Local anesthetics are the most common and important drugs in obstetric anesthesia; hence an adequate knowledge of these chemical agents is absolutely essential.

**Chemistry**

Chemically, local anesthetics are classified as amino-esters or amino-amides (Fig. 2-1). All clinically used local anesthetics (except cocaine) link a substituted aromatic ring via an ester or amide bridge and an intermediate alkyl chain to a tertiary amine. Commercially, most are packaged as hydrochloride salt, protonating the amino group to improve aqueous solubility. Amino-esters undergo hydrolysis by plasma cholinesterase (pseudo-cholinesterase) to derivatives of para-aminobenzoic

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Figure 2–1. Local anesthetics, esters and amides with chemical structures.
acid, which is a known allergen. Hence allergic reactions to amino-esters are not unusual. Conversely, amino-amides are metabolized by the liver to a variety of products with very low potential of triggering allergic reactions.

All local anesthetics except lidocaine contain a chiral carbon atom and thus exist as two enantiomers. Conventional preparations are racemic mixtures, but the development of techniques for bulk separation of optical isomers has led to the development of levobupivacaine and ropivacaine, which are marketed as pure left-handed (“L” or “S”) forms.

**Physicochemical Properties**

The physicochemical properties of local anesthetics correlate with some of their clinical properties (Table 2-1). *Lipid solubility* correlates with the potency of the local anesthetic. This effect is also seen with general anesthetics (the Meyer–Overton observation) and is sometimes attributed to easier passage through the lipid membranes of nerve cells by more lipophilic local anesthetics. More modern views of this observation suggest that it is the perineural lipid-rich tissues which actually form a depot of drug, enhancing continued blockade and thus clinical potency.

*Protein binding* correlates with the duration of action of local anesthetics. Local anesthetic is bound to two principal sites in plasma: (1) the high-affinity but low-capacity $\alpha_1$-acid glycoprotein and (2) low-affinity, high-capacity albumin. Although classically taught, this association is not thought to be causal. Plasma protein binding is closely related to lipophilicity, which actually is more responsible for long duration of action.

The $pK_a$ of local anesthetics correlates to some degree with the speed of onset of neural blockade. $pK_a$ is defined as the pH where 50% of the local anesthetic will remain in uncharged form and 50% will exist in charged form. Agents with $pK_a$ closer to the body’s pH will be less likely to be protonated and therefore exist more prevalently in the uncharged form (Table 2-1). This form is less polar and more easily able to diffuse across the nerve membrane, perhaps explaining a
<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Lipid Solubility</th>
<th>Protein Binding (%)</th>
<th>pKa (Unionized Fraction pH 7.4)</th>
<th>Molecular Weight</th>
<th>Potency</th>
<th>Speed of Onset</th>
<th>Duration of Action</th>
<th>UV/MV ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroprocaine</td>
<td>0.14</td>
<td>~0</td>
<td>8.7 (5%)</td>
<td>271</td>
<td>Low</td>
<td>Very rapid</td>
<td>Short</td>
<td>~0</td>
</tr>
<tr>
<td>Procaine</td>
<td>0.02</td>
<td>6</td>
<td>8.9 (3%)</td>
<td>236</td>
<td>Low</td>
<td>Rapid</td>
<td>Short</td>
<td>N/A</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2.9</td>
<td>64</td>
<td>7.7 (35%)</td>
<td>234</td>
<td>Medium</td>
<td>Rapid</td>
<td>Medium</td>
<td>0.5–0.7</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>0.8</td>
<td>78</td>
<td>7.6 (39%)</td>
<td>246</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>0.7–0.8</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.2</td>
<td>96</td>
<td>8.1 (15%)</td>
<td>288</td>
<td>High</td>
<td>Slow</td>
<td>Long</td>
<td>0.2–0.4</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>8.0</td>
<td>92–94</td>
<td>8.1 (15%)</td>
<td>274</td>
<td>High</td>
<td>Slow</td>
<td>Long</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Lipid solubility: Heptanol or octanol/buffer partition ratio; UV/MV ratio = ratio of concentration in umbilical vein to maternal vein; total concentration, not free drug concentration, is shown in the table (see text for details); N/A = not available.
more rapid onset of blockade. However, the astute reader will note that this mechanism is essentially the same as that asserted for lipid solubility, so the in vivo importance of this action is unclear. Indeed, chloroprocaine, with a pK\text{a} of 8.7, has the fastest onset of action in clinical practice among all local anesthetics for epidural blockade. Moreover, although the uncharged form is important for diffusion across the nerve membrane, it is believed that the charged form ultimately binds with the sodium channels intracellularly. Hence both forms of the local anesthetic are important for neural blockade.

Some local anesthetics possess \textit{intrinsic vasoactive properties}. Lidocaine produces modest vasodilation in low concentrations, possibly reducing its potency in vivo by increasing vascular uptake. Conversely, ropivacaine has been found to have dose-dependent vasoconstrictive activity,\textsuperscript{1} which might increase its duration of action, especially after local infiltration.

Passage of local anesthetics across the placenta is influenced by the physicochemical properties of the drugs. All local anesthetics are relatively small molecules, and therefore molecular weight does not affect their transport. Lipid solubility and degree of nonionization will affect the proportion of maternal venous concentration that exists in the fetal blood, because both enhance passage across the lipid membranes in the placenta (Table 2-1). However, more recent evidence suggests that free drug concentrations for all local anesthetics are in equilibrium across the placenta and in maternal and fetal blood, so the greater protein binding in maternal blood does not necessarily confer a safety advantage to the fetus.

**Other Factors Affecting Local Anesthetic Activity**

Besides intrinsic physicochemical properties, a number of clinically modifiable factors have a major effect on the degree of neural blockade achieved with local anesthetics.

**Volume and Concentration**

The total dose (mass or mg) of local anesthetic will ultimately dictate the onset, quality, and duration of the block. In
general, increased doses of the agents speed onset and lengthen
duration of the block. For example, increasing the concentra-
tion of bupivacaine from 0.125% to 0.5% while maintaining
constant volume improved the onset, quality, and duration (but
not dermatomal spread) of the block. Volume, concentration,
and dose, however, are intimately related, because dose =
volume \times concentration. Therefore, changing one parameter
necessarily changes the others, complicating the study of one
feature in isolation. Clinically, volume of drug has a profound
effect on the spread and quality of epidurally administered
local anesthetics, whereas total dose seems most important in
spinal anesthesia.

**Addition of Vasoconstrictor Agents**

Epinephrine is frequently used with local anesthetics to
improve the quality and duration of analgesia. Because of
the vasoconstriction produced by epinephrine more local
anesthetic will be available for neural blockade because of
less absorption through vascular beds. Norepinephrine and
phenylephrine have also been used for prolonging blockade,
though they are much less popular. Addition of epinephrine
will also decrease the peak plasma concentrations of cer-
tain local anesthetics, including mepivacaine and lidocaine.
Epinephrine is usually added to epidural lidocaine or bupi-
vacaine at concentrations of 1.7–5 μg/ml, or 1:600,000 to
1:200,000 (the latter is also the commercially available con-
centration). This lowers the median effective concentration of
local anesthetic by 30%. In addition, the duration of epidural
lidocaine and, to a lesser extent, bupivacaine is significantly
prolonged by the addition of epinephrine. In spinal anesthe-
sia, by contrast, epinephrine has minimal effects, increasing the
duration of motor but not sensory block with lidocaine, and
extending sensory block with bupivacaine by just 4–19 min.

**Site of Injection**

The onset of action of a local anesthetic varies depending
on the site of administration. Spinal and subcutaneous routes
are associated with a more rapid onset, whereas epidural and brachial plexus blocks are associated with a slower onset of action.

**Bicarbonate**

Local anesthetic solutions, particularly those containing epinephrine, are packaged at low pH to increase the shelf life of the agents. Addition of sodium bicarbonate (1 ml of a 1 M solution to 10 ml local anesthetic) will increase the pH of these solutions and thus the percentage of the nonionized or uncharged form, which is important for diffusion through the nerve membrane. Speed of onset and quality of the block are both improved with this maneuver. Addition of bicarbonate to bupivacaine is not recommended because of the chance of precipitation when the pH rises above 7.7. Laboratory evidence suggests that bicarbonate also enhances local anesthetic activity by other mechanisms distinct from its effect on pH, because its effect is more profound than that induced by equivalent alkalinization with other buffers.\(^5\)

**Mixtures of Local Anesthetics: Chloroprocaine and Other Drugs**

Historically, combinations of local anesthetics have been used both to shorten the onset of action as well as to improve the quality of the block. A combination of spinal 1% tetracaine and 10% procaine in equal volumes was associated with superior sensory anesthesia when compared with hyperbaric tetracaine (5% dextrose) alone.\(^6\) For epidural administration, it was once hoped that the rapid onset of 2-chloroprocaine and long duration of bupivacaine would produce a desirable combination. However, the use of 2-chloroprocaine shortened the duration of bupivacaine’s action.\(^7\) The mechanism of this interaction is unknown but may be related to inhibition of the binding of bupivacaine to membrane receptor sites in the presence of 2-chloroprocaine or its metabolite chloraminobenzoic acid.\(^8\)

The eutectic mixture of local anesthetics (EMLA) is a 1:1 mixture of prilocaine and lidocaine that induces cutaneous
anesthesia through intact skin. Applied in doses of 0.5–1 g under an occlusive dressing, it induces anesthesia for subsequent needle stick in 30–60 min.

Pregnancy

Pregnancy reduces the amounts of local anesthetic needed for both spinal and epidural anesthesia in parturients as compared with age-matched nonpregnant women. The onset of blockade is also faster with the use of spinal, epidural, and peripheral nerve blocks. Although various mechanisms for these observations have been proposed (including influence of mechanical factors in the epidural space and alterations in the central nervous system), the most likely explanation is an effect of progesterone on the sensitivity of nerve fibers themselves.

Temperature

Warming the local anesthetic to a temperature of 100°F has been shown to reduce the onset of epidural anesthesia blockade. A decreased pKa due to increased temperature is probably the mechanism.

Toxicity of Local Anesthetics

Local anesthetics can result in systemic toxicity manifest in the CNS or the cardiovascular system, as well as peripheral toxicity manifest as irreversible conduction blockade or other neurological symptoms. Local anesthetics may also cause untoward effects on the fetus.

Systemic Toxicity: CNS

The clinical features of systemic toxicity depend on the blood concentrations of the local anesthetics. In most cases, CNS symptoms will precede cardiovascular derangements. In lower concentrations, the patient may complain of (1) tinnitus, (2) light-headedness, (3) metallic taste, and (4) perioral numbness. With higher concentrations, convulsions and
unconsciousness, followed by respiratory arrest, may ensue. If a large bolus dose of local anesthetic is accidentally injected intravenously the parturient may manifest convulsions as the first sign. This may also occur if the pregnant woman receives large doses of diazepam or midazolam as premedication, because these drugs may mask the subjective symptoms associated with lower blood levels. Respiratory acidosis (increased PaCO₂ and low pH) decreases the convulsive threshold and may also increase drug delivery to the brain by increasing cerebral blood flow. Acidosis may also decrease the free plasma concentrations by reducing protein binding. The potency of local anesthetics closely parallels their relative toxic potential: bupivacaine > lidocaine >> chloroprocaine.

**Systemic Toxicity: Cardiovascular System**

Local anesthetics inhibit cardiac sodium channels and in some cases potassium and calcium channels. However, the heart is highly resistant to toxicity from lidocaine, and indeed seven times the convulsive dose is required to produce cardiovascular collapse with this drug (at plasma concentrations of approximately 25 μg/ml vs. 7–12 μg/ml). Cardiovascular toxicity may result indirectly from respiratory depression, however (at approximately 20 μg/ml). In contrast, high systemic levels of more potent local anesthetics (bupivacaine, etidocaine) produce cardiovascular toxicity at much lower multiples of the convulsive dose. This is due to their pro-arrhythmic effects on the pacemaker and conduction cells in the heart, decreasing the duration of the action potential and the effective refractory period. Thus reentrant-type ventricular dysrhythmias (ventricular tachycardia or fibrillation) may result.

Cardiovascular toxicity of local anesthetics appears significantly more likely with right-handed (R- or D-) isomers of potent lipophilic local anesthetics. This observation led to the development of levobupivacaine and ropivacaine, which are both packaged as pure L- or S-isomers. Levobupivacaine has essentially identical clinical properties as racemic bupivacaine, but is less toxic in both isolated cardiac and intact animal preparations. In human studies, racemic bupivacaine produces more signs of impending cardiovascular toxicity (changes in
the QT interval, decrease in cardiac performance) than does levobupivacaine. Ropivacaine also produces less cardiovascular toxicity in similar preparations and clinical trials. However, ropivacaine is also significantly less potent than bupivacaine; studies comparing the median effective concentration for labor analgesia demonstrate it to be 40% less potent. Nonetheless, even after accounting for this difference, ropivacaine is less toxic. Whether the toxicity difference is clinically relevant in obstetric anesthesia practice, where concentrations used are generally low and large bolus administration is rare, is a matter of some controversy given ropivacaine’s much higher cost.13

Peripheral Neurotoxicity

Despite decades of clinical experience with local anesthetics for neuraxial block and a paucity of reports of neurotoxicity, over the last two decades evidence has mounted to suggest that under certain circumstances, irreversible conduction blockade may occur with clinical use of certain local anesthetics.

First, 2-chloroprocaine preserved with sodium metabisulfite, which was intended for epidural administration, was associated with several cases of cauda equina syndrome (irreversible conduction blockade of L1 to sacral spinal roots) when unintentionally administered intrathecally. Although somewhat controversial, the mechanism appeared to be related to formation of sulfurous acid in CSF, derived from meta-bisulfite.14 In in vitro studies, meta-bisulfite and low pH, but not chloroprocaine itself, caused irreversible conduction blockade. However, others have argued exactly the opposite, that bisulfite is in fact protective and that chloroprocaine itself is neurotoxic.15 Fortunately, other preparations of 2-chloroprocaine have replaced the bisulfite-preserved form. For some time, the drug was packaged with EDTA; this preparation, however, was associated with significant back pain attributed to chelation of calcium in paraspinous muscles.16 Most recently, a preservative-free preparation has been marketed in a light-protected bottle. This formulation has been used apparently safely for spinal anesthesia.17

Second, 5% hyperbaric lidocaine has caused cases of irreversible blockade, especially when administered in large doses
via a spinal microcatheter. Shortly after the introduction of 27–32 G catheters, which could be placed through 25 G or 26 G spinal needles, case reports of cauda equina syndrome began to surface.\textsuperscript{18} Subsequent laboratory investigation demonstrated that lidocaine caused concentration-dependent neurotoxicity when applied directly to nerves.\textsuperscript{19} Other studies implicated pooling of hyperbaric local anesthetic in the posterior lumbosacral spinal canal (where the cauda equina fibers lay in the supine patient) when administered by the slow laminar flow caused by the narrow-gauge catheters.\textsuperscript{20} Though the catheters were withdrawn from the market, reintroduction in the near future appears likely, given extensive European experience and a recent multicenter North American randomized trial which demonstrated comparable safety and efficacy of rationally dosed microcatheters compared to conventional epidural catheters.\textsuperscript{21}

Finally, a milder form of apparent toxicity following hyperbaric spinal lidocaine has been termed transient neurologic symptoms (TNS). Other terms for the same syndrome include transient radicular irritation (TRI) and post-spinal pain syndrome (PSPS). These terms describe the development of short-lived back, buttock, or thigh pain unaccompanied by objective sensory or motor deficits, following spinal anesthesia. The onset of symptoms is typically within the first day, duration usually less than 5 days, and intensity moderate to severe (average VAS 6/10). NSAIDs provide the best available symptomatic treatment. Epidemiologic surveys and RCTs suggest it is far more common with lidocaine than other local anesthetics, is more likely after procedures in the lithotomy position, and probably more common in ambulatory surgical cases.\textsuperscript{22} Unlike the more severe cauda equina syndrome, concentration and dose of lidocaine are not risk factors. Moreover, experiments in volunteers suggest there is no objective neurotoxicity.\textsuperscript{23} Fortunately, the incidence in pregnancy appears to be much lower than in general surgical patients.\textsuperscript{24} Nonetheless, we prefer the use of mepivacaine 1.5%, made hyperbaric by the addition of 10% dextrose, for outpatient spinal anesthesia in pregnant patients (e.g., for cervical cerclage placement) due to the low incidence of TNS even in general surgical patients.\textsuperscript{25}
Adverse Effects on the Fetus

Local anesthetics administered in high concentrations can cause uterine artery constriction in isolated vessels. This observation grew from clinical reports of fetal bradycardia following paracervical block for labor analgesia, during which large doses of concentrated drug are deposited near the uterine arteries. In modern clinical use for epidural and spinal anesthesia, local anesthetics do not alter uterine or umbilical blood flow. Conversely, there is some evidence that even clinically encountered concentrations of local anesthetic may adversely affect blood flow distribution within the asphyxiated fetus. In preterm pregnant ewes, lidocaine interfered with the normal compensatory shunting of blood flow to the heart, brain, and adrenal glands during asphyxia. This effect was less pronounced in term fetuses or when bupivacaine was administered. The applicability of these results to human patients with possibly compromised fetuses is far from clear. However, some clinical evidence supports the use of chloroprocaine in preference to other local anesthetics in such settings.

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