissues that are highly perfused, that is, the brain, heart, liver and kidneys. Uptake by the brain and heart accounts for the pharmacological effects observed in these tissues. Distribution to and uptake by the liver are necessary for metabolism of the amide-linked local anesthetics.

Metabolism. Ester-linked local anesthetics are rapidly hydrolyzed by plasma cholinesterase (pseudocholinesterase). Chloroprocaine has an elimination half-life of 21 seconds in vitro and 3.1 minutes in vivo following epidural administration. The short in vivo half-life reflects the very rapid absorption of the drug from the epidural space as well as its rapid metabolism. Procaine and tetracaine are metabolized at a somewhat slower rate. Atypical plasma cholinesterase also degrades these drugs, although more slowly than the normal enzyme. With an absence of plasma cholinesterase, the ester-linked agents would be metabolized in the liver. Individuals with this enzyme deficiency would exhibit local anesthetic toxicity, although the characteristics of their regional anesthetic would be the same as in an individual with normal enzyme (see the previous information).

Metabolism of amide-linked local anesthetics occurs in the liver. Since these drugs must be transported to the liver, taken up by the liver and then metabolized, their elimination half-lives (2-3 hours) are much longer than those of the ester-linked agents. Finally, although cocaine possesses two ester linkages, it is degraded only very slowly by plasma cholinesterase. Its metabolism occurs primarily in the liver, although a substantial amount of the drug is excreted unchanged.

Excretion. Local anesthetics are lipid soluble compounds and pass through biological membranes with relative ease. Thus, only small amounts (generally less than 10%) of the local anesthetics (except cocaine) are excreted unchanged via the kidneys since most of the drug that filters through the glomeruli is reabsorbed in the renal tubules. Metabolic products from degradation in the plasma (esters) and liver (amides), however, are more polar than the parent compound and are eliminated by renal excretion.

Systemic pharmacology and toxicology
The primary therapeutic use of local anesthetics is to produce conduction blockade in the area where the agent is applied. However, systemic absorption or intravascular injection of these drugs can produce systemic effects, which predominantly involve the cardiovascular and central nervous systems. Although the effects on these systems are considered to be adverse or toxic when we are performing regional anesthesia, some effects have therapeutic applications.

Depressant actions on the central nervous system (CNS). Although seizures generally come to mind when considering systemic effects of local anesthetics, their effect upon the CNS is actually depressant. Moderate blood levels of local anesthetics, that is, those achieved during performance of major nerve blocks or after intravenous injection of moderate doses (such as 1 to 5 µg/ml of lidocaine), have an anticonvulsant action. These agents are also effective adjuncts for general anesthesia, which is attributable both to CNS depression and to their mild analgesic properties when given systemically. Lidocaine effectively reduces the SNS response to laryngoscopy and endotracheal intubation. Finally, suppression of the cough reflex by lidocaine reduces the incidence of coughing and bucking following insertion of an endotracheal tube or before its removal at the end of an anesthetic, and in patients undergoing bronchoscopy.

Convulsant properties. Local anesthetic-induced seizures occur because these agents initially depress the inhibitory pathways in the cerebral cortex. This allows the excitatory transmission of the CNS to function unopposed, which results in convulsive activity. Although it has not been precisely determined, convulsions occur at local anesthetic blood levels several times higher than those that have CNS depressant effects (approximately 15-20 µg/ml of lidocaine). These blood levels are generally reached only after inadvertent intravenous injection of a large dose or extravascular injection of an excessive dose of local anesthetic, but not after appropriate use of these agents for major nerve blocks.

Preconvulsant manifestations may precede a seizure, and include numbness and tingling of the lips, a metallic taste in the mouth, tinnitus, visual disturbances and lightheadedness or dizziness. Patients may be drowsy, disoriented or unconscious and may exhibit muscle twitching or tremors. These signs culminate in a generalized tonic-clonic seizure. With very high local anesthetic doses, the CNS excitation will be followed by CNS depression with termination of the seizure, and possibly respiratory arrest and death.
A local anesthetic-induced seizure, however, is not harmful in and of itself if appropriate measures are taken. Although cerebral oxygen consumption rises during a seizure, increases in cerebral blood flow can supply the increased demand provided oxygenation is adequate. Thus, establishing an airway and instituting ventilation with 100% oxygen is the initial therapeutic modality. Endotracheal intubation should be utilized when necessary, and is indicated if there is a risk of pulmonary aspiration of gastric contents (as in the patient with a full stomach). Appropriate management of ventilation can reduce the hypoxia and hypercarbia which develop rapidly during seizures, and prevent the enhancement of cardiovascular toxicity (see following) which occurs with these metabolic derangements. Once ventilation has been established, control of generalized seizure activity, if needed, can be accomplished with an intravenous dose of a benzodiazepine or short acting barbiturate.

Although appropriate treatment of a local anesthetic-induced seizure will almost always be successful, prevention of a seizure is obviously more desirable. Premedication with a barbiturate or benzodiazepine will elevate the seizure threshold to local anesthetics, and some advocate the use of these agents whenever a major regional anesthetic is to be performed. However, the risk of a seizure can be further reduced if a safe regimen for local anesthetic administration is employed.

First, it must be recognized that the often quoted “maximum allowable dose” of a local anesthetic (for example, 500 mg of lidocaine) is far in excess of the dose necessary to cause a seizure if it is given intravenously as a bolus. Thus, a small test dose of local anesthetic solution, which will produce premonitory CNS signs but not a seizure if injected intravenously, should be given initially. Addition of epinephrine, 5 μg/ml, to the test dose provides another means of detecting intravascular injection (by the development of tachycardia). The other safeguard is to inject no more than 5 ml of the local anesthetic solution at one time, with an interval of at least 1 minute between doses. If this regimen is followed, development of a seizure is very unlikely.

Cardiac effects. The direct effects of local anesthetics include depression of both the electrical and mechanical activity of the myocardium. Because of the therapeutic use of lidocaine for ventricular arrhythmias, most cardiac effects have been elucidated with this drug. Antiarrhythmic activity is produced by lidocaine blood levels of 2 to 5 μg/ml, which reduces excitability of automatic tissues (such as the Purkinje fibers) by prolonging the phase of slow depolarization, and depresses ventricular excitability. No effect, however, is observed on cardiac contractility with these blood levels. Higher blood levels prolong atrioventricular and intraventricular conduction times, resulting in an increased P-R internal and QRS duration, and decreased automaticity which produces sinus bradycardia and, ultimately, cardiac arrest. As the blood concentration reaches toxic levels, the drug also exerts a direct negative inotropic effect on the myocardium as evidenced by increased diastolic volume and decreased contractility, intraventricular pressure and cardiac output.

Vascular effects. Local anesthetics affect the peripheral vasculature by direct effects on vascular smooth muscle. A stimulatory effect, resulting in an increased peripheral vascular resistance, has been demonstrated following intraarterial injection of mepivacaine and lidocaine. Although this may be of clinical relevance if intraarterial injection occurs, the predominant vascular effect of local anesthetics is peripheral vasodilatation due to direct inhibition of the myogenic activity of vascular smooth muscle. Blood levels of lidocaine in the cardio-therapeutic range, and those occurring with major regional anesthetics, have minimal peripheral vascular effects. Toxic doses, however, do result in hypotension from direct vasodilatation, as well as from the depressant effects upon the heart.

Exceptions to these general observations do exist. For example, the uteroplacental vascular bed exhibits vasoconstriction when exposed to local anesthetics, but only at blood levels above that obtained during performance of major regional anesthetics. Additionally, cocaine, although producing an initial direct vasodilatation, results in prolonged vasoconstriction. This is a sympathomimetic effect due to inhibition of norepinephrine uptake by the sympathetic nerve endings, and not a direct effect of cocaine on vascular smooth muscle cells.

Indirect cardiovascular effects. Performance of spinal or epidural anesthesia may produce substantial cardiovascular effects that are independent of the systemic effects of local anesthetics. The SNS preganglionic outflow from the CNS includes segments T1 to L2. Thus, central neural blocks (spinal and epidural) can result in a substantial SNS blockade, and may produce a complete pharmacological sympathectomy if the anesthetic level extends to the high thoracic segments. If appropriate measures, such as fluid administration, are not
taken when a block is performed, hypotension may occur. This results from dilatation of the venous capacitance beds, primarily in skeletal muscle, which reduces venous return to the heart and decreases cardiac output. If an adequate amount of fluid is infused, however, venous return, cardiac output and blood pressure remain essentially unchanged. Blockade of the cardiac accelerator fibers (SNS outflows from T1 to T4) may also contribute to a hypotensive episode since compensation for a decreased venous return, by increasing heart rate and myocardial contractility, cannot occur.

Enhancement of SNS activity, however, can occur if a large dose of local anesthetic intended for the epidural space is injected intravenously as a bolus. During the resulting local anesthetic-induced seizure, cardiovascular depression may not be observed since SNS activity is markedly elevated at this time. In fact, hypertension and tachycardia are generally observed, although once the seizure ceases cardiovascular depression may be evident.

**Bupivacaine and etidocaine cardiotoxicity.** A final consideration pertaining to systemic cardiovascular toxicity of local anesthetics concerns the long acting and highly lipid soluble agents. Concern that bupivacaine and etidocaine exhibit greater cardiotoxicity than the shorter-acting local anesthetics (such as lidocaine) was first expressed by Albright. Although considerable controversy followed, it has now been documented that these agents are more likely to result in intractable ventricular arrhythmias or cardiac asystole if a large intravenous bolus is injected. This cardiotoxicity is enhanced if hypoxia and acidosis are present, conditions that can develop rapidly during a seizure. Therefore, adherence to a safe regimen for administration of these local anesthetics is mandatory. As described above for prevention of CNS toxicity, a test dose containing epinephrine is given first. If evidence of subarachnoid or intravascular injection is negative, the remaining dose of drug is administered incrementally (for example, at 5 ml per minute).

**Direct tissue toxicity**

Local anesthetics, in concentrations that are available for clinical applications, have not been shown to produce neural damage. This is evident from both in vitro experimentation and clinical usage. Concern that preservatives may be neurotoxic has led to the formulation of local anesthetics (that is, single dose vials for major nerve blocks) that do not contain the antifungal agent, methylparaben, although this agent has not been shown to cause neural damage when injected into the subarachnoid space of rabbits. Bisulfite, however, an antioxidant in formulations of chlorprocaine and local anesthetics containing epinephrine, can be neurotoxic. Identification of this agent's toxic potential followed investigations that resulted from reports of prolonged neural blockade which occurred after unintentional subarachnoid injection of large volumes of chlorprocaine (containing 0.2% bisulfite). Although it was initially felt that the local anesthetic was toxic, studies by Gissen et al. demonstrated that subarachnoid injection of bisulfite in a solution of low pH (as are chlorprocaine solutions), but not chlorprocaine itself, was neurotoxic. Subarachnoid injection of a large volume, which increases cerebrospinal fluid pressure and reduces spinal cord perfusion, also contributes to the neural complications. In order to reduce the potential for bisulfite neurotoxicity, its concentration in current formulations of chlorprocaine has been reduced to 0.07%.

Alkalization of solutions containing bisulfite may also reduce their neurotoxic potential. An additional precaution is to administer a small test dose, such as 3 ml, whenever a peridural block is performed. If, after 5 minutes, signs of subarachnoid injection are not evident, the remaining dose is injected incrementally at the rate of 5 ml per minute. Although this regimen may result in subarachnoid injection of the test dose, this volume of solution is without neurotoxic effects.

**Allergy**

True allergic reactions to local anesthetics, that is, reactions that are immunologically-mediated, are rare. Although patients may state that they are allergic, it is important to realize that many individuals mistake fainting or systemic toxicity from intravascular injection (dizziness, tinnitus, visual disturbances) for an allergic reaction. Contact dermatitis is the most common manifestation of allergy, although systemic responses including anaphylaxis have been reported.

The ester-linked local anesthetics are responsible for nearly all allergies to local anesthetics. This is felt to be due to the para-aminobenzoic acid (PABA) residue that is common to these drugs. Cocaine, which possesses two ester linkages but does not contain PABA, has not been shown to exhibit cross-sensitivity with the ester-linked drugs. Documented allergies to amide-linked local anesthetics are extremely rare, and cross-sensitivity with the ester-linked drugs does not occur. However, methylparaben (parahydroxybenzoic acid, methyl ester),
which is used in multiple-dose formulations of local anesthetics, is structurally similar to PABA and is a recognized cause of contact dermatitis. Some patients that were suspected of being allergic to lidocaine exhibited a skin reaction to methylparaben, but not to lidocaine. Thus, allergy to methylparaben may be mistaken for allergy to an amide-linked local anesthetic, and it is probable that cross-sensitivity between methylparaben and the ester-linked agents exists.

**Conclusion**

Local anesthetics have become an indispensable component of modern medical practice. Although they are extensively used in the specialty of anesthesiology, they find application in any discipline where local or topical anesthesia is required. In addition to their effect on nerve conduction, these agents can also exhibit systemic effects, predominantly on the central nervous system and cardiovascular system. Although the systemic effects may be intended (for example, use of lidocaine as an antiarrhythmic agent), the actions can be manifested as toxicity (seizures and profound cardiovascular depression). However, administration of local anesthetics in an appropriate manner, that is, by using test doses and incremental doses, dramatically reduces the risk of complications.

**REFERENCES**


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