Fetal toxicity of local anesthetics

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This article reviews mechanisms by which local anesthetics may compromise the fetus during conduction analgesia in obstetrics. In addition to presenting pertinent information about perinatal pharmacology of local anesthetics, the author discusses comparative effects of 2-chloroprocaine and amide-linked compounds. Recommendations are made for prevention of maternal hypotension and local anesthetic-induced seizures.

Over the past 20 years, local anesthetics have been used increasingly in obstetrics. Many parturients and perinatal team care members have appreciated the maternal-fetal benefits provided by regional analgesia (paracervical, pudendal, lumbar epidural, caudal and spinal blocks). These local anesthetic techniques have been investigated thoroughly in the laboratory and obstetrical suite, having evolved at a time when clinicians and basic scientists alike realized the need for better maternal care and improved neonatal outcome. Data derived from such studies indicate that local anesthetics produce negligible effects on the fetus or neonate when judiciously administered in a clinically acceptable manner.1

As a result, local anesthetic drugs are probably the most commonly used agents in obstetric anesthesia today.5 This is not to say that these compounds do not have the potential for producing significant fetal/neonatal morbidity. This article discusses the basic mechanisms by which local anesthetics may adversely influence the fetus, while focusing on recent information and controversy about the perinatal pharmacology of these drugs.

Direct toxicity
The relative ease of local anesthetic assay (G-L or HPL chromatography) attests to the rapidity of placental transfer of local anesthetics.8-4 These compounds undergo rapid, passive diffusion as a result of relatively high lipid solubility, a low molecular weight (<300) and partial nonionization at pH 7.4. Following initial use of local anesthetics, however, few clinicians were concerned about fetal effects, since neonatal status was as good or better following regional blocks when compared to parenteral analgesia/anesthesia.7

Yet, concerns arose during the use of paracervical blocks during labor and following accidental direct fetal injection of local anesthetic agents intended for paracervical, pudendal or caudal blockade.2 Fetal bradycardia, hypoxia, acidosis and occasionally death have been correlated with high fetal plasma concentrations of all local anesthetic amides within minutes after paracervical blocks.8,9 This suggests that local anesthetics, given paracervically, can be absorbed rapidly into the uterine circulation, leading to high fetal plasma levels and resulting in fetal cardiovascular depression. However, more recent information implicates...
another cause for post-paracervical block fetal bradycardia: local anesthetic-induced uterine vasoconstriction leading to placental hypoperfusion and fetal asphyxia. Van Dorsten and Miller link the bradycardia to umbilical artery spasm, increased fetal peripheral vascular resistance and hypertension, resulting in baroreceptor stimulation and vagal discharge. Thus, the actual cause of post-paracervical block bradycardia is controversial, but several points are quite clear: (1) the bradycardia signifies fetal distress and an increased likelihood of neonatal acidosis and depression; (2) it is induced either directly or indirectly by local anesthetics; (3) paracervical blocks should not be employed in high risk pregnancies or when fetal monitoring demonstrates compromised fetal status during labor.

Morishima and her colleagues have studied the direct toxicity of lidocaine and etidocaine (Durane®) given intravenously to fetal lambs in utero, neonatal lambs and adult sheep. Similar toxic manifestations occurred in the different age groups. In the fetus, the following sequence of events transpired as plasma lidocaine and etidocaine levels increased progressively: muscle twitching, tonic-clonic convulsions with seizure activity on EEG, hypertension and tachycardia during seizures, hypotension and bradycardia, acidosis, shallow tachypnea followed by respiratory arrest, and, finally, circulatory collapse. Interestingly, plasma lidocaine levels at time of seizure in adult sheep corresponded closely with levels known to occur in humans (≈ 11 μg/ml).

In contrast to common belief, fetal and neonatal lambs were no more sensitive to the toxic effects of lidocaine or etidocaine than adult sheep. In fact, CNS and cardiovascular toxicity occurred at higher plasma levels of local anesthetic in the fetus and neonate than in adults. This apparent "decreased sensitivity" of the fetus to lidocaine and etidocaine could result from a greater volume of distribution of these compounds (mainly in vessel-rich tissues) and from rapid placental transport of drug from fetal to maternal blood.

An increased volume of distribution of lidocaine in the fetus and newborn also accounts for prolonged half-lives of elimination (t1/2B) of local anesthetics in the newborn, since the neonate's hepatic and renal clearance of lidocaine is the same as in the adult. Table I demonstrates the half-life of elimination for several local anesthetic amides and 2-chloroprocaine Nesacaine®. It is important to remember that fetal acidemia impedes the placental transport of amide compounds from fetus to mother and, as a result, delays fetal elimination of local anesthetic amides. This phenomenon—termed "ion trapping of local anesthetic amides"—occurs when fetal plasma pH is significantly lower than pH in maternal plasma.

A study in baboon fetuses additionally demonstrates an increased sensitivity of the asphyxiated fetus to the toxic CNS and cardiovascular effects of lidocaine when compared to the non-asphyxiated fetus. This finding is attributed to increased uptake of lidocaine in fetal vessel rich tissues (such as the brain and heart) by means of (1) increased organ perfusion, (2) decreased plasma protein binding and (3) ionic trapping of lidocaine in acidotic tissues, all of which are known to occur during asphyxia. As a result, the smallest possible dose of local anesthetic amide should be utilized for regional blocks when the fetus is compromised or at increased risk for asphyxia. The safest local anesthetic in such circumstances is clearly 2-chloroprocaine, a rapidly hydrolyzed ester.

**Comparative toxicity**

With an elimination half-life of 21 seconds in maternal plasma and 43 seconds in fetal plasma, 2-chloroprocaine should be the safest local anesthetic, regarding maternal and fetal systemic toxicity. Chloroprocaine barely can be detected in

<table>
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<th>Table I</th>
<th>Half-life of elimination of local anesthetics commonly used in obstetrics*</th>
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<td>2-Chloroprocaine (Nesacaine®)</td>
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<td>Half-life:</td>
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<td>Adult</td>
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*2-Chloroprocaine, an ester, is rapidly hydrolyzed in maternal and fetal blood by plasma pseudocholinesterase. Lidocaine, mepivacaine, and bupivacaine are amides and undergo slower biodegradation in the liver. Breakdown products are eliminated by the kidneys.
fetal blood following lumbar epidural injections. As for amide-linked local anesthetics, significant plasma levels are detected in maternal and fetal blood following use in paracervical, pudendal, epidural and caudal blocks. During the normal conduct of these anesthetics, however, plasma levels usually remain lower than values associated with systemic toxicity.

Alarmingly high fetal levels only should occur after (1) inadvertent intravascular injections (e.g., a large dose into an epidural vein); (2) direct fetal injection (e.g., malpositioned needle intended for paracervical, pudendal, caudal block); (3) rapid absorption of local anesthetic into uterine circulation following paracervical block and (4) accumulation of lidocaine or mepivacaine (Carbo-
caine®) given continuously via epidural catheter for greater than 24 hours. As stated, fetal acidosis accentuates fetal tissue uptake and hinders transplacental elimination of the amide compounds from the fetus.

Some authorities advocate the use of bupiva-
caine—versus lidocaine or mepivacaine—in obstetrics, partly because of the widely held belief that bupivacaine (Marcaine®) crosses the placenta less extensively. Numerous studies have evaluated local anesthetic levels in fetal umbilical and maternal blood following various regional blocks for vaginal or cesarean delivery. Samples are drawn immediately after delivery from doubly clamped sections of umbilical cord and simultaneously from a maternal vein or artery. Following chromatographic analyses, comparisons are made by dividing umbilical venous plasma concentrations by levels in material plasma, yielding the Uv/M (or F/M) ratio. Table II summarizes Uv/M ratios for different local anesthetic amides in humans; values remain consistent in many studies. Interestingly, similar Uv/M ratios are seen in other species (e.g., primates, sheep, guinea pigs, etc.). While the lower Uv/M values for bupivacaine and etidocaine indicate less placental transport, this assumption simply is not valid. Lower Uv/M ratios occur with bupivacaine and etidocaine because (1) these drugs are bound more extensively to maternal plasma proteins than to fetal plasma proteins and (2) they have higher tissue-blood solubility coefficients in the fetus. As a result, they are taken up more extensively by fetal tissues (in comparison to lidocaine and mepi-
vacaine).

The amount of lidocaine, mepivacaine, bupi-
vacaine and etidocaine present in fetal tissues and blood (that is, the total placental transport) is the same when calculated in terms of percentage of these drugs administered to mother. Therefore, all local anesthetic amides cross the placenta in proportionate amounts, and the margin of safety in the fetus should be comparable following equipotent and clinically acceptable doses of these drugs to the mother. However, usage of mepivacaine has declined recently, because of a relatively longer half-life of elimination in the neonate (Table I).

In addition to a lower Uv/M plasma ratio and a theoretically lesser degree of placental transport, another reason accounts for the recent popularity of bupivacaine and also for the decreased use of lidocaine and mepivacaine in obstetrics. In 1974 Scanlon and coworkers reported that lidocaine and mepivacaine, when used for epidural analgesia during labor, compromised neonatal neurobe-

havior function. Scanlon’s modification of the Brazelton Neonatal Neurobehavioral Assessment Method—presently referred to as the Early Neo-
natal Neurobehavioral Score (ENNS)—detected significantly lower scores on tests of muscular strength and tone in infants whose mothers received continuous lumbar epidural blocks with lidocaine and mepivacaine compared with infants in a nonepidural group. In a subsequent study of epidural analgesia with bupivacaine, Scanlon et al. noted that infants in the epidural group did not differ significantly from nonepidural control infants in the previous study. They concluded that lidocaine and mepivacaine produced “floppy but alert babies,” making these compounds less desirable than bupivacaine and 2-chloroprocaine for use in obstetric regional anesthesia.

Aware of the reports by Scanlon et al., many

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<td>Fetal to maternal plasma concentration ratios at delivery, following maternal local anesthetic injections during labor or cesarean section</td>
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*2-Chloroprocaine is undetectable or present in very low concentrations due to rapid hydrolysis.
clinicians refrained from using lidocaine and mepivacaine, while others questioned the clinical significance of their findings. No study has associated the use of lidocaine or mepivacaine with poor maternal-infant bonding, feeding difficulties or subsequent impairment of neuropsychologic function. 23 Three more recent studies24-26 refute the data of Scanlon et al., in that neurobehavioral function was not substantially different in infants whose mothers received epidural anesthesia with lidocaine, bupivacaine or 2-chloroprocaine. Therefore, many authorities now believe that lidocaine is indeed safe for the neonate. It will well be the safest local anesthetic for use in obstetrics, considering the possible neurotoxic effect of 2-chloroprocaine and the potential cardiotoxic effect of bupivacaine in the mother.27 As a result, lidocaine recently has received renewed interest for its use in epidural anesthesia for labor or cesarean section.28

Indirect effects

The indirect (maternal) effects of local anesthetics unquestionably present greater hazards to the fetus, as compared to direct effects on fetal organs following placental transport. Maternal hypotension during regional blocks, seizure activity after inadvertent IV injections and uterine vasoconstriction resulting from high maternal plasma levels can produce severe fetal asphyxia by means of decreased uteroplacental perfusion.

Hypotension commonly occurs during epidural and spinal blocs for obstetrics but is usually most pronounced during cesarean section. However, sustained hypotension should be encountered infrequently if mothers are (1) prehydrated with balanced salt solution in a dose of 500 ml (in labor) or 1500 ml (prior to cesarean section), (2) nursed in the lateral tilt or decubitus position after initiation of epidurals and spinals and (3) given appropriate doses of IV ephedrine to prevent profound hypotension. Remember that the healthy human fetus can withstand temporary reductions in uterine blood flow (i.e., up to a 50% decrease) before becoming asphyxiated.27 This safety margin likely is not present, however, in high risk pregnancies where placental perfusion is already compromised.

This author recommends keeping maternal blood pressure at or above values known to be normal for the patient. For example, one can often find that a parturient's blood pressure is normally 90/60, or even lower, when reviewing blood pressure data from prenatal clinic records or inpatient charts. Typically, observed values of 130/80 or 140/90, often seen during labor or when patients are placed in a noisy, cold cesarean section room, do not represent normal or "baseline" blood pressures in most healthy parturients and should not be construed as such. Therefore, no data supports the often-stated premise that blood pressures should not be allowed to decrease by more than 25% from "baseline" (if baseline blood pressure is considered to be the value measured immediately prior to anesthesia). In circumstances where prenatal data are unavailable, systolic blood pressure should be kept above 100 mmHg or mean blood pressure above 80 mmHg in the healthy mother. In the author's institution, automated blood pressure monitors (Dinamap™ or Physiocontrol™) are used to assist in frequent blood pressure measurements and ephedrine is administered intravenously to keep blood pressure above the lowest value previously recorded in antenatal records. Using this method, significant maternal hypotension leading to fetal asphyxiation rarely occurs in our center.

Local anesthetic-induced seizures jeopardize the fetus in two ways: (1) maternal release of catecholamines which produce uterine vasoconstriction and decreased placental perfusion and (2) maternal hypoxemia and hypercarbia resulting from hypoventilation and from tonic-clonic muscle activity. Additionally, maternal regurgitation and aspiration of gastric contents can occur, leading to maternal and fetal hypoxemia. Obviously, little can be done to ameliorate the rise in plasma catecholamines once a seizure has occurred. Maintenance of good ventilation with pure oxygen and prevention of aspiration via cricoid pressure and readily available suction assume primary importance. Prolonged seizure activity, which occurs infrequently, or significant postictal depression indicate rapid tracheal intubation, which can be facilitated by 40-60 mg of succinylcholine. Local anesthetic seizures can be prevented or easily ameliorated by thiopental sodium, 50-100 mg, given intravenously. Larger thiopental doses are not required and should be avoided, because of possible cardiac depression in an already acidic myocardium.

Prevention of local anesthetic seizures remains the only effective treatment of resulting fetal asphyxia, because some degree of fetal hypoxemia and acidosis invariably occurs subsequent to seizure activity, and nothing can be done easily to correct the compromised fetus. Possible preventative measures presently generate much discussion at scientific meetings and in the literature.28 Shnider28 proposes the following maneuvers: (1)
aspirate the epidural catheter for blood prior to injecting the first and all subsequent doses; (2) use a test dose that contains not only a local anesthetic but also a marker (e.g. 1:200,000 epinephrine) and (3) administer the total epidural dose gradually—for example, give 5 ml then wait 30-60 seconds, 5 ml then wait 30-60 seconds and so on, looking for signs of an intravascular injection.

This author recommends the use of lidocaine, 1-2%, with 1:200,000 epinephrine for testing of all epidural catheters. Given in small doses, lidocaine more reliably produces the signs of mild CNS effect (tinnitus, metallic taste, etc.) than will other local anesthetics. Bupivacaine is least reliable in this respect, and we do not use bupivacaine until convinced that the catheter is positioned extravascularly. When injected intravenously, 15-20 µg of epinephrine will increase maternal pulse rate by 20-30 beats per minute within 30-60 seconds but should not significantly affect uterine blood flow.

A high index of suspicion also serves to prevent local anesthetic-induced seizures. The failure of an adequate epidural dose for labor (6-10 ml) to produce any signs of blockade indicates that the injection was given into an epidural vein instead of epidural space. In this case, one should not proceed with a larger dose, believing the previous dose to be insufficient. In addition, any change in the mother's mental status immediately following injection suggests IV catheter placement and precludes subsequent doses.

Even when present at plasma concentrations lower than required for seizure activity, local anesthetics can produce direct uterine vasoconstriction and an increase in myometrial tone. Greiss and coworker10 implanted uterine arterial cannulae, electromagnetic flow probes (distal to arterial cannulae) and intrauterine pressure balloons in pregnant ewes near term gestation. Following a sufficient period of recovery, they infused local anesthetics intra-arterially, finding that moderate levels of local anesthetics were associated with substantial reductions in uterine arterial flow (a local effect) and significant increases in intrauterine pressure (from uterine hypertonicity). They summarized that similar arterial concentrations of local anesthetics could occur after paracervical block or inadvertent IV injections. Such levels would not be achieved after uncomplicated continuous epidural, caudal or pudendal blocks. Interestingly, Greiss found bupivacaine to be the most noxious agent, followed in order by mepivacaine, lidocaine and 2-chloroprocaine. His data show that bupivacaine may not be the safest local anesthetic for use in obstetrics, at least in regard to uterine blood flow.

Conclusions

Recent evidence indicates that local anesthetics produce minimal fetal/neonatal effects following the normal conduct of obstetric regional blocks. Several circumstances can produce high fetal plasma levels of local anesthetics, but the fetus does not appear to be more sensitive to, nor have prolonged hepatic clearance of, the local anesthetic amides. In cases of fetal acidosis, however, amide-linked compounds will accumulate to a greater extent in fetal tissues, making 2-chloroprocaine the preferred agent during periods of distress. Previous reports linking bupivacaine to less placental transport and better neonatal neurobehavioral function have been refuted recently. Therefore, lidocaine has received renewed use for regional blocks in obstetrics, especially when considering possible deleterious effects of bupivacaine on the mother and on uterine perfusion. This is not to say that bupivacaine should not be utilized but that it should be used cautiously.

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