

2

Local Anesthetic Pharmacology



Chemistry	15
Physicochemical Properties	17
Other Factors Affecting Local Anesthetic Activity	19
Volume and Concentration	19
Addition of Vasoconstrictor Agents	20
Site of Injection	20
Bicarbonate	21
Mixtures of Local Anesthetics: Chloroprocaine and Other Drugs	21
Pregnancy	22
Temperature	22
Toxicity of Local Anesthetics	22
Systemic Toxicity: CNS	22
Systemic Toxicity: Cardiovascular System	23
Peripheral Neurotoxicity	24
Adverse Effects on the Fetus	26

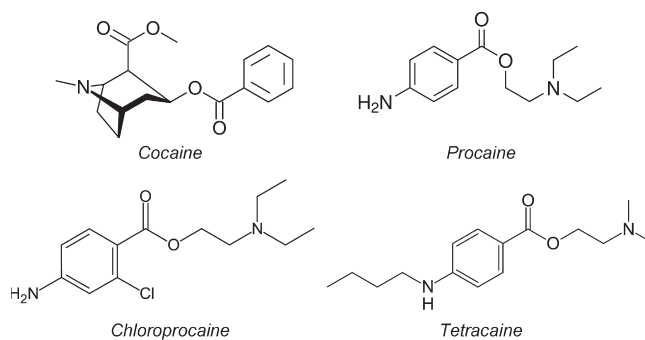
Local anesthetics are the most common and important drugs in obstetric anesthesia; hence an adequate knowledge of these chemical agents is absolutely essential.

Chemistry

Chemically, local anesthetics are classied 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

Esters



Amides

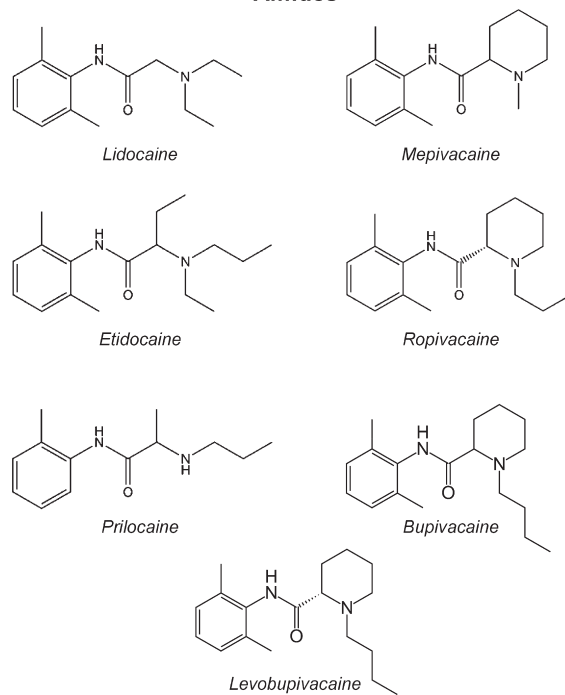


Figure 2-1. Local anesthetics, esters and amides with chemical structures.

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 α_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 pKa of local anesthetics correlates to some degree with the speed of onset of neural blockade. pKa 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 pKa 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 2-1. Properties of Local Anesthetics

Anesthetic	Lipid Solubility	Protein Binding (%)	pKa (Unionized Fraction pH 7.4)	Molecular Weight	Potency	Speed of Onset	Duration of Action	UV/MV ratio
Chloroprocaine	0.14	~0	8.7 (5%)	271	Low	Very rapid	Short	~0
Procaine	0.02	6	8.9 (3%)	236	Low	Rapid	Short	N/A
Lidocaine	2.9	64	7.7 (35%)	234	Medium	Rapid	Medium	0.5-0.7
Mepivacaine	0.8	78	7.6 (39%)	246	Medium	Medium	Medium	0.7-0.8
Bupivacaine	8.2	96	8.1 (15%)	288	High	Slow	Long	0.2-0.4
Ropivacaine	8.0	92-94	8.1 (15%)	274	High	Slow	Long	0.2

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_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 *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,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

20 LOCAL ANESTHETIC PHARMACOLOGY

general, increased doses of the agents speed onset and lengthen duration of the block. For example, increasing the concentration 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.² Volume, concentration, and dose, however, are intimately related, because $\text{dose} = \text{volume} \times \text{concentration}$. 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 certain local anesthetics, including mepivacaine and lidocaine. Epinephrine is usually added to epidural lidocaine or bupivacaine at concentrations of 1.7–5 $\mu\text{g/ml}$, or 1:600,000 to 1:200,000 (the latter is also the commercially available concentration). This lowers the median effective concentration of local anesthetic by 30%.³ In addition, the duration of epidural lidocaine and, to a lesser extent, bupivacaine is significantly prolonged by the addition of epinephrine. In spinal anesthesia, 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.⁴

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: Chlorprocaine 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

22 LOCAL ANESTHETIC PHARMACOLOGY

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.⁹ 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 system¹⁰), the most likely explanation is an effect of progesterone on the sensitivity of nerve fibers themselves.¹¹

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.¹²

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

24 LOCAL ANESTHETIC PHARMACOLOGY

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 metabisulfite.¹⁴ In *in vitro* studies, metabisulfite 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 paraspinal 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.¹⁸ Subsequent laboratory investigation demonstrated that lidocaine caused concentration-dependent neurotoxicity when applied directly to nerves.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.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.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.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.²³ Fortunately, the incidence in pregnancy appears to be much lower than in general surgical patients.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.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.²⁶ 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.²⁷

References

1. Wienzek H, Freise H, Giesler I, Van Aken HK, Sielenkaemper AW. Altered blood flow in terminal vessels after local application of ropivacaine and prilocaine. *Reg Anesth Pain Med.* 2007;32:233–239.
2. Littlewood DG, Scott DB, Wilson J, Covino BG. Comparative anaesthetic properties of various local anaesthetic agents in extradural block for labour. *Br J Anaesth.* 1977;49:75–79.
3. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ. Effect of epidural epinephrine on the minimum local analgesic concentration of epidural bupivacaine in labor. *Anesthesiology.* 2002;96:1123–1128.
4. Chambers WA, Littlewood DG, Scott DB. Spinal anesthesia with hyperbaric bupivacaine: effect of added vasoconstrictors. *Anesth Analg.* 1982;61:49–52.
5. Wong K, Strichartz GR, Raymond SA. On the mechanisms of potentiation of local anesthetics by bicarbonate buffer: drug structure–activity studies on isolated peripheral nerve. *Anesth Analg.* 1993;76:131–143.

6. Chantigian RC, Datta S, Berger GA, et al. Anesthesia for cesarean delivery using spinal anesthesia: tetracaine versus tetracaine and procaine. *Reg Anesth*. 1984;9:195.
7. Cohen SE, Thurlow A. Comparison of a chloroprocaine–bupivacaine mixture with chloroprocaine and bupivacaine used individually for obstetric epidural analgesia. *Anesthesiology*. 1979;51:288–292.
8. Corke BC, Carlson CG, Dettbarn WD. The influence of 2-chloroprocaine on the subsequent analgesic potency of bupivacaine. *Anesthesiology*. 1984;60:25–27.
9. Datta S, Lambert DH, Gregus J, Gissen AJ, Covino BG. Differential sensitivities of mammalian nerve fibers during pregnancy. *Anesth Analg*. 1983;62:1070–1072.
10. Fagraeus L, Urban BJ, Bromage PR. Spread of epidural analgesia in early pregnancy. *Anesthesiology*. 1983;58:184–187.
11. Bader AM, Datta S, Moller RA, Covino BG. Acute progesterone treatment has no effect on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesth Analg*. 1990;71:545–548.
12. Mehta PM, Theriot E, Mehrotra D, Patel K, Kimball BG. A simple technique to make bupivacaine a rapid-acting epidural anesthetic. *Reg Anesth*. 1987;12:135–138.
13. Panni M, Segal S. New local anesthetics. Are they worth the cost? *Anesthesiol Clin North America*. 2003;21:19–38.
14. Gissen AJ, Datta S, Lamber D. The chloroprocaine controversy. II. Is chloroprocaine neurotoxic? *Reg Anesth*. 1984;9:135–145.
15. Taniguchi M, Bollen AW, Drasner K. Sodium bisulfite: scapegoat for chloroprocaine neurotoxicity? *Anesthesiology*. 2004;100:85–91.
16. Fibuch EE, Oppper SE. Back pain following epidurally administered Nesacaine-MPF. *Anesth Analg*. 1989;69:113–115.
17. Casati A, Fanelli G, Danelli G, et al. Spinal anesthesia with lidocaine or preservative-free 2-chloroprocaine for outpatient knee arthroscopy: a prospective, randomized, double-blind comparison. *Anesth Analg*. 2007;104:959–964.
18. Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. *Anesth Analg*. 1991;72:275–281.
19. Lambert LA, Lambert DH, Strichartz GR. Irreversible conduction block in isolated nerve by high concentrations of local anesthetics. *Anesthesiology*. 1994;80:1082–1093.
20. Rigler ML, Drasner K. Distribution of catheter-injected local anesthetic in a model of the subarachnoid space. *Anesthesiology*. 1991;75:684–692.

28 LOCAL ANESTHETIC PHARMACOLOGY

21. Arkoosh VA, Palmer CM, Yun EM, et al. A randomized, double-masked, multicenter comparison of the safety of continuous intrathecal labor analgesia using a 28-gauge catheter versus continuous epidural labor analgesia. *Anesthesiology*. 2008;108:286–298.
22. Freedman JM, Li DK, Drasner K, Jaskela MC, Larsen B, Wi S. Transient neurologic symptoms after spinal anesthesia: an epidemiologic study of 1,863 patients. *Anesthesiology*. 1998;89:633–641.
23. Pollock JE, Burkhead D, Neal JM, et al. Spinal nerve function in five volunteers experiencing transient neurologic symptoms after lidocaine subarachnoid anesthesia. *Anesth Analg*. 2000;90:658–665.
24. Philip J, Sharma SK, Gottumukkala VN, Perez BJ, Slaymaker EA, Wiley J. Transient neurologic symptoms after spinal anesthesia with lidocaine in obstetric patients. *Anesth Analg*. 2001;92:405–409.
25. Liguori GA, Zayas VM, Chisholm MF. Transient neurologic symptoms after spinal anesthesia with mepivacaine and lidocaine. *Anesthesiology*. 1998;88:619–623.
26. Morishima HO, Santos AC, Pedersen H, et al. Effect of lidocaine on the asphyxial responses in the mature fetal lamb. *Anesthesiology*. 1987;66:502–507.
27. Abboud TK, Khoo SS, Miller F, Doan T, Henriksen EH. Maternal, fetal, and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine. *Anesth Analg*. 1982;61:638–644.