Integrated Laboratory Systems

Local Anesthetics That Metabolize to 2,6-Xylidine or *o*-Toluidine

Review of Toxicological Literature

Abridged Final Draft

Prepared for

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EXECUTIVE SUMMARY

The nomination of amide local anesthetics by a private individual is based on their widespread use in dentistry, general medicine, surgery, and in some consumer products (e.g., topical skin preparations). The amide local anesthetics bupivacaine, etidocaine, lidocaine, mepivacaine, and ropivacaine metabolize to 2,6-xylidine and 4-hydroxyxylidine. Prilocaine metabolizes to *o*-toluidine. Both 2,6-xylidine and *o*-toluidine have been shown to be carcinogenic in laboratory animals in NTP studies. Two other amide local anesthetics, pyrrocaine and trimecaine, that were considered for inclusion in this report were excluded after it was found that they are not used in the United States. For these reasons, the local anesthetics reviewed in this report are bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine.

Production, Use, and Exposure

There is no information available for the production volume of the amide local anesthetics. In 1990, U.S. sales of the injectable local anesthetics Xylocaine¤ (lidocaine hydrochloride) and Marcaine¤ (bupivacaine hydrochloride) were 22.5 million and 10.7 million dollars, respectively.

The amide local anesthetics block axonal nerve conduction by reaching the nerve axon and interfering with the function of the ion channels that control nerve impulse propagation. The amide local anesthetics are used intravenously, epidurally, topically, or subcutaneously to relieve pain during and after medical procedures. Lidocaine is also used as an antiarrhythmic agent. Long-acting, epidurally infused anesthetics such as bupivacaine and mepivacaine are becoming increasingly used in obstetrics and post-surgical management of pain. Topically applied anesthetics are used in dentistry and management of pain in the skin (e.g., burns, shingles). Lidocaine, in topical formulations for the treatment of skin irritation, is the only amide local anesthetic available over the counter.

Epidurally, intravenously, or subcutaneously administered amide local anesthetics would most likely result in acute exposure unless used for the management of pain during extensive, repeated dental or medical treatment. Epidural use of the long-acting local anesthetics such as bupivacaine and lidocaine can result in infusion periods of 96 hours for management of postoperative pain. Chronic use of lidocaine may occur from topical application to manage pain due to skin conditions such as shingles or burns. The exposure of the fetus to epidural local anesthetics given to the mother during delivery may be substantial. Studies with bupivacaine show that cord venous/maternal venous plasma concentration ratios of total bupivacaine are about 0.5; however, cord/maternal venous plasma ratios of unbound bupivacaine may be higher (>1) due to low protein binding in the fetus. Also, excretion of long-acting epidural anesthetics and their metabolites in neonates may persist for up to three days after delivery.

Analytical Determination

Analytical methods for determining amide local anesthetics and their metabolites in biological matrices and pharmaceutical preparations are described in some detail in Appendix J. In the 1970s and 1980s, packed-column gas chromatography (GC) methods predominated over capillary GC and HPLC (with ultraviolet detectors) methods. Packed-GC methods with

detection by mass spectrometry (MS), flame ionization detectors (FID), and nitrogen (N)-FID had sensitivities of at least 2.5 ng/mL (but usually greater than 20 ng/mL). Since the mid-1980s, capillary GC and HPLC have become more common. In the 1980s, capillary GC with detection by N-FID or MS with selected ion monitoring (SIM) to determine lidocaine, monoethylglycine-xylidide (MEGX), glycinexylidide (GX), and bupivacaine had high sensitivity peak levels of no more than 100 ng/mL. Other methods reported in the recent literature include capillary electrophoresis (CE), HPLC with a chiral stationary phase for enantiomeric separation, potentiometry using ion-selective electrodes, and fluorescence polarization immunoassay (FPIA). Sample preparation methods include microporous membrane liquid-liquid extraction and solid-phase extraction. Limits of detection (LOD) for the anesthetics and metabolites in plasma and urine for many methods are in the range 1 to 10 ng/mL.

Regulations

Local anesthetics are regulated by the Food and Drug Administration and Consumer Product Safety Commission (CPSC). The use and safety of the local anesthetics is reviewed and evaluated by the Center for Drug Evaluations and Research–Anesthetic and Life Support Advisory Committee. In 1994, the CPSC voted unanimously to require child-resistant packaging for lidocaine formulations (containing >5% lidocaine) due to many cases of accidental ingestion by children resulting in 16 deaths. In 1993, the FDA s Anesthetic and Life Support Advisory Committee voted unanimously that evidence of carcinogenicity of the lidocaine metabolite 2,6-xylidine was insufficient for labels to mention that it caused tumors in laboratory rats. The FDA now requires that products that may metabolize to aniline compounds (lidocaine, prilocaine, and EMLA [the eutectic mixture of lidocaine and prilocaine) carry a warning of carcinogenic risk in the package inserts.

Metabolism

General Metabolism and Excretion

Metabolism of the amide local anesthetics is extensive in all species and is the primary factor limiting the length and intensity of anesthesia and governing elimination from the body. General pathways in metabolism include aromatic ring and side-chain hydroxylation, N-dealkylation, and hydrolysis of the amide bond. In primates (including man) and dogs, N-dealkylation appears to be the predominant pathway to metabolites detected in urine samples, with subsequent hydroxylation primarily in the 4-position of the xylidine moiety. In the rat and guinea pig, hydroxylation products, primarily in the 3-position of the xylidine moiety, are the predominant species excreted, with minor amounts of dealkylated products detected. Hydroxylation at the 4-position of 2,6-xylidine may predominate in all species, probably due to the lack of steric interference by the alkyl chain or pipecolyl ring (Dring, 1976).

Hydroxylation may occur primarily prior to amide hydrolysis, with minor amounts of metabolites being hydroxylated after hydrolysis. The local anesthetics along with their metabolites are predominantly excreted in the urine, with a small fraction excreted in the feces. Almost all of the hydroxylated metabolites are recovered in the urine as glucuronide or sulfate conjugates. Urinary excretion of unhydroxylated dealkylated metabolites (e.g., xylidine, PPX) is very low (~1-5%) after administration of the local anesthetics. The predominant metabolite excreted in the urine after lidocaine administration is 4-hydroxyxylidine (65-80% of the dose) and may be the predominant metabolite of the other amide local anesthetics. Unfortunately,

most studies have not been designed to detect the hydrolysis products containing the xylidine moiety.

In the liver, local anesthetics are metabolized by certain cytochrome isozymes. The metabolism of ropivacaine is mediated oxidatively by hepatic cytochrome P450 (CYP) 1A2 and 3A4 in humans and in rat hepatic cytochromes. Cytochromes CYP3A4 in humans and CYP2C11 and CYP2B1 in rats are responsible for the deethylation of lidocaine to MEGX *in vitro*. P450 isozymes 1A2 and 3A4 have been found to be involved in the metabolism of about 50% and 7%, respectively, of all prescribed drugs. The CYP1A2 enzyme is constitutively expressed in the liver and comprises about 10% of the total P450 in the liver. The CYP1A1 enzyme is only expressed after exposure to certain chemical inducers in human tissue. CYP3A4 comprises from 30% to 60% of the total liver P450s. It is possible that drug interactions may occur which decrease the metabolism of the local anesthetics. For example, 3'-hydroxyropivacaine, the major *in vivo* metabolite of ropivacaine, is formed by CYP1A. If another drug is used concomitantly with ropivacaine and has a higher affinity for the CYP1A enzyme, then the half-life of elimination of the local anesthetic from the blood may be increased.

While there is large interindividual variation in metabolism within each study, examination of the means reveals a general pattern of metabolism within each species. There are very pronounced interspecies variations in the location of hydroxylation and amount of dealkylation of the amide local anesthetics. 3-Hydroxylation on the xylidine moiety is predominant in rodents while 4-hydroxylation predominates in primates. Biliary excretion of lidocaine is much more pronounced in rodents than it is in humans. One metabolite of lidocaine, 2-aminomethylbenzoic acid, has been found in rabbits, dogs, and possibly guinea pigs, but has not been detected in humans. The interspecies differences in the metabolism of lidocaine are best presented in Keenaghan and Boyes (1972).

Respired CO_2 is a route of elimination in mice but has not been adequately measured in humans. Respired CO_2 contained between 10.5 and 11.4% of the radiolabeled dose of mepivacaine when administered to mice.

The placental transfer of three metabolites of etidocaine was related to the lipophilicity of the metabolites. The greater the lipophilicity, the greater the cord/maternal plasma ratio.

Metabolism of drugs in the human neonate is less than in the human adult due to the immaturity of hepatic enzyme systems. This is also true in the case of the local anesthetics. The mean dose of mepivacaine excreted in the urine of human neonates unchanged is 43.4%, while only 3.5% is excreted in the urine of human adults unchanged. The mean percentage of lidocaine excreted unchanged in the urine of human neonates is 19.7%; however, 4.2% remains unchanged in the urine of adult humans.

Urinary excretion of the local anesthetics is pH-dependent. Acidic urine results in increased concentrations of the local anesthetics and some metabolites in the urine, whereas alkaline urine yields lower concentrations. For the most part urinary excretion of metabolites is pH independent.

Very little local anesthetic is eliminated in the feces of humans and only slightly more is eliminated in the urine of rodents. In rodents, it is thought that the metabolites excreted in bile are reabsorbed through the intestines to the bloodstream.

In the case of lidocaine and prilocaine, there is some evidence of *in vivo* and *in vitro* extrahepatic metabolism. Extrahepatic formation of MEGX after lidocaine hydrochloride injection was demonstrated in an anhepatic patient awaiting a liver transplant. It has been further

shown *in vitro* that extrahepatic metabolism in rats may occur in the kidney and lung, but not the brain. A very slow rate of MEGX and 3-hydroxylidocaine formation (0.022-0.024 nmol/min/mg protein) was observed in rat kidney microsomes as well as a slow rate of formation of MEGX (0.87 nmol/min/mg). The rate of formation of MEGX and 3-hydroxylidocaine by rat hepatic microsomes was 4.84 and 0.64 nmol/min/mg, respectively. There is evidence that CYP2B1 may be the sole isoenzyme responsible for the de-ethylation of lidocaine in rat pulmonary and renal microsomes. Extrahepatic clearance of prilocaine in humans is thought to occur because of its high hepatic extraction (2.85 L/min), which is higher than the hepatic blood flow rate in humans (~1.5 L/min).

Evidence for the Formation of Xylidine, *o*-Toluidine, and Other Metabolites

On the basis of structure, 2,6-xylidine could possibly be formed by the hydrolysis of the amide linkage in local anesthetics containing the xylidine moiety (all local anesthetics reviewed in this report except prilocaine). The hydrolysis of the amide linkage of prilocaine results in the formation of *o*-toluidine.

A review of the literature reveals that the major metabolites associated with the selected local anesthetics in this report are 4-hydroxyxylidine, hydroxylated parent compounds, and other hydroxylated dealkylated metabolites. The predominant metabolite excreted in the urine after lidocaine administration is 4-hydroxyxylidine (65-80% of the dose) and may be the predominant metabolite of the other amide local anesthetics containing the xylidine moiety. 2,6-Xylidine (XYL) should be considered a minor metabolite of the amide local anesthetics containing the xylidine moiety, except ropivacaine. No 2,6-xylidine was detected in human urine after administration of ropivacaine. *o*-Toluidine is a minor metabolite of prilocaine. Selected metabolites of the local anesthetics and their amounts in humans and rats are provided in the table following this metabolism summary. As can be seen in the table, there is still a large portion of the dose of the local anesthetics, other than lidocaine, that has not been accounted for.

Xylidine has been detected in the urine of humans after administration of etidocaine and in several species after administration of lidocaine. Concentrations of xylidine detected in 24-hour urine collections from human volunteers were 0.46% of the administered dose after etidocaine administration and 0.84-1.0% after lidocaine administration. The highest concentration of xylidine was detected in the urine of guinea pigs after lidocaine administration (16.2% of the administered dose). Only one study was located that sought to determine the concentration of xylidine in the urine of humans after administration of bupivacaine. No xylidine was found in the urine, but details of the study were not available.

Xylidine has been detected in the urine of neonates after the administration of anesthetics to the mother during delivery. After administration of etidocaine to seven mothers, xylidine (trace-1.9 µg in 5 neonates) and 4-hydroxyxylidine (2-6 µg in 3 neonates) were determined in 48-hour urine collections from the neonates. It was interesting that the neonates that produced xylidine had no detectable concentrations of 4-hydroxyxylidine and vice versa. Also, a set of twins was able to form one metabolite and not the other, which implicates genetic variables in neonatal metabolism.

Two metabolites, *N*-hydroxyxylidine from lidocaine and *o*-toluidine from prilocaine, have been shown to form hemoglobin adducts. Xylidine-hemoglobin adducts have been detected in the blood of tobacco smokers and nonsmokers after the proposed reaction of hemoglobin with *N*-hydroxyxylidine. In a study of nine patients undergoing treatment for cardiac arrhythmia,

concentrations of xylidine-hemoglobin adducts ranged from 110 to 690 ng 2,6-xylidine/g hemoglobin. Two patients had measurable xylidine-hemoglobin adducts prior to lidocaine infusion; one patient between 50 and 100 ng xylidine/g hemoglobin and the other had a concentration of 423 ng/g hemoglobin.

MEGX and GX are formed from the N-dealkylation of lidocaine. Concentrations of MEGX and GX determined in human urine samples range from 1.7-12.68% of the administered dose and 0.55-2.3% of the dose, respectively. Both MEGX and GX are hydroxylated on the xylidine ring after lidocaine administration to yield 3- and 4-hydroxymethylethylglycinexylidide, and 3- and 4-hydroxyglicinexylidide.

Pipecoloxylidide (PPX; pipecolylxylidide) is the N-dealkylated product of the amide local anesthetics that contain a pipecolyl moiety as the hydrophobic substituent attached to the amide intermediate bupivacaine, mepivacaine, and ropivacaine. PPX does not appear to be a major metabolite of these anesthetics; however, it should be remembered that PPX is about twice as neurotoxic as bupivacaine. Excretion of PPX after administration of bupivacaine revealed that the two are differentially excreted in breast milk. While the mean bupivacaine serum and breast milk concentrations were highest two hours after epidural injection (0.23 and 0.09 µg/mL, respectively), the mean serum and breast milk PPX concentrations were highest 12 hours after administration (0.17 and 0.25 µg/mL, respectively).

The metabolites of the amide local anesthetics contain properties on their own that may affect the pharmacokinetics or toxicity of the local anesthetic. The *N*-hydroxyamine metabolite of lidocaine, *N*-hydroxylidocaine, and the dealkylated metabolite of prilocaine, *o*-toluidine, both form hemoglobin adducts resulting in hemoglobinemia after administration of each of the two local anesthetics. The lidocaine metabolites MEGX and GX have antiarrhythmic properties that may contribute to the antiarrhythmic activity of lidocaine. The antiarrhythmic properties of MEGX are approximately 80% of those of lidocaine. The hydantoin etidocaine metabolite 3-(2,6-dimethylphenyl)-5-ethyl-2,4-imidazolidininedione, which comprised 10% of the dose excreted in the urine, may contribute to the lower toxicity of etidocaine when compared to bupivacaine since hydantoins are known to have anticonvulsant properties.

Recommendations for Future Metabolism Studies

Lidocaine is the only amide local anesthetic for which most of the administered dose has been characterized. This was due to the fact that the Keenaghan and Boyes (1972) study of metabolism used lidocaine randomly tritiated in the benzene moiety. Less than 50% of the dose of the other amide local anesthetics (bupivacaine, etidocaine, mepivacaine, prilocaine, and ropivacaine) has been recovered in the urine. The characterization of the metabolism of these anesthetics is lacking due to the labeling of the anesthetics in the pipecolyl or carbonyl moiety, which does not account for xylidine or phenolic compounds. The design of future metabolite studies should allow for the accurate determination of the formation of xylidine and 4-hydroxyxylidine in urine, plasma, and other tissues after local anesthetic administration. More current tissue distribution studies to determine metabolite concentrations are also needed since there is evidence of extrahepatic metabolism in rat pulmonary, renal, and nasal microsomes *in vitro*. Also extrahepatic metabolism is supported by the clearance rates of the local anesthetics in human clinical studies, which are higher than hepatic clearance rates. Metabolism in the skin should be determined since lidocaine and prilocaine may persist in damaged skin for hours after application, and since there may be chronic dermal exposure to damaged skin from formulations

containing lidocaine. Many of the over-the-counter formulations are recommended for sunburns. It has been shown that lidocaine may inhibit the DNA repair of thymidine dimers in *Escherichia coli* after exposure to ultraviolet (UV) radiation. Since lidocaine has been found to be metabolized by rat nasal microsomes and nasal carcinomas have been detected in rats after exposure to the lidocaine metabolite 2,6-xylidine, the risk of applying lidocaine to the nasal cavity for the treatment of migraines should be assessed.

Careful attention should be devoted to sample work-up and analytical methods used to determine the concentration of metabolites. Standardization of sampling and analysis methods would be effective in establishing accurate information for the comparison of metabolism of the amide local anesthetics. Injection speed during analysis may be important for accurate separation of 3'- and 4'-hydroxylated metabolites. Both enzyme and acid hydrolysis should be employed to separate conjugated metabolites from unconjugated metabolites. Urinary excretion of metabolites of the amide local anesthetics may not accurately reflect the concentration of the metabolites in plasma. *In vitro* methods for the quantitative determination of metabolites do not accurately represent the actual *in vivo* urinary excretion of these metabolites due to the many physiological factors, especially hepatic blood flow and plasma protein binding, that affect the metabolism of the amide local anesthetics.

Pharmacokinetics

The potency and duration of action of the amide local anesthetics are closely related to the physical-chemical properties and structure of the individual anesthetic, respectively. The amide local anesthetics are weak bases that are variably lipophilic. The more highly substituted the alkyl or tertiary amines on or near the tertiary amine or in the aromatic ring, the more lipophilic the anesthetic. It is the lipophilicity, measured by the octanol/aqueous buffer partition coefficient that positively correlates with the anesthetic potency. Bupivacaine and etidocaine are the most potent and most lipophilic amide local anesthetics. The degree of interindividual variation in pharmacokinetic parameters seen in most studies is probably due to variations in factors that control clearance, such as blood flow, pH in blood and tissues, hepatic clearance rates, and possibly plasma protein concentrations. The amide local anesthetics in this report, except for ropivacaine are racemic mixtures containing both (R)- and (S)-enantiomers. The (S)-enantiomers of bupivacaine and prilocaine have been shown to have higher total body clearance and lower toxicity than the (R)-enantiomers in humans and dogs.

Absorption and distribution of amide local anesthetics varies depending on many factors, such as site and method of administration, blood flow characteristics, plasma protein binding, plasma pH, and the physical properties of the local anesthetic (i.e., pK_a, hydrophobicity, etc.). Absorption from the site of injection depends on the blood flow–the higher the blood flow, the more rapid the rate at which plasma concentrations increase and the greater the peak plasma concentrations of the drug. When a local anesthetic is injected, the rate of absorption is greatest after intercostal block, followed by epidural, brachial plexus, and lower limb blocks, with subcutaneous (s.c.) infiltration being the slowest. If vasoconstrictors, such as epinephrine, are administered with the local anesthetic, then the rate of absorption into systemic circulation is reduced, usually allowing the safe dose of the anesthetic to be increased by 50-100%.

Subcutaneous and dermal application of the local anesthetics (prilocaine and lidocaine only) results in prolonged persistence of the local anesthetics at the site of application. Local anesthetics do not readily penetrate healthy human skin in their salt form; however, effects may

be seen if applied in their base form. Dermal absorption will be affected by the vehicle that contains the local anesthetic. The maximum anesthetic effect was observed one hour after application of lidocaine. The onset of anesthetic action after dermal application can be correlated with the local anesthetic s solubility in medium-chain triglycerides, which have properties similar to stratum corneum lipids. Dermal absorption of local anesthetics is affected by the vasculature of the area of application, age of the patient and condition of the skin. Lidocaine plasma concentrations after dermal application have been observed to peak 32 hours or longer after application in some individuals. In neonates, dermal absorption is more rapid than in adults due to the immaturity of the skin, which behaves more like a mucous membrane.

The absorption of the local anesthetics from the epidural space is biphasic, with an initial rapid phase followed by a slower terminal phase. Absorption from the epidural space into the blood is almost as rapid as absorption after dermal exposure. This may be due to the effect of the anesthetic on the local tissue vasculature. Bupivacaine and lidocaine have both been shown to produce vasodilation at the area of administration, thereby increasing the rate of absorption to the bloodstream from the site of administration. Another factor that may contribute to the slower absorption of the local anesthetics from the epidural space is its high fat content. The more lipid-soluble compounds, such as bupivacaine and ropivacaine, are released more slowly from the epidural space than the less lipid-soluble anesthetic lidocaine.

The transport of the amide local anesthetics across biological membranes is by passive diffusion, which in the case of the amide local anesthetics, is dependent on the pH. Higher concentrations of the anesthetic will be found in the tissue or compartment with lower pH. Decreasing the pH of the urine results in increased concentrations of the local anesthetic excreted in the urine. However, the excretion of metabolites in urine is not usually affected by pH.

The plasma protein binding of the amide local anesthetics by α_1-acid glycoprotein and albumin buffers the anesthetic dose from the tissues by sequestering it since mostly the unbound molecules are transported across biological membranes and into tissues. As much as 95% of the dose may be bound to plasma proteins in the case of bupivacaine and ropivacaine. Protein binding and pH play important factors in the transport of local anesthetics across the placenta. Acidosis of the fetus in mothers administered local anesthetics during delivery can result in higher fetal plasma and tissue concentrations of the local anesthetic. Even though plasma protein levels are lower in the fetus and the neonate, the greater volume of distribution and increased urinary excretion in the neonate maintain plasma concentrations similar to or close to concentrations seen in the mother.

The distribution of local anesthetics is characterized by a biphasic model, an α-phase and a β-phase. The α-phase is characterized by the rapid absorption of the anesthetic by the organs and tissue and is measured by the α-phase half-life ($T_{1/2\alpha}$). The $T_{1/2\alpha}$ of the amide local anesthetics is relatively rapid and is usually about 20 minutes or less. However, once the tissues become saturated with the maximum concentration of local anesthetic, then the elimination of the local anesthetic rapidly decreases until it approaches the $T_{1/2\beta}$. The $T_{1/2\beta}$ is the total body clearance of the local anesthetic due to hepatic extraction and excretion. The $T_{1/2\beta}$ is under the influence of plasma protein binding of the local anesthetic, as well as hepatic clearance.

Local anesthetics are distributed throughout all body tissues, but the concentrations in each tissue will vary. The more highly perfused tissues, such as the lungs, heart, liver, and kidney, will have higher concentrations of the local anesthetic than less perfused organs. The lungs sequester large amounts of local anesthetics after administration so that plasma

concentrations of local anesthetic decrease considerably after passing through the lungs. The highest percentage of local anesthetic is found in the skeletal muscle, probably because it is the tissue that comprises the majority of human mass and not because there is a higher affinity for the local anesthetics in the skeletal muscle.

The placental transfer of the local anesthetics by passive diffusion is affected by the drug s molecular weight, lipid solubility, pK_a, protein binding, fetal pH, and fetal absorption. The amide local anesthetics readily cross the placenta by passive diffusion in the unbound un-ionized form. Studies have shown that the cord-to-maternal plasma concentrations of local anesthetics equilibrate quickly across the placenta and reach a relatively constant level 15-30 minutes after administration to the mother due to the high lipid solubility of the un-ionized form and their low molecular weight. The rate of transfer of a drug across the placenta is measured by the umbilical venous/maternal venous ratio (UV:MV) upon administration of the drug, and while fetal tissue saturation is incomplete, the umbilical artery/maternal venous (UA:MV) concentration ratio should increase to reach a plateau that approaches the UV:MV. During maternal drug absorption, a small gradient may exist if there is fetal metabolism. Both UV:MV and UA:MV are affected by transplacental pH and governed by the gradient of transplacental -glycoprotein. The main cause of interindividual variation should be overcome by examining the UA:UV ratio, which gauges the extent of fetal equilibration and is not affected by α-glycoprotein concentration. The decreased amount of protein binding in the fetus and neonate would likely result in greater volume of distribution and may contribute to the reduced rate of elimination in the fetus. Elimination half-life of the local anesthetics in the human neonate is about 2-3 times longer than elimination in adults. The differences in UV:MV concentration ratios for the local anesthetics probably are due to the differences in protein binding; however, the concentration of *unbound* local anesthetic in the plasma of both mother and fetus should be the same at equilibrium.

Several factors may confound pharmacokinetics studies. Many human pharmacokinetics studies, especially the fetal transfer and obstetrics studies, allow supplemental dosing to achieve an effective level of pain management, which will vary greatly for each individual. This variability of the dose in human pharmacokinetics studies complicates dose interpretation. Also, many drugs that may effect the metabolism or pharmacokinetics of the amide local anesthetics, such as opioids, cemetidine, or propanalol, are routinely administered during medical treatment requiring local anesthesia. The interindividual variability in protein binding of the local anesthetics will effect the transfer across biological membranes, which may affect elimination rates and transfer across the placenta. Since most of the local anesthetic dose is contained in plasma, analyzing plasma will lead to higher concentrations than would be found in whole blood.

Summary of Selected Metabolites of Local Anesthetics and Their Amounts in Urine of Humans and Rats

Criteria	Local Anesthetic					
	Bupivacaine	**Etidocaine**	**Lidocaine**	**Mepivacaine**	**Prilocaine**	**Ropivacaine**
Percentage of Dose in Human Urine:						
Unchanged	0.13-6.0%	0.21%	2.1-4.76%	<5%		1.0%
2,6-Xylidine	n.f.[a]	0.46-2.16%	0.84-1.0%	-	X	-
Hydroxylated 2,6-xylidine	-	3.23-8.3	60.5-80.1%	-	X	-
o-Toluidine	X	X	X	X	0.75%	X
Hydroxylated *o*-toluidine	X	X	X	X	36.9%	X
MEGX	X	X	1.7-12.68%	X	X	X
GX	X	X	0.55-2.3%	X	X	X
PPX	1.21-5.0%	X	X	1.0-1.2%	X	2.8%
Hydroxylated parent compound	3.75-5.37%	~10.0%	0.2-1.58%	17.7-29.5%	-	37.3%
Other metabolites not mentioned above	4.9% and some not quantitated but considered to be minor	29.5%	36.38-36.68%	<10%	-	2.2%
Percentage of Dose in Urine of Rats:						
Unchanged	2.8-3.4%	n.a.	0.2%	-	-	n.a.
2,6-Xylidine	-	n.a.	1.5%	-	X	n.a.
Hydroxylated xylidine	X	n.a.	minute-12.4%	-	X	n.a.
o-Toluidine	X	n.a.	X	X	-	n.a.
MEGX	X	n.a.	0.7%	X	X	n.a.
GX	X	n.a.	2.1%	X	X	n.a.
PPX	0.3-1.1%	n.a.	X	X	X	n.a.
Hydroxylated parent compound	19.8-73.6%	n.a.	9.0-36.2%	50.0-59.2%	-	n.a.
Other metabolites not mentioned above	1.6-6.0%	n.a.	minute-36.9%	-	-	n.a.

An X in a column indicates that the compound is not a possible metabolite of that local anesthetic.
Dashes in a column indicates that the metabolite has not been detected in any studies.
n.a. = information not available because no studies were found
n.f. = not found in one study (Mather et al., 1971; Cited by Tucker and Mather, 1979) but study details were not provided.

Some Pharmacokinetic Parameters of the Amide Local Anesthetics

Local Anesthetic	RAP	PB (%)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (hours)		UV/MV	V_{DSS} (L)	CL (L/min)	E_H (%)
				Adult	Neonate				
Bupivacaine	4	95	2.7	3.5	8.1	0.33-0.59	72	0.47-0.58	38
Etidocaine	2	94-95	2.2	2.6	6.42	0.23-0.55, 0.16-1.38[a]	133	1.11-1.22	74
Lidocaine	1	64-70	1.0	1.6, 1.8	3.05, 3.16	0.51	91	0.95	65
Mepivacaine	1	75-77	0.7	1.9, 3.17	8.95, 8.69		84	0.78	52
Prilocaine	1	40-55	0.5	1.5			261	2.84	
Ropivacaine	4	94		1.75			59	0.73	49

[a] This value is in whole-blood rather than plasma

Abbreviations: CL = rate of clearance from plasma; E_H = hepatic extraction; PB = Percent of local anesthetic bound to protein in plasma at 1 µg/mL serum, higher concentrations of the local anesthetic in plasma will decrease the percent bound to protein; RAP = relative anesthetic potency when compared to lidocaine; $t_{1/2\alpha}$ = half-life of elimination from plasma; $t_{1/2\beta}$ = half-life of absorption to tissue from plasma; UV/MV = umbilical venous/maternal venous plasma or serum concentration ratios; V_{DSS} = volume of distribution at steady state

Human Data

Systemic Effects

Local anesthetic drugs are potentially toxic if they are administered in high doses or into the wrong anatomic site, reaching the major target organs of toxicity, the brain and heart. The central nervous system (CNS) is more susceptible to the systemic actions of the drugs than the cardiovascular system (CVS) [which is also true in animals]. Therefore, CNS toxicity usually occurs before and is a good warning of CVS toxicity induced by local anesthetics. CNS toxicity ranges from excitation to convulsions. Symptoms and signs include feelings of lightheadedness, drowsiness, nervousness, irrational conversation, and tremors, and may be followed by seizures, respiratory arrest, myocardial depression, and even death. If the local anesthetic is rapidly administered by i.v. injection or given as a large dose, CNS depression immediately follows excitation, indicating that a dose-dependent and blood concentration-dependent action on the system may be exerted by the local anesthetic. The therapeutic blood-plasma/serum concentrations range from 0.25-5 g/mL for bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. The toxic levels range from 1-10 g/mL. A comatose-fatal blood-plasma/serum concentration of 10 g/mL was reported for lidocaine and ~20 g/mL for prilocaine. The maximum tolerated doses for the above local anesthetics, excluding prilocaine, range from 1.4-9.8 mg/kg.

In regards to the CVS, local anesthetics can have a direct effect on both the heart and peripheral blood vessels. Although they have a suppressant effect on the heart, they can also act as vasodilators. Some local anesthetics, particularly the potent, highly lipid-soluble, highly protein-bound agents (e.g., bupivacaine and etidocaine) have induced sudden cardiovascular collapse, ventricular arrhythmias and fibrillation, and even death. The primary cardiac electrophysiologic effect is a lowering of the maximum rate of depolarization in Purkinje fibers and ventricular muscle. The drugs can also exert an effect on the mechanical activity of cardiac

muscle. At certain doses, they can serve as effective anticonvulsant agents and antiarrhythmic agents.

Clinically, local neurotoxicity can occur after an accidental subarachnoid injection of an epidural dose of a local anesthetic; up to 30 mL of anesthetic solution can be injected inadvertently into the subarachnoid space. Clinically used local anesthetics, however, rarely produce localized nerve damage. Intramuscular injection of the drugs has resulted in skeletal muscle changes. Bupivacaine and etidocaine were observed to cause more localized skeletal muscle damage versus lidocaine, mepivacaine, and prilocaine. The damage was reversible, with muscle regeneration complete within two weeks following injection.

Reproductive and Teratological Effects

Intracervical and intraspinal administration of bupivacaine to women have resulted in specific developmental abnormalities in the CVS and in behavioral and other postnatal effects on the newborn, respectively. Parenteral administration of lidocaine to pregnant women has shown specific developmental abnormalities in the CNS. In two male subjects given 1% lidocaine hydrochloride into the base of each cavernosum during a routine circumcision, impotence resulted.

The primary source of epidemiological data on potential teratogenic effects of local anesthetics is the Collaborative Perinatal Project. Bupivacaine, etidocaine, prilocaine, and pyrrocaine were not included and have not been adequately studied for teratogenic effects. There are no reports of congenital anomalies in children born to women who had these drugs administered during pregnancy.

Neonatal Effects

Acid-base status, Apgar scores, and neurobehavioral assessments have shown that local anesthetics have negligible effects on the neonate. However, significant behavioral differences (e.g., total looking times, preferences for visual stimuli) between infants (ranging in age from 20 hours to six days) exposed to local anesthetics during gestation and unexposed infants have been observed. Studies on whether epidural anesthesia adversely affects newborn behavior are conflicting.

Methemoglobinemia

Large doses of prilocaine have resulted in the development of methemoglobinemia; in general, at least a 600-mg dose is needed to produce clinically significant levels when administered epidurally in adults. Peak values of methemoglobin were reached six hours after administration of prilocaine but disappeared after 24 hours in most patients. The duration and intensity of cyanosis correlated with the duration and extent of methemoglobinemia. Lidocaine and xylidine intoxication has also produced methemoglobinemia. In contrast to prilocaine, single doses of lidocaine (500 mg) produced detectable amounts of methemoglobin but no cyanosis. Mepivacaine may induce methemoglobinemia as well as cyanosis.

Methemoglobin was detected in the blood of infants whose mothers were given epidural analgesia with prilocaine for delivery. Overall, direct application of EMLA (lidocaine-prilocaine cream) has not produced the condition. However, the combined use of EMLA (containing 12.5 mg prilocaine) and caudal anesthesia (5.4-6.7 mg/kg prilocaine) for herniotomy in premature infants resulted in toxic methemoglobinemia.

The Toxicity of Regional versus General Anesthesia

Regional anesthesia is preferred to general anesthesia during labor because of the fewer maternal deaths and serious injuries that occur. The toxic effects of regional anesthesia using amide local anesthetics on the fetus are primarily caused by maternal hypotension and seizures; effects of local anesthetics on the newborn infant are minimal and short-lived. General anesthesia results in brief, minimal depression of the healthy term neonate and greater occurrences of lower neonatal Apgar scores and respiratory depression.

Immunotoxicity

The few occurrences of allergic reactions (e.g., cutaneous lesions, edema, asthma, and anaphylactoid reactions) to amino amide local anesthetics have been linked with the presence of methylparaben, a preservative used in some commercial preparations of the agents and a compound that is chemically related to *p*-aminobenzoic acid and also a known allergen.

Lidocaine, in contrast to bupivacaine and mepivacaine, has been found to significantly inhibit natural killer (NK) cytotoxicity at low concentrations. In newborns delivered by elective cesarean section under epidural anesthesia (lidocaine hydrochloride with epinephrine), NK cell activity was significantly lowered compared to those delivered without labor by elective cesarean section under general anesthesia (thiopentone) but similar to those delivered vaginally with uncomplicated labor (no analgesia). Furthermore, in newborns born by cesarean section with epidural lidocaine anesthesia, neutrophil chemotaxis levels were significantly lowered compared to those of the other two groups; a significant inverse relationship between chemotaxis and lidocaine levels was observed.

Animal Data

Acute Toxicity

Lethal dose values for local anesthetics and their metabolites in several species via various routes (e.g., implantation, intraspinal, parenteral, and subcutaneous) have been reported. In rats, the oral LD_{50} value was 317 mg/kg with lidocaine. Using lidocaine hydrochloride monohydrate, the value was 292 mg/kg in mice. With mepivacaine, a value of >5000 mg/kg was obtained for both rats and mice. Oral LD_{50} values for metabolites were the following: >500 mg/kg with 4-hydroxy-2,6-xylidine in the rat; 234 mg/kg with MEGX in the mouse; 520 mg/kg in mice and 670 mg/kg in rats with *o*-toluidine; and 707 and 840 mg/kg, respectively, with 2,6-xylidine.

Only studies in mammals (laboratory rodents, rabbits, cats, dogs, monkeys, pigs, and sheep) were considered for inclusion. Endpoints studied included CNS and CVS toxicity (most commonly, ventricular arrhythmias and cardiovascular collapse), muscle degeneration and regeneration (particularly in rats), and maternal and fetal toxicity during delivery (mostly in sheep). Studies with bupivacaine comprised the largest amount of data. No effort was made to collect and summarize the lidocaine toxicity literature; the comprehensiveness of literature searches was complicated by the total numbers of lidocaine publications in the biomedical databases searched.

Short-term and Subchronic Exposure

In male rats, intrathecal implantation of 0.75% bupivacaine for up to eight days caused sensory anesthesia. When injected into the plantaris muscle of rats (0.15 mL of 0.5% w/v

bupivacaine hydrochloride in saline) daily for ten weeks, muscle degeneration and regeneration occurred. The mean weights of the muscle, the number of total branched fibers, and the maximum absolute twitch and tetanic tensions were increased compared to controls. When anesthetic-impregnated silastic cuffs containing 5-60% by weight bupivacaine were implanted into the soleus and/or lumbricalis muscles of rats and rabbits for three to 11 days, acetylcholine sensitivity was found in all muscle fibers. In pigs, epidural administration of bupivacaine (4 mL of 0.5% compound twice daily) for seven days caused slight inflammatory changes in ligamentum flavum and dura mater. In dogs, continuous intrathecal infusion (5.7-11.1 mg of 0.15-0.37% bupivacaine hydrochloride) for three to 16 weeks caused a markedly decreased response to toe-pinch of the hind limbs. Upon termination of bupivacaine infusions, all animals except one returned to fully normal gait.

Four potentially applicable lidocaine studies were not reviewed. No studies were available for the other amide local anesthetics.

Chronic Exposure

In rats, injection of bupivacaine (0.6 mL of 0.75% compound) into the right anterior tibial muscle daily for six months caused muscle fibers to be smaller than controls. Numerous internal nuclei, extensive fiber splitting, whorling of the intermyofibrillar network, and an enlarged zone of terminal innervation were also observed.

In newborn mdx mice and C57BL/10ScSn mice serving as controls, bupivacaine (0.1 mL of 0.5% compound) was injected into the right soleus muscle intermittently for up to nine or 12 months. At nine months, the muscle of the mdx mice had much variability in muscle fiber size; there was an increase in the percent small fibers compared with control mice. At nine and 12 months, the pattern of distribution of the fiber diameter for the right soleus muscle was more evenly distributed than the saline-injected left soleus muscle, while in control mice the pattern of distribution in the right soleus muscle did not differ from the left. In mdx mice, endomysial collagen content was higher than that of control mice.

Three potentially applicable lidocaine studies were not reviewed. No studies were available for the other amide local anesthetics.

Synergistic or Antagonist Effects

No synergism or antagonism has been observed in mixtures of either amide-amide or amide-ester local anesthetics. When added to solutions of local anesthetics, vasoconstrictors produce variable results, depending on the local anesthetic used and the type of anesthesia. In surface anesthesia, epinephrine and norepinephrine increased the action of local anesthetics at the superficial level. In lingual anesthesia, no effect was seen. In infiltration, conduction, spinal, and epidural anesthesia, vasoconstrictors increased the duration of anesthesia. In conduction and infiltration anesthesia, greater activity was observed with epinephrine versus norepinephrine.

The addition of glucose has inactivated some local anesthetics but not that of lidocaine. In the presence of carbon dioxide, the activity of solutions of lidocaine and mepivacaine was increased. Polymers have also increased the duration of action of local anesthetics. In the presence of the cholinergic substance pyridostigmine, the anesthetic effect of lidocaine was increased in surface anesthesia. The activity of the drug was also increased in surface, infiltration, and conduction anesthesia with the prior parenteral administration of the antidepressants imipramine and amitriptyline.

In dogs, i.v. lidocaine (0.01, 0.1, 1.0, and 10 mg/kg) worsened bronchoconstriction induced by histamine by reducing plasma catecholamine concentrations. In a cross-over study using human volunteers, pretreatment with erythromycin and itraconazole, inhibitors of CYP3A4, significantly increased peak plasma concentration of oral lidocaine (1 mg/kg). In rats, coinfusion of bupivacaine (2 mg/kg/min) with its desbutyl metabolite PPX resulted in a potentiation of the cardiac toxicity of the local anesthetic; there was a significant decrease in the doses causing arrhythmia and asystole. The decrease in the heart rate was greater than using either compound alone; two of six animals experienced cardiovascular collapse within five minutes.

Reproductive and Teratological Effects

When administered *in vitro* for 30 minutes to mouse oocytes, bupivacaine (0.01-100 g/mL) caused fertilization and embryo developmental effects at the highest concentration.

In rhesus monkeys, no neonatal neurobehavioral effects of bupivacaine (epidural catheter infusion of 0.60 mg/kg of a 0.5% compound for 22 minutes) were observed. In cognitive testing, relatively low performance levels were attained in the bupivacaine infants. During the visual novelty preference test, they directed more, shorter fixations at visual stimuli. Furthermore, observation of behavior maturation patterns showed that the increase in manipulatory activity that normally occurs at two months of age was delayed in bupivacaine-exposed infants, while the increase in motor disturbance behaviors that normally occur at ten months of age was prolonged.

When pregnant rats were treated continuously with lidocaine doses equivalent to or up to five times the i.v. human dose, no teratogenic effects were observed in the offspring. However, when given as single injections in doses up to two times the hourly human dose, lidocaine resulted in neonatal behavioral changes in the offspring. In pregnant mice, single injections of lidocaine in doses 50 to 70% of the daily human infusion dose produced increased frequencies of CNS anomalies in the embryos. When treated with daily i.p. injections in doses equivalent to those used for regional block in women undergoing follicular aspiration immediately following fertilization, delayed embryonic development occurred. When given to baboons and sheep late in pregnancy, lidocaine (dose not provided) produced changes in perinatal adaptation.

In the offspring of pregnant rats and rabbits treated with up to two times the maximum recommended human dose, etidocaine produced no teratogenic effects. Prilocaine in doses up to three times the maximum human dose produced no adverse effects. In rats injected with the highest recommended mepivacaine human dose (6 mg/kg) on day 11 of pregnancy, significant abnormalities in behavioral test performance were observed in the offspring.

Carcinogenicity

No animal studies were available. In a U.S. case-control study, one of 361 brain tumor cases had an association with lidocaine.

Initiation/Promotion Studies

No studies were available.

Anticarcinogenicity Studies

No *in vivo* studies were identified. Several studies evaluated cytotoxicity and inhibitory effects *in vitro*, which are discussed below under "Other Data".

Genotoxicity

In the absence of metabolic activation (S9), lidocaine (dose not provided) was negative in the *Escherichia coli* DNA-polymerase-deficient assay system. In UV-irradiated cells of *E. coli*, lidocaine inhibited the excision-repair process. In *Salmonella typhimurium* strains TA98 and TA1900, lidocaine (8 mg/plate), in the presence and absence of S9, was not mutagenic. In intact murine L1210 cells, lidocaine (8 mM) produced no significant DNA damage compared to control cells; however, its addition to bleomycine (BLM) A_2-pretreated cells significantly increased DNA breakage by 4.4-fold.

No studies were identified for the other amide local anesthetics.

Cogenotoxicity

No studies were available.

Antigenotoxicity

No studies were available.

Immunotoxicity

No studies were available.

Other Studies

Cytotoxicity

In human M14 melanoma cells, treatment for two hours with bupivacaine hydrochloride (1.8 mM) reduced cell survival by 50%. A combination treatment with a temperature of 37 ¡C lowered ATP content by 86% but increased ADP and AMP content, and decreased the adenylated energy. Bupivacaine was found to also stimulate the basal rate of lactate production by 42%. When cells were exposed to 0.8 mM bupivacaine for up to 30 minutes, the cellular content of bupivacaine was greater at 42 ¡C than at 37 ¡C. Treatment of cells at 37 ¡C with 1.8 mM bupivacaine caused changes in the mitochondrial structure, the inner membrane, and the matrix, whereas cells heated at 42 ¡C for 50 minutes with 0.8 mM bupivacaine resembled untreated cells.

In mouse epidermal cells, lidocaine (1 mM) was an effective inhibitor of ornithine decarboxylase (ODC) induction by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and UV. Cells treated during and after TPA or after UV resulted in differential effects of 7% of TPA control and 18% of UV control.

In an epithelioid-type C3H mouse embryo cell line, lidocaine (1, 10, and 100 g/mL) produced no multinucleation.

Addition of lidocaine (0.1-10 mM) to cultured murine L1210 cells incubated with BLM A_2 potentiated BLM A_2 cytotoxicity. A combination of 10 M BLM A_2 and 8 mM lidocaine caused a 1000-fold increase in cell kill versus the use of the antitumor agent alone; with 30 M BLM A_2, lidocaine increased cytotoxicity by more than 8000-fold. Furthermore, the local anesthetic (at 8 mM) reduced the total amount of cell-associated radioactivity compared to that seen with incubation of [^{3}H]BLM A_2 alone. Lidocaine (0.8 mM) also increased BLM A_2 cytotoxicity toward human head and neck squamous carcinoma cells.

When human osteoblastic Saos-2 cells were exposed for 48 hours to prilocaine (up to 10 mM), cell viability was decreased in a dose- and time-dependent manner. Co-incubation with

cycloheximide, however, increased the cell viability of the treated cells in a dose-dependent fashion; cell death was up to three times lower than that of the prilocaine-only treated cells.

Ropivacaine Effect on the Energy Metabolism of Ehrlich Ascites Tumor Cells

In Ehrlich ascites tumor cells, ropivacaine (up to 3.5 mM) inhibited the rate of oxygen consumption in the absence and presence of hydrophobic anion tetraphenylboron (TPB^-). Ropivacaine (2 mM) alone also partially reactivated oligomycin-inhibited respiration in the cells, but addition of TPB^- lowered the rate of oxygen uptake to a level close to that with oligomycin alone. In addition, low concentrations of ropivacaine were significantly effective in reducing oxygen consumption on uncoupled respiration of the cells.

Ropivacaine also improved total lactate production. In the absence of TPB^-, ropivacaine (up to 1 mM) produced no changes in the rate of production; the maximum was reached at 3 mM. In contrast, in the presence of TPB^-, ropivacaine immediately raised the rate; the maximum was reached at 2 mM.

Ropivacaine (dose not provided) was observed to also decrease the total adenine content by 50%. Depending on the concentration (not specified), ropivacaine decreased or collapsed mitochondrial membrane potential within the cells.

Porphyria

The following amide local anesthetics have been classified as unsafe for use in acute porphyria: etidocaine, lidocaine, mepivacaine, prilocaine, and pyrrocaine.

Structure-Activity Relationships

This section reviews the toxicity of several metabolites of the amide local anesthetics discussed in this report, including trimecaine (metabolite mesidine or 2,4,6-trimethylaniline). These are pipecolic acid, PPX, *o*-toluidine, and 2,6-xylidine.

Mesidine

Acute toxicity: In rats, an oral LD_{50} value of 660 mg/kg was reported for the hydrochloride form.

Subchronic exposure: In subchronic oral exposure studies, the compound resulted in growth inhibition and an increase in mean liver weights and kidney weights in both female and male rats, and an increase in the heart rate and testes mean weights of male rats only. Significant pathological changes in the liver and proliferation of bile ducts was also found. When injected as mesidine hydrochloride into the femoral vein of rats, methemoglobin formation was observed.

Carcinogenicity: In rats, mesidine produced heptaomas, cholangiocarcinomas, and severe cirrhosis of the liver.

Genotoxicity: In mice, mesidine produced DNA damage in liver cells as well as damage in bone marrow cells. It was mutagenic in *S. typhimurium* in the presence of metabolic activation and was positive for DNA repair in Chinese hamster hepatocytes.

Pipecolic Acid

Acute toxicity: In mice, an i.p. LD_{50} value of 610 mg/kg was reported. The mean convulsant activity was 0%.

Genotoxicity: Pipecolic acid was not mutagenic in *S. typhimurium* but was toxic to the bacteria at concentration >0.15 M.

PPX

Acute toxicity: In mice, an i.p. LD_{50} value of 140 mg/kg was calculated, and a mean convulsant activity of 100% was obtained with a concentration of 400 mg/kg. In rats, i.v. infusion of PPX produced seizure activity and asystole. The decrease in arterial blood pressure was greater than that from bupivacaine alone. In addition, plasma concentrations of PPX measured at 5 minutes were slightly higher than the bupivacaine concentrations. Coinfusion of PPX with bupivacaine produced a potentiation of the cardiac toxicity of the latter compound in rats.

o-Toluidine

Acute toxicity: In male Sprague-Dawley rats, an oral LD_{50} of 900 mg/kg body weight was calculated for undiluted *o*-toluidine. In mice, rats, and rabbits, the values were 515, 670, and 843 mg/kg body weight, respectively. An oral LD_{50} value of 2951 mg/kg was obtained for the hydrochloride form. In rabbits, *o*-toluidine was a mild irritant on the skin and a severe irritant on the eyes.

Short-term exposure: In rats, short-term studies with *o*-toluidine produced splenic congestion, increased hematopoiesis, hemosiderosis with bone marrow hyperplasia, epithelial changes in the bladder, methemoglobinemia, reticulocytosis, and anemia. Methemoglobinemia was also observed in mice, cats, and dogs.

In both mice and rats, *o*-toluidine hydrochloride in the diet caused a dose-dependent reduction in mean body weight gain, pigment deposition in the spleens of rats only, and renal and splenic pigmentation in mice.

Chronic exposure: Exposure to the hydrochloride resulted in reduced mean body weights in both animals. In rats, mortality was dose-related.

Reproductive and teratological effects: Topical application of *o*-toluidine to the skin of rats had paternal (e.g., spermatogenesis), maternal (e.g., changes or disorders in the menstrual cycle), and newborn effects (e.g., reduced weight gain).

Carcinogenicity: When fed to rats for 91 days, *o*-toluidine caused epithelial changes in the bladder. Given for two years in the diet, it produced hepatomas. In 83% of the rats, s.c. fibromas or fibrosarcomas were found. Subcutaneous injections of *o*-toluidine for over 397 days produced hyperplasia of the basal cells in the Zymbal glands.

When administered in the feed to mice, *o*-toluidine hydrochloride for 101 to 104 weeks produced several types of sarcomas of the spleen and other organs and hemangiosarcomas and hemangiomas of the abdominal viscera in both sexes. In males, mesotheliomas of the abdominal cavity or scrotum, an increased incidence of fibromas of the s.c. tissue, and hemangiosarcomas at

multiple sites occurred. In females, transitional-cell carcinomas of the urinary bladder, an increased incidence of fibroadenomas or adenomas of the mammary gland, and hepatocellular carcinomas or adenomas were observed.

In rabbits and guinea pigs, repeated s.c. injections of *o*-toluidine produced papillomas in the bladder. Injections in the hamster have resulted in no cancer.

Genotoxicity: Studies with *o*-toluidine have produced equivocal results. The overall conclusion regarding the mutagenicity of the compound was "nondefinitive" by the *Salmonella* Work Group for the U.S. EPA's Gene-Tox Program.

2,6-Xylidine

Acute toxicity: As 2,6-xylidine hydrochloride, an oral LD_{50} value of 2042 mg/kg was obtained in male Osborne-Mendel rats. In male Sprague-Dawley rats and CF_1 mice, the values were 1230 mg/kg and 710 mg/kg, respectively. As 2,6-xylidine, LD_{50} values for rats ranged between 630 and 1310 mg/kg. Administered as a single i.v. dose, 2,6-xylidine produced methemoglobinemia in cats but not dogs.

Short-term exposure: A study in dogs found decreased body weight, hyperbilirubinemia, hypoproteinmeia, and significant fatty degenerative changes in the liver. In rats, short-term exposure to 2,6-xylidine produced growth inhibition (weight retardation), red blood cell changes toward target cell anemia, pathological changes in the liver and kidney, slight chronic congestion in the spleens, pneumonia, ovarian cysts, distented uterine horns, an increase in microsomal glucuronyltransferase levels, and decreases in body weight and hemoglobin, erythrocyte, and hematocrit levels.

Chronic exposure: Studies in rats produced a reduction in body weight gain at a dose of 3000 ppm and in survival at levels of ≥1000 ppm.

Carcinogenicity: In studies with rats, 2,6,-xylidine in the feed produced papillary adenomas and carcinomas of the nasal cavity, as well as malignant mesenchymal tumors and rhabdomyosarcomas. Increased incidences of s.c. tissue fibromas and/or fibrosarcomas also occurred in both sexes, while neoplastic nodules of the liver were seen only in females.

Genotoxicity: The genotoxicity of 2,6-xylidine in *S. typhimurium* have been conflicting. In *E. coli* phage inhibition capacity was observed, and in hamster ovary cells cytogenic analysis and sister chromatid exchanges were seen. 2,6-Xylidine, however, failed to induce unscheduled DNA synthesis in rat hepatocytes, micronuclei in the bone marrow of mice, chromosome damage in polychromatic erythrocytes, and preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes, and blood extracts from mice. Its ability to covalently bind to DNA ethmoid turbinates and liver of rats after oral pretreatment, however, indicated that 2,6-xylidine may be genotoxic under certain conditions.

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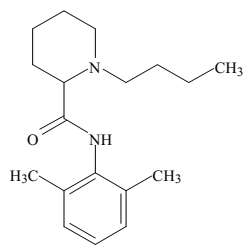
1.0 BASIS FOR NOMINATION

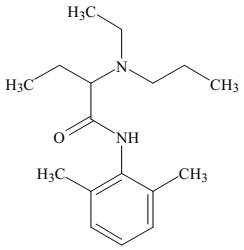
The nomination of dental local anesthetics by a private individual is based on their widespread use in dentistry, general medicine, surgery, and in some consumer products (e.g., topical skin preparations). The amide local anesthetics bupivacaine, etidocaine, lidocaine, and mepivacaine metabolize to 2,6-xylidine. Another amide local anesthetic that metabolizes to 2,6-xylidine is pyrrocaine, which is no longer used in the United States. The local anesthetic trimecaine, which would metabolize to the xylidine structural analogue mesidine (2,4,6-trimethylbenzeneamine), was also considered for inclusion in this report but was not due to its apparent lack of use in the United States. Prilocaine metabolizes to *o*-toluidine. Both 2,6-xylidine and *o*-toluidine have been shown to be carcinogenic in laboratory animals in NTP studies (Haseman et al., 1984; NTP, 1979, 1990). There are insufficient data on the mutagenicity and chronic toxicity of local anesthetics, including information on carcinogenicity. For this reason, the following report focuses on the amide local anesthetics available in the United States that metabolize to 2,6-xylidine and *o*-toluidine.

2.0 INTRODUCTION

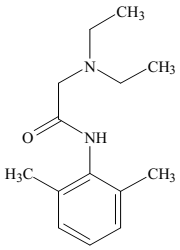
Figure 1. Structures of Local Anesthetics That Metabolize to 2,6-Xylidine or *o*-Toluidine



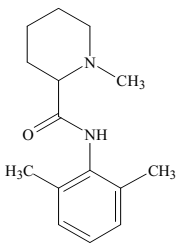
Bupivacaine



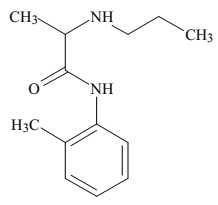
Etidocaine



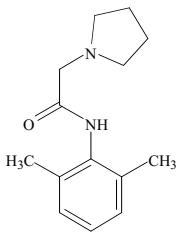
Lidocaine



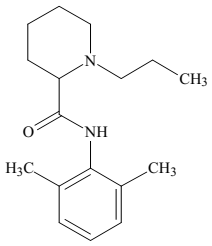
Mepivacaine



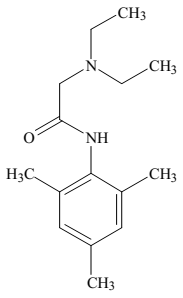
Prilocaine



Pyrrocaine



Ropivacaine



Trimecaine

2.1 Chemical Identification and Methods of Analysis

2.1.1 Chemical Identification

Compound	CASRN	Other Names/Synonyms
Bupivacaine	38396-39-3 (Replaced 2180-92-9)	1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; *dl*-1-Butyl-2',6'-pipecoloxylidide; 1*n*-Butyl-2',6'-dimethyl-2-piperidinecarboxanilide; *dl*-*N*-*n*-Butylpipecolic acid 2,6-xylidide; 1-Butyl-2-(2,6-xylylcarbamoyl)piperidine; *dl*-1-*n*-Butylpiperidine-2-carboxylic acid 2,6-dimethylaniline; *dl*-Bupivacaine.
		Trade Names: Anekain (Pliva), Marcain (Winthrop)
hydrochloride	18010-40-7	**Trade Names:** Carbostesin* (Astra), Marcaine* (Winthrop)
hydrochloride monohydrate	14252-80-3	**Trade Names:** Marcain (BDH), Marcaina (Pierrel), Carbostesin (Woelm)
Etidocaine	36637-18-0	(–)-*N*-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide; 2-(Ethylpropylamino)-2',6'-butyroxylidide
hydrochloride	36637-19-1 (Replaced 52300-99-9)	**Trade Names:** Duranest* (Astra), Dur-Anest* (Astra)
Lidocaine	137-58-6	2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide; 2-Diethylamino-2',6'-acetoxylidide; ω-Diethylamino-2,6-dimethylacetanilide; Lignocaine
		Trade Names: Cuivasil (IDC), Duncaine, Leostesin (Leo Pharmaceuticals), Lidothesin, Rucaina, Xylocaine (Astra Pharmaceuticals), Xylocitin, Xylotox
hydrochloride	73-78-9	
hydrochloride monohydrate	6108-05-0	**Trade Names:** Lidesthesin (Ritsert), Lignavet (C-Vet), Odontalg (Giovanardi), Sedagul (Wild), Xylocard (Astra), Xyloneural (Nicholas)
Mepivacaine	96-88-8	*N*-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 1-Methyl-2',6'-pipecoloxylidide;*dl*-*N*-Methylpipecolic acid 2,6-dimethylanilide; *dl*-*N*-Methylhexahydropicolinic acid 2,6-dimethylanilide
hydrochloride	1722-62-9	**Trade Names:** Carbocaina (Pierrel), Carbocaine hydrochloride (Winthrop), Chlorocain (Pharmaceutical Manufacturing), Meaverin (Woelm); Mepicaton (Pharmaton), Mepident (Parke Davis), Mepivastesin (Espe), Optocain (Bayer), Scandicain (Bofors); Polocaine* (Astra)
Prilocaine	721-50-6	*N*-(2-methylphenyl)-2-(propylamino)propanamide; α-Propylamino-2-methylpropionanilide; *N*-(α-Propylaminopropionyl)-*o*-toluidine; 2-Propylamino-*o*-propionotoluidide
hydrochloride	1786-81-8	**Trade Names:** Citanest (Astra Pharmaceuticals), Xylonest (Astra Pharmaceuticals); Propitocaine

Compound	CASRN	Other Names/Synonyms
Pyrrocaine	2210-77-7	*N*-(2,6-Dimethylphenyl)-1-pyrrolidineacetamide; 1-Pyrrolidineaceto-2',6'-xylidide; 2-(1-Pyrrolidinyl)-2',6'-acetoxylidide; 1-Pyrrolidinoaceto-2,6-dimethylanilide; EN-1010
		Trade Names: Endocaine (Endo), Dynacaine
hydrochloride	2210-64-2	
Ropivacaine	84057-95-4	(*S*)-*N*-(2,6-Dimethylphenyl)-1-propyl-2-piperidinecarboxamide; (*S*)-(-)-1-propyl-2,6-pipecoloxylidide; l-*N*-*n*-propylpipecolic acid-2',6'-xylidide
monohydrochloride	98717-15-8	
monohydrochloride monohydrate	132112-35-7	
Trimecaine	616-68-2	2-Diethylamino-2',4',6'-trimethylacetanilide; N-Sym-trimethylphenyldiethylaminoacetamide; 2-Diethylaminoacetyl-2',4',6'-trimethylanilide
hydrochloride	1027-14-1	**Trade Names:** Mesocaine, Mesidicaine, Mesokain

Sources: Budavari (1996) and *Rippel (1990)

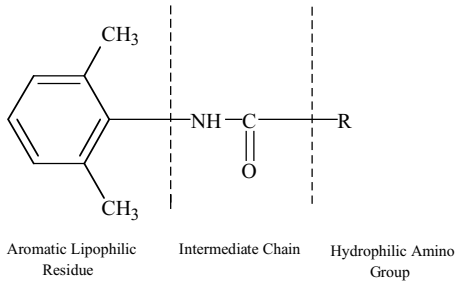
2.1.2 Analytical Determination

In the 1970s and 1980s, packed-column gas chromatography (GC) methods predominated for determining lidocaine and lidocaine metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) and bupivacaine, etidocaine, mepivicaine, and their common metabolite 2',6'-pipecoloxylidide (PPX). Detection methods included mass spectrometry (MS), flame ionization detectors (FID), and nitrogen (N)-FID. Sensitivities were at least 2.5 ng/mL, but were usually greater than 20 ng/mL. A few studies used capillary GC with detection by N-FID or MS with selected ion monitoring (SIM) to determine lidocaine, MEGX, GX, and bupivacaine with high sensitivity peak levels of no more than 100 ng/mL. A few high performance liquid chromatography (HPLC) studies used ultraviolet (UV) detection at 195-205 nm. Since the mid-1980s, capillary GC and HPLC methods have become more commonly used. Other methods reported in the recent literature include capillary electrophoresis (CE), HPLC with a chiral stationary phase for enantiomeric separation, potentiometry using ion-selective electrodes, and fluorescence polarization immunoassay (FPIA). Sample preparation methods include microporous membrane liquid-liquid extraction and solid-phase extraction. Plasma and urine LODs for many methods are generally in the range 1 to 10 ng/mL. Appendix J aims to identify the analytes, separation and detection methods, the matrix, and the limits of detection

(LOD) and quantitation (LOQ), when available, for each amide local anesthetic in biological matrices and pharmaceutical preparations.

2.2 Chemical Properties

In general, the amide local anesthetics in this report contain this general structure:



Compounds which usually exhibit local anesthetic activity have an aromatic and amine moeity, seperated by a lipophilic hydrocarbon chain and a polar group (Covino, 1986; Covino and Vasallo, 1976; all cited by Lenz et al., 1992). These molecular divisions are important in conveying certain physiological activities, such as solubility, time of onset of anesthesis, and degradability. Most local anesthetics are weak basic tertiary amines, which are comprised of three structural components: an aromatic moiety, and ester/amide linkage and an amine (McCarthy and Tuman, 1997). Aminoesters, such as tetracaine, have an ester linkage between the benzene ring and the intermediate chain that can be metabolized by ester hydrolysis primarily in the plasma by the enzyme pseudocholinesterase. However aminoamides, such as bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine, posses an amide linkage between the benzene ring and the intermediate amine group and are not metabolized by pseudocholinesterase.

Except for lidocaine, which contains no chiral bonds, and ropivacaine, which is only the *S*-isomer, these amide local anesthetics are a mixture of *R*- and *S*-enantiomers.

Table 1. Properties of Local Anesthetics That Metabolize to 2,6-Xylidine or *o*-Toluidine

Local Anesthetic	Properties							
	Molecular Formula	Molecular Weight	Physical State	Boiling Point (…C)	Melting Point (…C)	Solubility in Water	Lipid Solubility (25 ¡C)	pK_a (25 ¡C)
Bupivacaine	$C_{18}H_{28}N_2O$	288.43			107-108	Soluble	346	8.2
hydrochloride monohydrate	$C_{18}H_{28}N_2O•HCl• H_2O$	342.90			255-256	40 mg/mL		
Etidocaine	$C_{17}H_{28}N_2O$	276.42					800	8.1
hydrochloride	$C_{17}H_{28}N_2O•HCl$	312.88			203-203.5	Soluble		
Lidocaine	$C_{14}H_{22}N_2O$	234.34	needles	$180\text{-}182_{4\ mm\ Hg}$, $159\text{-}160_{2\ mm\ Hg}$	68-69	Insoluble	43	8.2
hydrochloride	$C_{14}H_{22}N_2O•HCl$	270.80			127-128			
hydrochloride monohydrate	$C_{14}H_{22}N_2O•HCl• H_2O$	288.81	crystals		77-78 (Crystals) 127-129 (Anhydrous)	Soluble		
Mepivacaine	$C_{15}H_{22}N_2O$	246.35	crystals		150-151		21	7.9
hydrochloride	$C_{15}H_{22}N_2O•HCl$	282.80			262-264	Soluble		
Prilocaine	$C_{13}H_{20}N_2O$	220.31	white needles, odorless	$159\text{-}162_{0.1\ mm\ Hg}$	37-38		25	8.0
hydrochloride	$C_{13}H_{20}N_2O•HCl$	256.77	white crystals		167-168	Soluble		
Pyrrocaine	$C_{14}H_{20}N_2O$	232.33	crystals		83			
hydrochloride	$C_{14}H_{20}N_2O•HCl$	256.77	crystals		205	Soluble		
Ropivacaine	$C_{17}H_{26}N_2O$	274.41	crystals		144-146		115	8.2
Monohydrochloride	$C_{17}H_{26}N_2O•HCl$	310.87	crystals		260-262	Soluble		
Monohydrochloride Monohydrate	$C_{17}H_{26}N_2O•HCl• H_2O$	328.88	crystals		269.5-270.6			
Trimecaine	$C_{15}H_{24}N_2O$	248.37	crystals	$187_{6\ mm\ Hg}$; $154\text{-}155_{0.6\ mm\ Hg}$	44			
hydrochloride	$C_{15}H_{24}N_2O•HCl$	284.83	crystals		140			

Source: Budavari (1996). Lipid solubility and pK_a values taken from Feldman (1994).

2.3 Commercial Availability

The companies that supply these local anesthetics as well as the packaging amounts are contained in the table below.

Table 2. U.S. Suppliers of Local Anesthetics During 1998

Corporation	Location	Supplies	Bulk Supplier	High Purity Supplier	Bulk and High Purity Supplier
Aceto Corporation	Lake Success, NY	BUP1, BUP2	LID1, LID3, MEP2,		
Accurate Chemical and Scientific Corp.	Westbury, NY	LID1			
Acros Organics	Pittsburgh, PA	LID1			
Alfa Chemicals	Kings Point, NY	BUP2, LID3			
American Radiolabeled Chemicals	Saint Louis, MO	LID4			
Atomergic Chemetals Corporation	Farmingdale, NY		BUP1, LID1, LID3, MEP1		
Ceres Chemical Company	White Plains, NY				BUP2, MEP2, PRI1
ICN Biomedicals, Inc.	Costa Mesa, CA	LID1, PRI1			
Integra Chemical Company	Renton, WA	LID1, LID3			
Interchem Corporation	Paramus, NJ		LID1, LID3		
Monomer-Polymer & Dajac Laboratories, Inc.	Feasterville, PA	LID1, LID3			
Napp, Inc.	Saddle Brook, NJ		BUP1, ETI, LID1, LID3, PRI1, PRI2		
Pfaltz & Bauer, Inc.	Waterbury, CT	LID1, LID3			
Reasearch Biochemicals International	Natick, MA			LID2, LID3	
Ruger Chemical Company	Hillside, NJ		LID1		
Salor (A Division of Aldrich Chemical Co.)	Milwaukee, WI		LID1		
Sigma Chemical Company	Saint Louis, MO	BUP3, LID1, LID2, LID5, PRI2			
Spectrum Quality Products, Inc.	Gardena, CA	BUP3, MEP2, PRI2	LID1, LID5		
Triple Crown America, Inc.	Perkasie, PA				BUP1, LID1, MEP1
TCI America, Inc.	Portland, OR	LID1			
Wacker Silicones Corporation	Adrian, MO			LID1	
Wyckoff Chemical Company	South Haven, MI				LID1

Sources: ChemSources USA, 1999, and American Chemical Society, 1999.

BUP1 = Bupivacaine
BUP2 = Bupivacaine hydrochloride
BUP3 = Bupivacaine hydrochloride, monohydrate
ETI = Etidocaine
LID1 = Lidocaine
LID2 = Lidocaine *N*-ethyl bromide, quaternary salt
LID3 = Lidocaine hydrochloride
LID4 = Lidocaine hydrochloride (Carbonyl-$_{14}$C)
LID5 = Lidocaine hydrochloride monohydrate
MEP1 = Mepivacine
MEP2 = Mepivacine hydrochloride
PRI1 = Prilocaine
PRI2 = Prilocaine hydrochloride

3.0 PRODUCTION PROCESSES

Bupivacaine hydrochloride is produced by the reaction of 2,6-xylidine and piperidine-2-carboxylic acid chloride hydrochloride. The product, pipecoloxylidide (PPX), is then alkylated with 1-butylbromide to form bupivacaine hydrochloride (Rippel, 1990).

Mepivacaine is prepared by treating 2,6-xylidine magnesium bromide with ethyl-1-methyl-2-piperidinecarboxylate. It can also be prepared by hydrogenation and then N-methylation of pipecolic acid 2,6-xylidide (PPX) (Rippel, 1990).

Etidocaine is synthesized by acylating 2,6-xylidine with 2-bromobutyric acid. The bromine atom in the resulting compound is then replaced with iodine by boiling with potassium iodide in methanol. Treating the reaction mixture with *n*-propylamine gives an *n*-propylamino compound, which is finally alkylated with diethyl sulfate (Rippel, 1990).

Lidocaine hydrochloride is prepared by the reaction of 2,6-xylidine and chloroacetyl chloride in glacial acetic acid with the addition of sodium acetate. The resulting product, chloroacetyl-2,6-dimethylanilide, is then boiled with diethylamine in a solvent such as benzene. Crystallization of the hydrochloride occurs with one molecule of water, which can be removed by drying (Rippel, 1990). It is produced by Wycoff Chemical Company, located in South Haven, Michigan (SRI, 1999).

Prilocaine is the result of treating 2-aminotoluene with 2-bromopropionyl chloride and then *n*-propylamine (Rippel, 1990).

In patents awarded to Astra Laekemeded AB of Sweden, ropivacaine was produced by the amidation of (*L*)-pipecolic acid chloride hydrochloride by 2,6-xylidine. The (*L*)-pipecolic acid precursor was prepared by resolution of racemic pipecolic acid with (+)-tartaric acid (Ekenstam and Bovine, 19987; Ekenstam et al., 1985).

4.0 PRODUCTION AND IMPORT VOLUMES

Production statistics for the local anesthetics were only available from 1980 to 1984. In 1980, production of all local anesthetics was 61.5 short tons and lidocaine production comprised 41% of the total (36.5 tons) (USITC, 1981). In 1982, production of all local anesthetics was 53 short tons and lidocaine production comprised 28% of the total (30 tons) (USITC, 1983). In 1984, production of all local anesthetics was 77 short tons and lidocaine production was not reported (USITC, 1985). This is the reported production of bulk medicinal chemicals only.

5.0 USES

Local anesthetics are used to produce anesthesia by blocking the conduction of nerve impulses in sensory and motor nerve fibers (Lenz et al., 1992). Local anesthetics may be used in either human or veterinary medicine. All of the local anesthetics mentioned in this report are used in human medicine. In veterinary medicine, mepivacine and bupivacaine can be used, but lidocaine is preferred because of its chemical stability, sedative effects, lack of tissue damage, low hypersensitivity, and antiarrhythmic effect (Muir and Hubbell, 1989).

In human medicine, local anesthetics may be used in local infiltration, peripheral nerve blocks, intravenous (i.v.) regional blocks, central neural blockade, or topical anesthesia. Local anesthetics used in local infiltration are injected subcutaneously or intradermally in the region where the anesthetic effect is needed (Strichartz and Berde, 1994). As a peripheral nerve block, local anesthetics are applied regionally to inhibit nerve impulses in the peripheral nervous system. Minor nerve blocks involve the nerve blockade of one nerve entity, such as the ulnar or radial nerve. Major blocks may involve the blocking of two or more distinct nerves or nerve plexus. Peripheral nerve blocks are used for post-operative surgery and brachial plexus block (e.g., upper limb surgery). Central neural blocks may be either spinal or epidural.

Local anesthetics have become increasing utilized in the blockade of pain during normal and cesarean deliveries in pregnant women. In 1992, as many as 29% of women used epidural anesthesia for the relief of pain during hospital deliveries in the United States, a 100% increase over use in 1981 (Hawkins, 1994; Cited by King, 1997). In a survey of 750 hospitals in the United States from 1981 to 1997, the number of women requesting epidural or spinal injections of local anesthetics during obstetric procedures tripled at large hospitals (from 22 to 66%), and from 1992 to 1997, the number doubled at smaller hospitals (from 21 to 42%) (Grady, 1999). At St. Lukes-Roosevelt Hospital Center in New York City, one physician reported the use of epidural regional anesthesia among all women giving birth at the hospital increased from around 10% in 1989 to about 90% in 1999.

The choice of which local anesthetic to use is determined by the type and duration of treatment to be applied. Bupivacaine is used in extradural obstetric procedures and in post-operative analgesia because it has very little effect on motor blockade, allowing necessary muscles to be used during the delivery. Currently, bupivacaine is the most widely used drug for epidural anesthesia (Gustorff et al., 1999); however, the use of ropivacaine for epidural

anesthesia is increasing since studies have shown that it is as effective as bupivacaine, but ropivacaine results in less motor block and less systemic toxicity (Knudsen et al., 1997; Brockway et al., 1991; both cited by Gustorff et al., 1999). Etidocaine, on the other hand, posseses a very rapid onset of action. It too has a long duration of action; however, etidocaine results in profound motor blockade. This drug is used only when motor sensory (nerves that control movement) should be suppressed (i.e., surgery on limbs).

Lidocaine (given epidurally) is the preferred anesthetic for the relief of post-operative pain in children (Kakiuchi et al., 1999). Lidocaine is also used topically for the management of post-operative peripheral pain as a result of surgery (Kokinsky et al., 1999). Lidocaine is used for the management of pain due to severe burns due to its analgesic and anti-inflammatory effectsPal et al., 1997). The use of lidocaine in burn treatment is controversial due to toxic reactions (allergic reactions and decreased epithelialization) which have developed during treatment, but have not been proven to be caused by lidocaine (Pal et al., 1997). It is usually applied as an aerosol to the site of the wound after such procedures as circumcision and tonsillectomy. Topical aerosol lidocaine (10%) is used in adults for post-operative relief of peripheral pain after herniorraphy and hysterectomy (Kokinsky et al., 1999).

Topical anesthetics may be used for the management of pain due to hemorrhoids, toothaches, or skin ailments. However, lidocaine is the only local amide anesthetic in this report that is sold in over-the-counter preparations (2.5-5.0% lidocaine) in the United States for the relief of burns and irritation of the skin.

Lidocaine (2.5%) is combined with prilocaine (2.5%) in the EMLA prescription formulation cream, which is used to soothe painful skin conditions such as shingles (Varicella Zoster) (Auwaerter, 1998). EMLA is also used on donor sites for cutting of split skin grafts, for pain-free venepuncture, pain relief from molluscum contagiosum in children, and removal of genital warts and other superficial surgical procedures (Juhlin et al., 1989). EMLA is the topical anesthetic of choice for male circumcision (Brown et al., 1999). EMLA is not recommended for use in infants younger than six months of age in Canada and is only licensed for use in infants older than one month in the United States (Gazarian et al., 1995).

Besides being used as a topical anesthetic, lidocaine also is used as an antiarrhythmic agent; however, it should be administered parenterally due to its short half-life (von Philipsborn et al., 1985). The quantification of the formation of the lidocaine metabolite (MEGX) following

i.v. administration of lidocaine (usually 1 mg/kg) has been proposed to evaluate liver function of cirrhotic patients, but there are still some questions concerning the validity of this application (Schinella et al., 1993; Munoz et al., 1999; Balistreri et al., 1992; Oellerich et al., 1990; Reichen, 1993).

Lidocaine has also been approved for use as an intranasal spray for the treatment of migraine (Deshpande et al., 1999). The nasal delivery of lidocaine is of importance since the metabolite of lidocaine, 2,6-xylidine, has been linked to the formation of nasal carcinomas in rats and nasal microsomes of rats have been shown to metabolize lidocaine *in vitro* (Koujitani et al., 1999). Lidocaine was also found to be effective in the reduction of sensitivity of upper airway reflexes associatied with the classic symptomas of upper espiratory tract infection (common cold) (Hall et al., 1999). A new dental anesthetic delivery sytem, Dentipatch¤, contains a fiber patch impregnated with lidocaine. When the patch is applied to the gums, lidocaine is realeased. In children, bupivacaine and lidocaine are most frequently used for brachial plexus blocks and major neuraxial blocks (intra- and post-operative pain management) (Brown et al., 1999). Bupivacaine is used in pediatric thoracic and abdominal procedures as well as lower limb blocks.

Local anesthetic bases have poor solubility in water, but are generally soluble in organic solvents due to their hydrophobicity (Strichartz and Berde, 1994). Because of this, local anesthetics are usually marketed as water-soluble hydrochloride salts.

Local anesthetic formulations may also contain the vasoconstrictor epinephrine (adrenaline) to shorten the induction time and increase the duration and intensity of the nerve blockade (Bonica et al., 1980; cited by Schierup et al., 1988). The risk of toxicity is reduced when epinephrine is used because drug absorption is retarded due to slow release from the area of administration. This is especially true when local anesthetics are used for local infiltration, with lidocaine having the most prolonged duration (Strichartz and Berde, 1994).

In 1990, U.S. sales of the injectable local anesthetics Xylocaine¤ (lidocaine hydrochloride) and Marcaine¤ (bupivacaine hydrochloride) were 22.5 million and 10.7 million dollars, respectively (Lenz et al., 1992).

Pyrrocaine, developed in 1960, was used mainly as an infiltration and nerve block dental anesthetic (2.0% solution) in the 1960s and favored due to its rapid onset; however, there is no evidence that it is currently used commercially (Zsigmond and Patterson, 1969).

Table 3 describes the use of local anesthetics in human, as well as veterinary, medicine.

Table 3. Uses of Local Anesthetics

Local Anesthetic	Introduction	Use	Concentration (%)	Form	Area of Use	Trade-Names
In Human Medicine:						
Bupivacaine	1963	Peripheral Nerve Blocks	0.25-0.75	Solution	Lumbar epidural	
		Epidural	0.25-0.75	Solution	Lumbar epidural	
		Infiltration, Parenteral	0.25-0.5	Solution	Area to be anesthetized	Marcaine, Sensorcaine
		Spinal Anesthesia	0.5-0.75	Solution	General	
Etidocaine	1972	Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	Duranest-MPF
		Peripheral Nerve Blocks	1.0-1.5	Solution	Lumbar epidural	
		Epidural	1.0-1.5	Solution	Lumbar epidural	
Lidocaine	1948	Topical-General	2.0-10.0	Solution	Tracheobronchial tree, nose	Xylocaine
			2.0	Jelly	Urethra	Xylocaine
			10.0	Suppositories	Rectum	Xylocaine
		Topical-Dental	2.0-4.0	Solution	Oropharynx	Zilactin-L, Xylocaine
			2.0	Viscous	Oropharynx	Xylocaine Viscous
			10.0	Aerosol	Gingivival mucosa, Post-operative wound pain	Xylocain
			4.6	Dermal Patch	Gingivival mucosa	DentiPatch
		Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	Xylocaine, Nervocaine, Lidoject, Dilocaine, Dalcaine, Duranest
		Regional Intravenous	0.25-0.5	Solution	Area to be anesthetized	
		Peripheral Nerve Blocks	1.0-2.0	Solution	Lumbar epidural	
		Spinal Anesthesia	1.5, 5.0	Solution	General	
		Anirrythmic			Inravenous	
		Migraine Headaches	4.0	Solution	Nasal Spray	

Table 3. Uses of Local Anesthetics (Continued)

Local Anesthetic	Introduction	Use	Concentration (%)	Form	Area of Use	Trade-Names
Mepivacaine	1957	Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	Carbocaine, Isocaine, Polocaine
		Peripheral Nerve Blocks				
		Epidural	0.25-0.5	Solution	Lumbar epidural	
		Spinal Anesthesia	0.5-0.75	Solution	General	
Prilociane	1960	Topical				
		Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	Citanest Forte, Citanest Plain
Pyrrocaine	1960					
Ropivacaine	1996	Peripheral Nerve Blocks	0.25-0.5			
		Epidural	0.25-0.5	Solution	Lumbar epidural	
		Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	
In Veterinary Medicine:						
Bupivacaine		Topical	0.25	Cream, Solution, Aerosol		
		Infiltration	0.25-0.5			
		Intraperitoneal, Interpleural	0.25-0.5			
		Epidural, Spinal	0.25-0.5			
Lidocaine		Topical				
		Epidural, Spinal	2.0			
Mepivacaine		Topical				

Human use data taken from Strichartz and Berde (1994); veterinary use information taken from Pascoe (1997).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

Environmental exposure may occur during manufacture and production or by disposal of products containing local anesthetics. No information was located concerning the fate of local anesthetics in the environment, but environmental exposure to local anesthetics is expected to be minimal.

7.0 HUMAN EXPOSURE

Human exposure occurs by the topical application or injection of a local anesthetic or combination of local anesthetics during medical treatment. Oral ingestion may also occur if a local anesthetic is applied topically to the oropharynx area. The amount and duration of exposure depend on the type of anesthetic used and the method of administration. The doses of local anesthetics, duration of application, and the duration of effect are given in **Table 4**.

Topical application of lidocaine and EMLA cream (2.5% lidocaine, 2.5% prilocaine) may result in chronic exposure in order to manage pain from chronic or reoccurring conditions, such as skin wheels, sunburn, or shingles; whereas, other administration methods of local anesthesia result in only acute exposure. Lidocaine is available in several over-the-counter (OTC) formulations sold in stores and over the Internet (e.g., Afterburn¤ Aloe Gel [0.5% lidocaine, Tender Corp.]; Bactine¤ liquid [2.5% lidocaine, Bayer Corp.]; and Solarcaine¤ Aloe Gel [0.5% lidocaine, Schering-Plough]. These OTC formulations are generally used for the temporary relief of painful skin conditions, such as sunburn, windburn, minor burns, chapped, or irritated skin, which would result in acute or subchronic exposure. The OTC preparations contain no more than 2.5% lidocaine weight per volume (w/v) and can be applied three to four times a day in adults (InteliHealth—Home to Johns Hopkins Health Information, 1994). The prescription formulations usually contain 5.0% lidocaine w/v. Chronic exposure to lidocaine may occur when used to treat the pain associated with shingles (herpes zoster). Shingles, a second outbreak of the virus that causes chickenpox, will occur in approximately 1 in 5 adults over the age of 50 (Mayo Clinic, 1997). The latent virus causes postherpetic neuralgia - a painful skin condition caused by damage to nerve fibers that can continue after the rash and blisters of shingles have subsided. Half of the people over 60, and 75% of the people over 70 who develop shingles will also develop postherpetic neuralgia (Mayo Clinic, 1997). The pain from postherpetic neuralgia may persist for months or even years after the episode of shingles. There is evidence that

lidocaine may remain at the dermal site of application for an extended time, with peak concentrations occuring as long as 24 hours after a single topical applicationof a 5.0% lidocaine formulation (Dal Bo et al, 1999). However, blood absorption from mucous membranes (i.e., gigiva, nasal passages) is much more rapid and would not lead to a great accumulation of lidocaine at the site of administration (Noven Pharmaceuticals, 1997). It is difficult to determine the extent of exposure of humans to chronic applications of topical anesthetics since no studies were found that determined the plasma levels of lidocaine after repeated topical administration.

Chronic exposure may also occur as a result of lidocaine use for extensive or repetitious dental procedures. For example, a full mouth reconstruction could require the injection of 5-8 cc of 2% lidocaine (10-16 mg) per weekly or biweekly session for up to six months (Nickel, 1996).

The dose of intravenous, infiltration, epidural or spinal injections of local anesthetics may vary depending on the local anesthetic, amount of analgesia desired, location of administration, desired time of onset and duration of anesthetic effect. There is evidence from the studies reviewed that bupivacaine and ropivacaine are the only local anesthetics which may result in the longest exposure periods as a result of epidural infusion for post-operative pain or for the management of pain during certain medical procedures. The use of epidural anesthesia for post-operative pain management resulted in an infusion period of 72 hours (Scott et al., 1997). Epidural infusion of bupivacaine and ropivacaine, seperately for two periods (each lasting three days and seperated by a one week interval), were used during brachytherapy in a 21 month old girl (Gustorff et al., 1999).

Many new application methods for transdermal and intradermal administration of the amide local anesthetics have been approved for use in the United States. A commercially available device for the controlled release (electrotransport or iontophoresis) of lidocaine transdermally is currently being marketed under the name Phoresor (Edgren et al., 1993). A method of pediatric iontophoresis is currently marketed as Numby Stuff¤ (Iomed ¤) and is used with a special formulation of lidocaine (Iontocaine¤) to reduse the pain associated with needle sticks in children (PSL Group, 1999). A patch marketed under the tradename DentiPatch¤ is also available for the transdermal delivery of lidocaine via the gingiva (Noven Pharmaceuticals, 1999). Another patch, Lidoderm¤ (Endo Pharmaceuticals), was the first patch approved for relief of pain specifically associated with shingles; however, it is only approved for 12 hour use in a 24 hour period to avoid toxic doses (Saper, 1999). One study touted the advantages of using

a jet injection route for intradermal application of lidocaine for the management of pain during i.v. catheterization (Zsigmond et al., 1999). Lidocaine has also been approved for use as an intranasal spray for the treatment of migraine (Deshpande et al., 1999).

Because of the current widespread use of local anesthetics, mainly bupivacaine and mepivacaine, in pregnant mothers to relieve pain during delivery, it is becoming more important to assess the exposure of the neonate to local anesthetics and the potential risk. In a study of merconium extracted from randomly chosen neonates, 33.7% had been exposed to lidocaine, 18.4% has been exposed to mepivacaine, and 3.1% were exposed to bupivacaine (Ostrea et al., 1998 and Ostrea et al.,1999).

The dose and concentration of local anesthetics used during delivery has decreased in the past few years due to the need for less motor blockade during anesthesia (King, 1997). This has been achieved by the addition of lipid-soluble opioid drugs that potentiate the anesthetic effect, such as morphine or fentanyl, to the anesthetic regime during delivery. Today the combination used most often is spinal, epidural or spinal-epidural adminstration with bupivacaine (0.125%) and either fentanyl, sufentanil or meperidine (King, 1997; James, 1997).

Neonates may be exposed to topical EMLA or lidocaine, commonly used today for needle sticks and male circumcision (Woodman, 1999). In 1984, 76.4% of male babies born in the United States were circumcised; however, a majority of doctors do not use local anesthetics during circumcision (Davenport and Romberg, 1984; Wellington and Ryder, 1993); cited by Woodman, 1999). Information on blood concentrations in the neonate after topical administration of EMLA and lidocaine may be found in **Section 9.1.2**.

Treament of cardiac arrhythmia results in high doses of lidocaine than are normally used in other treatments. The usual dose of lidocaine used for local anesthesia is 1 mg/kg; however, when lidocaine is used for cardiac arrhythmias the dose can be as high as 50 mg/kg (Bryant et al., 1994).

Table 4. Human Therapeutic Dose and Exposure Levels for Local Anesthetics

Anesthetic and Intended Use	Concentration (%)	Usual Dose (mg)	Maximum Dose (mg) *	Duration of Anesthetic Effect (hours) *
Bupivacaine				
Infiltration	0.25-0.5		175 (225)	0.25-0.5 (0.5-1.5)
Minor Nerve Block	0.25	12.5-50		3.0-6.0 (4.0-8.0)
Major Nerve Block	0.25-5.0		225	6.0-12.0
Epidural	0.25-0.75	37.5-225		3.0-5.0
Spinal	0.5-0.75	15-22.5		1.25-2.5
Etidocaine				
Infiltration	0.5-1.0		300 (400)	2.0-2.5 (2.5-7.0)
Minor Nerve Blocks	0.5	25-100		2.0-4.0 (3.0-7.0)
Major Nerve Blocks	0.5-1.0		400	6.0-12.0
Epidural	1.0-1.5	150-300		3.0-5.0
Lidocaine				
Topical (OTC)	0.5%			
Topical (Rx)	5.0%			
Infiltration	0.5-1.0		300 (500)	0.5-1.0 (2.0-6.0)
Minor Nerve Blocks	1.0	50-200		1.0-2.0 (2.0-3.0)
Major Nerve Blocks	1.0-1.5		500	2.0-4.0
Epidural	1.0-2.0	150-500		0.5-1.5
Spinal	1.5, 5.0	30-100		0.5-1.5
Mepivacaine				
Infiltration	0.5-1.0		300 (500)	0.75-1.5 (2.0-6.0)
Minor Nerve Block	1.0	50-20		1.0-2.0 (2.0-3.0)
Major Nerve Block	1.0-1.5		500	3.0-5.0
Epidural	1.0-2.0	150-500		1.0-3.0
Spinal	4.0	40-80		0.5-1.5
Prilocaine				
Infiltration	0.5-1.0		500 (600)	0.5-1.5 (2.0-6.0)
Minor Nerve Blocks	1.0	50-200		1.0-2.0 (2.0-3.0)
Major Nerve Blocks	1.0-2.0		600	3.0-5.0
Epidural	1.0-3.0	150-600		1.0-3.0

Primary source: Strichartz and Berde (1994)
* Parenthetical data indicate solutions containing epinephrine.

8.0 REGULATORY STATUS

Local anesthetics are regulated by the Food and Drug Administration (FDA) under the authority of the Federal Food, Drug, and Cosmetic Act. U.S. government regulations pertaining to local anesthetics are summarized below. A special committee, Center for Drug Evaluations and Research—Anesthetic and Life Support Advisory Committee, was established in May 1978 to review and evaluate the use and safety of marketed and investigational drugs in the field of anesthesiology. However, this committee s authority is to expire on May 1, 2000, unless the Commissioner of Food and Drugs determines otherwise (Federal Register, 1998).

In 1997, the FDA, with assistance from its Scientific Advisory Committees and other outside consultants, the American Pediatrics Committee on Drugs, and consultants to the Pharmaceutical Manufacturer s Association developed guidelines for the clinical evaluation of new drugs which included local anesthetics (FDA, 1977).

In 1992, the Consumer Product Safety Commission (CPSC), under the authority of the Poison Prevention Packaging Act, published a Federal Register Notice to approve mandatory child-resistant packaging for all forms of lidocaine (>5.0 mg) and dibucaine (>0.5mg) available over-the-counter and by prescription. This action was in response to reports from the Poison Control Center of 750 cases of ingestion of lidocaine and dibucaine by children, resulting in 16 deaths and several cases of serious illness (CPSC, 1994). Some issues were raised about the technical feasibility of packaging some of the products for child-resistance; however, in 1994 the CPSC voted unanimously to require child-resistant packaging but to delay the final rulemaking until April 8, 1995. The effective date of the packaging requirements was April 10, 1996 (Federal Register, 1995).

In 1993, the FDA s Anesthetic and Life Support Advisory Committee voted 6-0 that evidence of carcinogenicity of the lidocaine metabolite 2,6-xylidine was in sufficient for labels to mention that it caused tumors in laboratory rats (Washington Drug Lett., 1993a; Anonymous, 1994). The Committee did want to wait for results of human liver slice studies before finalizing the vote.

The FDA now requires that products that may metabolize to aniline compounds carry a warning of carcinogenic risk in the package inserts (Nickel, 1996; Nickel, undated letter). These include formulations of EMLA, lidocaine, and prilocaine. These package inserts state that the metabolite of prilocaine, *o*-toluidine, has been found to be carcinogenic in both mice and rats,

and that 2,6-xylidine, the metabolite of lidocaine, was found to cause tumors in rats (Medical Economics Company, 1998; Health Central Online Pharmacy, 2000; Astra Pharmaceuticals, 1998).

Table 5. Regulations Relevant to Local Anesthetics

Regulation		Summary of Regulation
CPSC	CFR 16 Part 1700.14	Products containing more than 5 mg of lidocaine in a single package shall be subject to the provisions of Part 1700.14(a) and (b). The packaging is required to protect children from serious injury or illness due to exposure to the contents. A sample of the safety packaging is to be sent to the Consumer Product Safety Commission.
FDA	CFR 21 Part 2.110	This section pertains to products that pose a serious hazard to the public health. Since chlorofluorocarbons have been shown to deteriorate the ozone layer and consequently cause increased rates of skin cancer. All drugs that are contained in cans with chlorofluorcarbon propellants shall be subject to re-application as a new drug. Anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application are exempt from this re-application process.
	CFR 21 Part 14.7c1	Establishes the Center for Drug Evaluations and Research — Anesthetic and Life Support Advisory Committee to review and evaluate data on the safety and effectiveness of marketed and investigational human drugs for use in the field of anesthesiology and surgery. Effective May 1, 1978.
	CFR 21 Part 25.33	This section gives the FDA authority to enact and oversee food and drug policies in order to comply with the National Environmental Policy Act (NEPA) of 1969. All agencies of the Federal Government must comply with section 102(2) of NEPA except where complience would be inconsistent with other statutory requirements . Veterinary anesthetic manufacturers are not required to submit an environmental impact statement or environmental assessment for the use of their products in animals.
	CFR 21 Part 310.545	This section lists certain ingredients that are present in over-the-counter (OTC) drug products and the intended uses of these products. However, there is not enough data available on these ingredients to establish the safety and effectiveness of these ingredients. Lidocaine is listed as an ingredient in poison ivy, poison oak, and poison sumac drug products. Lidocaine and lidocaine hydrochloride are listed as ingredients in oral health care products (nonantimicrobial).

Table 5. Regulations Relevant to Local Anesthetics (Continued)

Regulation		Summary of Regulation
FDA	CFR 21 Part 310.500	This section describes the conditions required to market the oral cardiac treatment drug, Digoxin. Digoxin labels contain a section on treatment of arrhythmias induced by digoxin. Lidocaine is listed as one of the drugs which has been approved for the treatment of digoxin intoxication.
	CFR 21 Part 333.120	Topical antimicrobial drug products and permitted combinations of active ingredients are described in this section. Provided that the antimicrobial drug product meets the test standards for potency and moisture set forth in CFR 21 Part 448.510a(b) any single generally recognized as safe amine or caine type local anesthetic may be used in combination with any of the following antibiotic(s): bacitracin ointment and Bacitracin-neomycin sulfate-polymixin B sulfate ointment. Provided that the antimicrobial drug product meets the test standards for potency and moisture set forth in CFR 21 Part 448.510e(b) any single generally recognized as safe amine or caine type local anesthetic may be used in combination with any of the following antibiotic(s): bacitracin-polymixin B sulfate topical aerosol and bacitracin zinc-neomycin sulfate-polymixin B sulfate ointment. Provided that the antimicrobial drug product meets the test standards for potency and moisture set forth in CFR 21 Part 448.513c(b) any single generally recognized as safe amine or caine type local anesthetic may be used in combination with any of the following antibiotic(s): bacitracin zinc-polymixin B ointment and neomycin sulfate-polymixin B sulfate cream.
	CFR 21 Part 346	Lidocaine (2-5%), Tetracaine (0.501%), and Tetracaine hydrochloride (0.5-1%) are listed as topical local anesthetic active ingredients in anorectal drug products for OTC use. These local anesthetic ingredients may be used in combination with other ingredients as set forth in 21 CFR, Part 346.22. These other ingredients include vasoconstrictors, antipruritics, keratolytics, astringents, and analgesics. This section also regulates the labeling of anorectal drug products.
	CFR 21 Part 348.10	Lidocaine is approved as an active ingredient in metered male genital desensitizer sprays at a concentration of approximately 10 mg per spray. Labeling requirements for these products are also set forth in this part.

Table 5. Regulations Relevant to Local Anesthetics (Continued)

Regulation		Summary of Regulation
FDA	CFR 21 Part 369.20	The recommended warning and caution statements for external local anesthetics are set forth in this part. The product label should read: *Caution*-Do not use in the eyes. If the condition for which this preparation is used persists or if a rash or irritation develops, discontinue use and consult a physician.
	CFR 21 Part 448.510	States that certain antibacterial formulations containing bacitracin may also contain a suitable local anesthetic . See also CFR 21 Part 333.120
	CFR 21 Part 522	Any new animal drug in an injectable or implantable form is listed in this section. A new animal drug is one: that is intended for use in any animal other than man or is included in animal feed, whose composition is not generally regarded as safe and effective under the conditions prescribed, recommended or suggested in the labeling thereof that has been tested in laboratory investigations for a certain use in animals but has not been used for that intended purpose for any length of time. Lidocaine injection with epinephrine is listed in Part 522.1258. Its sponsor was Steris Laboratories, Inc., located in Phoenix, AR. Mepivacaine hydrochloride injection is listed in Part 522.1372. Its sponsor was Pharmacia & Upjohn Co., located in Kalamazoo, MI. Sodium pentabarbital with a local anesthetic is listed in Part 522.1704. Its sponsor was Schering-Plough Animal Health Corp., located in Union, NJ. The dosing as well as labeling requirements are also listed for each new drug
	CFR 21 Part 524.390c and 524.1484b,c,d,f,k	Lists dosages for ophthalmic and topical new animal drugs. The products are for the treatment of dermatitis and external ear conditions (ototis externa) in animals and usually contain between 4.2 and 5.0 mg of tetracaine. The sponsors as well as the application and labeling criteria for each product are also described.
	CFR 21 Part 862.3555	A lidocaine test system is described. It is a device intended to measure lidocaine, an antiarrythmic and anticonvulsive drug, in serum and plasma . Measurements taken by this device are used to diagnose and treat lidocaine overdose and to monitor lidocaine concentrations during therapy.

9.0 TOXICOLOGY DATA

General toxicology data contained in Section 9.1.1 and toxicology data following Section 9.1.2 (Disposition, Metabolism, and Pharmacokinetics) have been omitted in this abridged version of the Final Review of Toxicological Literature.

9.1.2 Disposition, Metabolism, and Pharmacokinetics

9.1.2.1 General Discussion

9.1.2.1.1 Mode of Action of the Amide Local Anesthetics

A typical peripheral nerve consists of multiple bundles of axons (fascicles). Each bundle of axons is held together by the endoneurium and wrapped in a membrane called the perineurium. Several perineurium bound axon bundles are held together by the epineurium. An axon (nerve fiber), with its own cell membrane, is encased in a Schwann cell sheath that has its own membrane. The majority of large motor and sensory nerve fibers are encased in multiple layers of specialized Schwann cells, called myelin. The myelin serves as an insulator from the surrounding salt medium and greatly increases the speed of nerve conduction through the axoplasm. There are periodic interruptions in the myelin sheath around the axons. These interruptions are known as the nodes of Ranvier and it is here that the Na^+ channels for nerve impulse and propagation are located. There are some nonmyelinated axons, such as autonomic postganglionic C fibers, which have ion channels distributed all along the axon (Strichartz and Berde, 1994).

Nerve conduction occurs by altering the neural membrane permeability of sodium and potassium ions into the axon at the ion channels, creating an electrochemical potential. Local anesthetics work by reaching the nerve axon and interfering with the function of the ion channels that control nerve impulse propagation. It appears that there is a single site for local anesthetic binding on the sodium channel, and by binding there, conformational changes occur in the channel proteins which prevent opening of the channel. The speed at which this occurs is dependent on the local anesthetics hydrophobicity of the base and cation species and the pK_a . For an anesthetic molecule to reach this site of action, it must traverse the multiple lipid membranes and connective tissue of the nerve (Strichartz and Berde, 1994).

It is not clear which form of the local anesthetic, cation or neutral base, is most responsible for anesthesia. The neutral base in the axonal external medium may be the active

species or membrane penetration and transport, with the favored permeability of neutral base over charged ion, may be essential for channel blocking . Another possibility is that cationic species may be acting from the cytoplasmic surface as a result of direct control of axoplasmic pH or internal perfusion with permanently charged quaternary amine homologues (Strichartz and Berde, 1994).

9.1.2.1.2 Structural and Physical-Chemical Properties and Their Relation to Pharmacokinetics

The potency and duration of action of the local anesthetics are primarily related to the physical-chemical properties and structure of the local anesthetic, respectively. The amide local anesthetics are weak bases that are variably lipophilic. The more highly substituted the alky or tertiary amines on or near the tertiary amine or in the aromatic ring, the more lipophilic the anesthetic. It is the lipophilicity, measured by the octanol/aqueous buffer partition coefficient, that positively correlates the anesthetic potency (Strichartz and Berde, 1994). This is because lipophilic compounds penetrate nerve membranes more readily than hydrophilic compounds, resulting in a greater concentration of the drug at the interior sodium ion channel receptor (Lenz et al., 1992). In clinical trials, the correlation of hydrophobicity to anesthetic potency is not as clear as *in vitro* results and may be due to such factors as vasodilation caused by the anesthetics themselves and tissue redistribution of anesthetic (Strichartz and Berde, 1994; Lenz et al., 1992).

The amount of un-ionized and ionized forms of a local anesthetic in solution are represented by the pK_a. The pK_a is the pH at which there are equal molar concentrations of the un-ionized (B) and ionized (BH^+) form of the local anesthetic, and this relationship is represented by the following equation:

$$[BH^+]/[B] = 10^{(pKa - pH)}$$

The pK_a can shift due to certain environmetal factors such as temperature and ionic strength as well as the medium surrounding the drug (Sanchez et al., 1987; cited by Strichartz and Berde, 1994). In the apolar membrane, the average pK_a is lower than that in solution so that the concentration of the un-ionized base is 10 times the concentration of the ionized cations (Schreier et al., 1984; cited by Strichartz and Berde, 1994). As the pH of the medium is increased above the pK_a, then the equilibrium shifts towards a greater concentration of the base form (Strichartz and Berde, 1994). If the pH decreases due to addition of acid or CO_2, the water

solubility increases (Widman, 1975). Local anesthetics with low pK_as, such as lidocaine, generally have a more rapid onset of anesthesia due to the high concentration of the un-ionized form of the drug at physiologic pH. This allows for more of the un-ionized form to accumulate in the site of action (Glazer and Portenoy, 1991). Bupivacaine is one of the most potent local anesthetics. It has a relatively moderate-to-long duration of onset due to its moderate pK_a. Because of bupivacaine s high affinity for protein binding, it is held in the neural membrane longer and more tightly than other local anesthetics, resulting in a longer and more profound sensory inhibition (Lenz et al., 1992)

Etidocaine and bupivacaine are much more potent (longer acting and greater degree of anesthesia) than lidocaine and mepivacaine (Scott, 1975; cited by Tucker et al., 1977).

Table 6. Relative *In Vitro* Conduction Blocking Potency and Physical-Chemical Properties of Local Anesthetics

Anesthetic	Relative Conduction Blocking Potency[a]	pK_a (25 °C)	pK_a (36 °C)	Lipid Solubility (25 °C)	Hydrophobicity [b] (36 °C)
Mepivacaine	1.5	7.9	7.7	21	130
Prilocaine	1.8	8.0	8.0	25	129
Lidocaine	2	8.2	7.8	43	366
Ropivacaine	7	8.2	–	115	–
Bupivacaine	8	8.2	8.1	346	3,420
Etidocaine	8	8.1	7.9	800	7,320

Sources: Strichartz and Berde (1994) and Strichartz et al. (1990; cited by Feldman, 1994).
[a] Data derived from C fibers of isolated rabbit vagus and sciatic nerve
[b] Hydrophobicity equals octanol/buffer partition coefficient of the base; ratio of concentrations

The structure of the local anesthetics, rather than physical-chemical properties, have the greatest influence on their clearance and metabolism by the liver (Tucker et al., 1977). For example, cyclization of the N-alkyl chain retards the net metabolism and hepatic clearance of the anesthetics (Tucker, 1975; cited by Tucker et al., 1977).

9.1.2.1.3 Absorption of Amide Local Anesthetics

Absorption and distribution of amide local anesthetics varies depending on many factors, such as site and method of administration, blood flow characteristics, plasma protein binding, plasma pH, and the physical properties of the local anesthetic (i.e., pK_a, hydrophobicity, etc.).

Absorption from the site of injection depends on the blood flow–the higher the blood flow the more rapid the rate at which plasma concentrations increase and the greater the peak plasma concentrations of the drug (Arthur et al., 1993). Delaying absorption of local anesthetics from the site of application into the blood can result in a considerable decrease in the toxicity (Luduena et al., 1971). Theoretically, a person with a cardiac output of 4 L/min injected i.v. with 400 mg of a drug for 1 minute would have a peak plasm concentration of 100 g/mL (Arthur et al., 1993). When a local anesthetic is injected, the rate of absorption is greatest after intercostal block, followed by epidural, brachial plexus, and lower limb blocks, with subcutaneous (s.c.) infiltration being the slowest (Arthur et al., 1993). If vasoconstrictors, such as epinephrine, are administered with the local anesthetic, then absorption is reduced, usually allowing the safe dose of the anesthetic to be increased by 50-100%.

Subcutaneous and dermal application of the local anesthetics results in prolonged persistance of the local anesthetics at the site of application (prilocaine and lidocaine in this report). Local anesthetics do not readily penetrate healthy human skin in their salt form; however, effects may be seen if applied in their base form (Leopold and Maibach, 1999). Dermal absorption will be affected by the vehicle that contains the local anesthetic. The maximum anesthetic effect was observed one hour after application of lidocaine. The onset of anesthetic action after dermal application can be correlated with the local anesthetics solubility in medium chain triglycerides which has properties similar to stratum corneum lipids. Dermal absorption of local anesthetics is affected by the vasculature of the area of application, age of the patient and condition of the skin. Lidocaine plasma concentrations after dermal application have been observed to peak 32 hours or longer after application. In neonates, dermal absorption is more rapid due to the immaturity of the skin, which behaves more like a mucous membrane (Essink-Tebbes et al., 1999).

Absorption from the epidural space after epidural administration of local anesthetics is much slower than after i.v. administration (Katz et al., 1993). This may be due to the effect of

the anesthetic on the local tissue vasculature. Bupivacaine and lidocaine have both been shown to produce vasodilation at the area of administration, thereby increasing the rate of absorption to the bloodstream from the site of administration (Katz et al., 1993). Another factor which may contribute to the slower absorption of the local anesthetics from the epidural space is its high fat content. The more lipid soluble compounds, such as bupivacaine and ropivacaine, are released more slowly from the epidural space than the less lipid soluble anesthetic lidocaine (Katz et al., 1993). The absorption of the local anesthetics from the epidural space is biphasic, with an initial rapid phase followed by a slower terminal phase (Katz et al., 1993; Tucker and Mather, 1975; Burm, 1989).

After a local anesthetic reaches the circulatory system, it will pass through the right side of the heart, then to the lungs, and finally to the organs with high blood flow and high affinity the brain, heart, kidney, liver, and spleen (Hansson, 1971; Arthur et al., 1993). After a small i.v. bolus dose of lidocaine (0.5 mg/kg) in volunteers and patients, it was found that as much as 50 to 70% of the dose was taken up by the lungs on first pass and that uptake in patients with lung insufficiency was not markedly different (Jorfeldt et al., 1979, 1983; cited by Burm, 1989). Lung uptake is promoted by the relatively low pH of the fluid in the lungs when compared to plasma (Burm, 1989). A pH decrease in the cells of the lungs may result in diffusion trapping, a condition in which the transmembranous passage of local anesthetics in their un-ionized form is followed by dissociation in partially ionized components in the cell (Catchlove, 1972; cited by Widman, 1975). This trapped, dissociated, anestheticly active form may then cause unexpected toxic reactions (Widman, 1975). This is important when giving anesthetics as an antiarrythmic, considering that circulation will be impaired and acidosis is a likely result. The lungs may temporarily sequester, and possibly metabolize, large amounts of local anesthetics; however, as the dose increases, the distribution decreases so that the lungs may not be able to prevent a toxic reaction should a rapid i.v. injection be given (Arthur et al., 1993). A small fraction of the anesthetic dose may distribute slowly into the fat and muscle because of their low blood supply; but because of the hydrophobicity of the local anesthetics, there could be absorption and temporary storage in the fat before redistribution into the blood stream (Arthur et al., 1993). Children, especially infants, have more rapid heart rates and may predispose to accumulation of bupivacaine in the myocardium (Badgewell et al., 1990b; cited by Brown et al., 1999). One must still remember that the distribution characteristics of the amide local

anesthetics are similar because greater tissue affinity of the more lipophilic anesthetics, bupivacaine and etidocaine, is offset by extensive plasma protein binding (Burm, 1989).

Epinephrine (adrenalin) can be administered concomitantly with a local anesthetic to prolong the duration of anesthetic action, as well as reduce the absorption of the local anesthetic to the blood stream, thereby keeping the maximum plasma concentration of the local anesthetic low and decreasing the risk of systemic toxicity (L fstr m, 1971). The addition of epinephrine to the anesthetic dose can decrease plasma concentrations of the local anesthetic by as much as 50%, as in the case of bupivacaine (Reynolds et al., 1989). In short-acting local anesthetics, such as lidocaine, epinephrine may prolong the duration of anesthesia fourfold; however, the addition of epinephrine in long-acting local anesthetics such as bupivacaine did not significantly increase the duration of anesthetic effect (L fstr m, 1971). In obstetric medicine, epinephrine has α - and β-adrenoreceptor stimulating properties, which may increase the tonus of the myometrial muscle and weaken myometrial contractility, thereby reducing uterine blood flow and prolonging delivery (Ralson and Schnider, 1978; cited by Schierup et al., 1988).

Local anesthetics, like most drugs, will bind to plasma proteins to some degree. The two serum proteins involved with amide local anesthetics are α_1-acid glycoprotein and albumin (Arthur et al., 1993). α_1-Acid glycoprotein readily binds drugs but has a limited capacity for them, but albumin has a low affinity and a large capacity. As the concentration of a local anesthetic in serum increases, the percentage that is bound to the two proteins decreases (**Table 7**) (Arthur et al., 1993). Attempts have been made to correlate local anesthetic toxicity with protein-binding characteristics; however, the assumption that greater protein affinity resulted in less tissue absorption and hence less toxicity was not true. In two separate studies, it was found that alteration of the plasma protein concentrations did not attenuate the accumulation of lidocaine or bupivacaine in the brain of rats (Pardridge et al., 1983; Terasaki et al., 1986). Denson et al. (1984) showed that protein binding is usually measured *in vitro* under equilibrium conditions and is very different from the conditions of rapid absorption in humans. Also, the bound drug in plasma is in equilibrium with the unbound, so that drug from either fraction is able to diffuse down a concentration gradient and bind to tissue. This is evident with prilocaine, which has the lowest protein affinity in serum, but has the least toxicity. This low toxicity could be due to low binding to nerve cell protein (Arthur et al., 1993). While protein binding may not

be important in determining the diffusion of amide local anesthetics into tissue, it is one of the most important factors determining the transfer of local anesthetics across the placenta.

Differences in the amount of α_1-acid glycoprotein in various types of patients will affect the concentration of free local anesthetic in plasma. For example, neonates have a very low concentration of α_1-acid glycoprotein in plasma and will have much higher free local anesthetic fractions (Tucker, 1994). Plasma binding of bupivacaine and lidocaine in the human neonate is about 50% of that found in an adult (Tucker et al., 1970; cited by Pedersen et al, 1982). However, the total body clearance of local anesthetics in the neaonte and the greater volume of distribution may offset the low plasma binding (Pedersen et al., 1982). Patients with inflammatory disease, cancer, postmyocardial infarction, and post-operative patients have a higher concentration of binding protein, resulting in lower free drug fractions (Tucker, 1994).

Table 7. Approximate Percentages of Local Anesthetics That Are Protein-Bound at Two Different Serum Concentrations

Local Anesthetics	Percent Bound	
	1 g/mL serum	50 g/mL serum
Bupivacaine	95	60
Etidocaine	95	60
Ropivacaine	94	63
Lidocaine	70	35
Mepivacaine	75	30
Prilocaine	40	30

Source: Arthur et al. (1993)

9.1.2.1.4 Pharmacokinetics of Amide Local Anesthetics

The elimination of local anesthetics from plasma is characterized by biphasic elimination, an α-phase and a β-phase. The α-phase is characterized by the rapid absorption of the anesthetic by the organs and tissue and is measured by the α-phase half-life ($T_{1/2\alpha}$). The $T_{1/2\alpha}$ of the amide local anesthetics is so rapid that it is usually less than 6 minutes (Caldwell et al., 1976 abstr.). However, once the tissues become saturated with the maximum concentration of local anesthetic, then the elimination of the local anesthetic rapidly decreases until it approaches the $T_{1/2\beta}$. The $T_{1/2\beta}$ is the total body clearance of the local anesthetic due to hepatic extraction and

excretion. The $T_{1/2\beta}$ is under the influence of plasma protein binding of the local anesthetic, as well as hepatic clearance.

Because the amide local anesthetics have a stimulant effect on the circulatory system, systemic accumulation may be accompanied by increases in heart rate, cardiac output, and hepatic blood flow. Since the kinetics of these drugs is perfusion limited, then cardiovascular effects can be expected to influence their absorption and disposition by feedback (Tucker et al., 1977).

The placental transfer of the local anesthetics by passive diffusion is affected by the drug s molecular weight, lipid solubility, pK_a, protein binding, fetal pH, and fetal absorption (Banzai et al., 1995; Johnson et al., 1995 abstr.). The amide local anesthetics readily cross the placenta by passive diffusion in the unbound un-ionized form (Reynolds, 1979; cited by Hamshaw-Thomas and Reynolds, 1985). Studies have shown that the cord-to-maternal plasma concentrations of local anesthetics equilibrate quickly across the placenta and reaches a relatively constant level 15-30 minutes after adminstration to the mother due to the high lipid solubility of the un-ionized form and their low molecular weight (Tucker, 1994; Terama and Rajam ki, 1971). The rate of transfer of a drug across the placenta is measured by the umbilical venous/maternal venous ratio (UV:MV) upon administration of the drug, and while fetal tissue saturation is incomplete, the umbilical artery/maternal venous (UA:MV) concentration ratio should increase to reach a plateau that approaches the UV:MV (Reynolds et al., 1989). During maternal drug absorption, a small gradient may exist if there is fetal metabolism. Both UV:MV and UA:MV are affected by transplacental pH and governed by the gradient of transplacental α-glycoprotein (Petersen et al., 1981; O Brien et al., 1982; Kennedy et al., 1979; all cited by Reynolds et al., 1989; Hamshaw-Thomas and Reynolds, 1985). The main cause of interindividual variation should be overcome by examining the UA:UV ratio which gauge the extent of fetal equilibration and is not affected by α-glycoprotein concentrations (Reynolds et al., 1989). The decreased amount of protein binding in the fetus and neonate would likely result in greater volume of distribution and may contribute to the reduced rate of elimination in the fetus (Morgan et al., 1978). Elimination half-live of the local anesthetics in the human neonate is about 2-3 times longer than elimination in adults (Tucker and Mather, 1979). The differences in UV:MV concentration ratios for the local anesthetics proboably are due to the differences in

protein binding; however, the concentration of *unbound* local anesthetic in the plasma of both mother and fetus should be the same at equilibrium (Burm, 1989).

Since the amide local anesthetics are weak bases with pK_as ranging from 7.9 to 8.2, the pH of the medium is important for the amount of dissociation and passive transfer across biological membranes (M ller-Holve et al., 1986).

The location and rate of administration of the amide local anesthetics have a pronounced effect on drug distribution and the onset of anesthesia. The onset of anesthesia may vary by as much as 15 minutes when injected into different segments of the spinal column (Data et al., 1995). Local anesthetics are injected over an extended period of time when properly administered. This gives time for the local anesthetic to recirculate, reaching an equilibrium concentration in the plasma with adequate metabolism and elimination rates to keep this equilibrium below toxic concentrations. When a local anesthetic is inadvertently mistaken for another drug and accidentally administered, it is likely to be injected rapidly since the rate of infusion is not important for some pharmaceuticals. First-pass metabolism is then very important to prevent toxic amounts of a local anesthetic from reaching vital organs and tissues. The interplay of hepatic metabolism, extrahepatic metabolism, plasma protein concentrations, blood flow characteristics and elimination will play an important part in tempering the dose.

Table 8. Mean Percentage of the Local Anesthetic Dose Excreted Unchanged and Mean Biological Half-Life in Adults and Neonates

Local Anesthetic	Mean Percentage of Dose Excreted Unchanged in the Urine		Mean Biological Half-life (hr)	
	Adults	Neonates	Adults	Neonates
Mepivacaine	3.5	43.4	1.9, 3.17	8.95, 8.69
Lidocaine	4.2	19.7	1.6, 1.8	3.05, 3.16
Bupivacaine			3.5	8.1
Etidocaine		14.6	2.6	6.42

Source: Morgan et al. (1978)

Metabolism of the amide local anesthetics occurs primarily in the liver by N-dealkylation and/or hydrolysis, with subsequent hydroxylation. The amount of dealkylated and hydroxylated products vary according to species and local anesthetic administered. N-dealkylation appears to

be the primary mechanism of detoxification in humans and primates, while hydroxylation is the major route of metabolism in rodents and sheep. In all species, almost all hydroxylated metabolites, and some unhydroxylated, are excreted as glucuronide and sulphate conjugates. It has been suggested that the aniline metabolites may follow a volatile pathway of excretion (e.g., lung rather than kidney) (Nickel, 1996).

There is a concern with small children and neonates that the enzyme systems that metabolize local anesthetics are not fully developed and may result in more prolonged serum concentrations of the anesthetic and its metabolites (Essink-Tebbes et al., 1999).

9.1.2.2 Bupivacaine

9.1.2.2.1 Metabolism of Bupivacaine

The proposed metabolites of bupivacaine are listed in **Table 9** and the metabolic pathway is presented in **Figure 2**. Differences in metabolites detected in the urine samples of various species are shown in **Table 10**.

Metabolism of bupivacaine occurs primarily in the liver, with urinary and biliary excretion of bupivacaine and its metabolites. The primary liver enzyme responsible for the dealkylation of bupivacaine to PPX was shown to be CYP3A4 *in vitro* using human liver microsomes, although CYP2C19 and CYP2D6 may play a minor role in the formation of PPX (Gantenbein et al., 2000). Biliary excretion appears to be more extensive in rats than in primates (Goehl et al., 1973).

Bupivacaine is extensively metabolized in all species tested, as is evident from the small amount of unchanged bupivacaine excreted in the urine. The urinary excretion of bupivacaine is pH dependent, but the excretion of its desbutyl metabolite, PPX, is not (Friedman et al., 1982). The metabolism and metabolites of bupivacaine are similar to those of mepivacaine and ropivacaine.

Metabolism of bupivacaine in humans, and other primates, occurs primarily by N-dealkylation, followed by hydroxylation, usually of the aromatic or pipecolyl ring (Goehl et al., 1973). Dealkylation of bupivacaine gives desbutylbupivacaine (PPX). In humans, the major metabolites detected in the urine after dosing with a racemic mixture of bupivacaine were, in the order of decreasing concentration, levo and dextro enantiomers of PPX, 4'-hydroxybupivacaine, and 3'-hydroxybupivacaine (Fawcett et al., 1999). There was large variability in the rates of

clearance of the enantiomers, leading the investigators to conclude that the metabolism of bupivacaine may be mediated by different amounts of microsomal enzymes such as P450 isoforms, each with different substrate stereoselectivities.

In rats, metabolism is primarily by hydroxylation, with minor amounts of dealkylated products (Caldwell et al., 1977 abstr.; Goehl et al., 1973). 3'-Hydroxybupivacaine (12.1% of the dose) and 4'-hydroxybupivacaine (7.7%) were the major metabolites seen in 24-hour urine collections from rats. Only small quantities of the dealkylated products PPX (0.3% of the dose) and pipecolic acid (1.6%) were determined in a 24-hour urine sample.

In rats and humans, a large fraction of the hydroxylated metabolites of bupivacaine are excreted as glucuronide conjugates in the urine. In rats, about 80-97.8% of 3'-hydroxy- and 4'-hydroxybupivacaine were detected as glucuronide conjugates (Goehl et al., 1973; Caldwell et al., 1978).

Only one study was found that tried to determine the concentration of 2,6-xylidine in urine after exposure to bupivacaine, and no xylidine was found (Mather et al., 1971 and unpublished data; cited by Tucker and Mather, 1979); however, the details of the study were not available. In the studies reviewed, it is often difficult to identify or assess the amount of all excreted metabolites since only derivatives of the ^{14}C- or ^{3}H-labeled pipecolyl moiety of the bupivacaine molecule were determined. In all of the studies reviewed where pipecolic acid was detected and quantitated using a radioactive label on the pipecolyl moiety, it could be assumed that equal quantities of 2,6-xylidine were also formed as a product of the hydrolysis of PPX. However, further hydroxylation of any 2,6-xylidine may occur resulting in minor amounts of 2,6-xylidine. If this is the case, then the formation of 4-hydroxyxylidine after administration of bupivacaine may be substantial in primates and humans, but not in rats. To our knowledge, no one has tried to determine the amount of 4-hydroxyxylidine after bupivacaine administration.

The excretion of PPX into breast milk after administration of bupivacaine during delivery in mothers revealed that bupivacaine and PPX are differentially excreted into breast milk (Ortega et al., 1999). While the mean bupivacaine serum and breast milk concentrations were highest 2 hours after epidural injection (0.23 and 0.09 µg/mL, respectively), the mean serum and breast milk PPX concentrations were highest 12 hours after administration (0.17 and 0.25 µg/mL, respectively). The mean breast milk/serum ratio at peak concentrations was only 0.39 for

bupivacaine, but 1.47 for PPX. This is an important factor when considering that the toxicity of PPX is twice that of bupivacaine (Bruguerolle et al., 1994; cited by Ortega et al, 1999).
The antiulcerative drug cimetidine, an H2-receptor agonist that is capable of impairing oxidation in the liver, has been shown to noncompetitively inhibit the metabolism of bupivacaine *in vitro* in rat hepatocytes at concentrations of 100 g/mL (396 M) (Thompson et al., 1987). However, cimetidine did not appear to affect the metabolism or clearance of bupivacaine significantly in *in vivo* human studies. The synergism/antagonism of cimetidine is important since it is used as an anesthetic premedication for the prevention of acid aspiration syndrome (Pihlajamaki et al., 1988).

9.1.2.2.2 Pharmacokinetic of Bupivacaine

The percentage of the dose that was bound to plasma proteins was found to be 95.2% in humans *in vivo* (Emanuelsson et al., 1995).

There are notable differences in the duration of bupivacaine persistence in plasma after different forms of administration. When bupivacaine was epidurally infused at a rate of 25 mg/hr in young healthy human adult males for 21 hours, the mean peak plasma level was 0.90 µg/mL at the termination of infusion (Emanuelsson et al., 1995).
Due to the increased use of bupivacaine as an epidural anesthetic in obstetrics, there are numerous studies of the pharmacokinetics of bupivacaine in the mother, fetus, and neonate. Today, bupivacaine is most often used in epidural analgesia in combination with narcotics such as fentanyl or sufentanil (Walker, 1997). This combination provides a more rapid onset of anesthesia, more complete and longer lasting pain relief, and less motor blockade than if either drug were used alone. Concentrations of bupivacaine in the maternal plasma of 18 pregnant women peaked 10 minutes after the termination of epidural infusion (dose: ≥35 mg) with plasma concentration ranges between 91 and 430 ng/mL (mean ~200) (Caldwell et al., 1978). Bupivacaine appeared in the blood of the fetus (29 ng/mL) ten minutes after the end of infusion. The fetal venous plasma concentrations of bupivacaine reached a plateau after 75 minutes (44 ng/mL) and lasted until the end of fetal sampling at ninety minutes after epidural administration to the mother. Similar concentrations of bupivacaine in the fetus were found at 20 minutes (29 ng/mL) and 60 minutes (34 ng/mL) in another study (Caldwell et al., 1976 abstr.). The mean umbilical venous/maternal venous bupivacaine concentrations have been measured between 0.33

and 0.59 (Fernando et al., 1997; Caldwell et al., 1978; Cooper et al., 1977). In all studies reviewed involving the use of bupivacaine during delivery there was no correlation between bupivacaine use and lower Apgar scores. In one study, neonates born to 40 women that had received bupivacaine during delivery had Apgar scores above seven when measured five minutes after delivery (Fernando et al, 1997). In a study of 19 mothers and their babies, 11 neonates had eliminated all bupivacaine in plasma 24 hours after delivery and 8 had bupivacaine concentrations between 0.005 and 0.01 μg/mL (Cooper et al., 1977).

The terminal phase half-life in the mother is significantly increased after epidural administration of amide local anesthetics due to the slow absorption of the drug from the epidural space into the blood stream (Morgan et al., 1978). This is of particular importance when considering fetal exposure to local anesthetics. The $T_{1/2\alpha}$ has been measured as 5 minutes in pregnant mothers administered bupivacaine epidurally (Caldwell et al., 1976 abstr.) and 7.0 ± 2.4 minutes in 6 human volunteers injected i.v. (Boyes et al., 1971; cited by Scott et al., 1973). The mean $T_{1/2\beta}$ in mothers has been measured as 1.05 to 1.25 hours (63 to 75 minutes) (Caldwell et al., 1976 abstr., 1978) and 76.4 ± 55.6 minutes in 6 healthy human volunteers (Boyes et al., 1971; cited by Scott et al., 1973). Bupivacaine elimination from the blood of neonates was biphasic, with a rapid initial phase in the first two hours after birth, followed by a much slower elimination phase (mean $T_{1/2\beta}$ = 25 hours). The initial rapid elimination phase in neonates may be due to first-pass absorption into the newly matured lungs. The longer time for elimination in neonates could be attributed to either greater tissue absorption or decreased elimination (Caldwell et al., 1976 abstr., 1978). The coadministration of epinephrine with bupivacaine results in half the plasma levels of patients receiving bupivacaine alone at the same dose (Reynolds et al., 1989).

Bupivacaine is a mixture of enantiomers levobupivacaine [(*S*)-(—)-bupivacaine] and dexbupivacaine [(*R*)-(+)-bupivacaine]. Dexbupivacaine has been determined to be more potent in its ability to block sodium channels because of its ability to bind more rapidly and more tightly than levobupivacaine (Anesthetic & Life Support Advisory Committee, 1999). The greater anesthetic potency of dexbupivacaine also results in its greater toxicity when compared to that of levobupivacaine. It has been found that the ratio of renal to total bupivacaine clearance in humans is much higher for (*R*)-(+)-bupivacaine than for (*S*)-(—)-bupivacaine (Fawcett et al., 1999).

Table 9. Bupivacaine, Its Salts, and Its Metabolites

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
BUP	Bupivacaine; (±)-Bupivacaine; Marcaine; *DL*-Bupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-2«,6«-pipecoloxylidide	$C_{18}H_{28}N_2O$	38396-39-3	517
BUP	Bupivacaine; (±)-Bupivacaine; Marcaine; *DL*-Bupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-2«,6«-pipecoloxylidide	$C_{18}H_{28}N_2O$	2180-92-9 (replaced by 38396-39-3 ca. 1991)	1128
BUPÆH_2CO_3	Bupivacaine carbonate; Bupiv-Carb	$C_{18}H_{28}N_2O•2CH_2O_3$	55750-21-5	3
(R+)-BUP	(+)-Bupivacaine; (*R*)-(+)-Bupivacaine; (*R*)-Bupivacaine; *D*-(+)-Bupivacaine; *d*-Bupivacaine	$C_{18}H_{29}ClN_2O$	27262-45-9	90
(S-)-BUP	(-)-Bupivacaine; (*S*)-(-)-Bupivacaine; (*S*)-Bupivacaine; *L*-(-)-Bupivacaine; Levobupivacaine	$C_{18}H_{29}ClN_2O$	27262-47-1	114
BUPÆHCl	Bupivacaine hydrochloride	$C_{18}H_{29}ClN_2O$	18010-40-7	144
BUPÆHCl	Bupivacaine hydrochloride	$C_{18}H_{29}ClN_2O$	14252-80-3	40 Irestadt et al. (1976)
PPX	2«,6«-Pipecoloxylidide [racemic]; 2«,6«-Pipecolylxylidide; PPX; *N*-Desbutylbupivacaine; Mono-*N*-demethylmepivacaine; *N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	15883-20-2	45 Goehl et al. (1973)
(R)-PPX	(*R*)-2«,6«-Pipecoloxylidide; (*R*)-Desbutylbupivacaine; (-)-2«,6«-Pipecoloxylidide	$C_{14}H_{20}N_2O$	27262-43-7	10 Fawcett et al. (1999) (Bupivacaine)
(S)-PPX	(*S*)-2«,6«-Pipecoloxylidide; (*S*)-Desbutylbupivacaine; (+)-2«,6«-Pipecoloxylidide; (2*S*)-*N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	27262-40-4	20 Fawcett et al. (1999)

Table 9. Bupivacaine, Its Salts, and Its Metabolites (Continued)

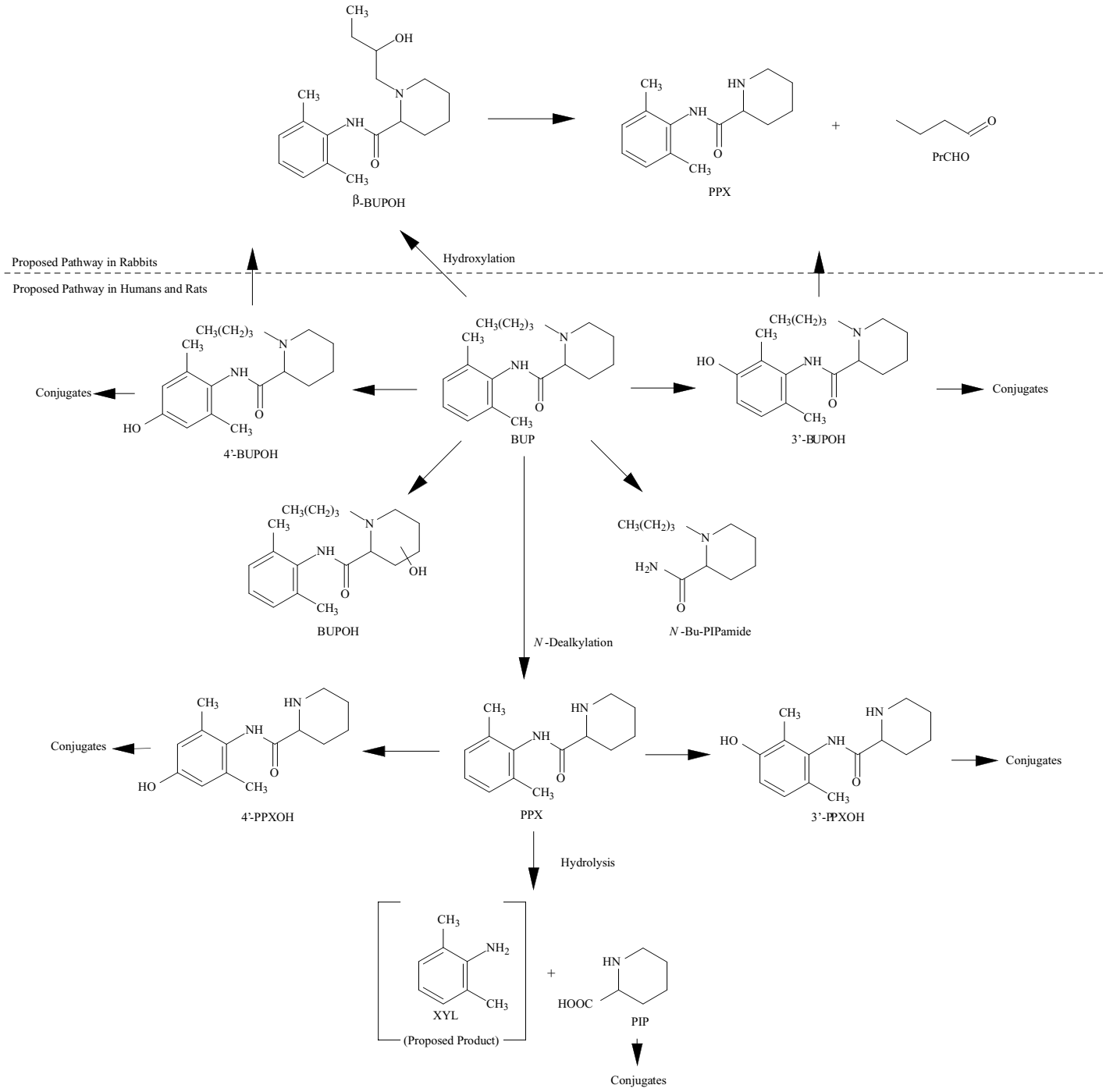
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
N-Bu-PIPamide	*N*-Butylpipecolyl-2-amide; 1-Butyl-2-piperidinecarboxamide; *N*-Butylpiperidine-2-carboxylic acid amide **[Mentioned in Dennhardt et al. (1978a), Dennhardt and Konder (1980), and Dennhardt (1981) as "unexpected and unexplained." Formation of this compound would appear to require cleavage by hydrogenolysis of the C-N bond between the *m*-xylene and amino moieties of 2,6-xylidine.]**	$C_{10}H_{20}N_2O$	67810-45-1	1 Dennhardt & Konder (1980)
3«-BUPOH	3«-Hydroxybupivacaine; 1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-3«-hydroxypipecolo-2,6«-xylidide	$C_{18}H_{28}N_2O_2$	51989-46-9	10 Dennhardt & Konder al. (1980)
(R)-3«-BUPOH	(2*R*)-3«-Hydroxybupivacaine; (2*R*)-1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-08-0	1 Fawcett et al. (1999)
(S)-3«-BUPOH	(2*S*)-3«-Hydroxybupivacaine; (2*S*)-1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-03-5	1 Fawcett et al. (1999)
4«-BUPOH	4«-Hydroxybupivacaine; 1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	51989-47-0	13 Dennhardt & Konder (1980)
(R)-4«-BUPOH	(2*R*)-4«-Hydroxybupivacaine; (2*R*)-1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-05-7	1 Fawcett et al. (1999)
(S)-4«-BUPOH	(2*S*)-4«-Hydroxybupivacaine; (2*S*)-1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-01-3	1 Fawcett et al. (1999)
BUPOH	Hydroxybupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)hydroxy-2-piperidinecarboxamide [unspecified attachment for hydroxyl group]	$C_{18}H_{28}N_2O_2$	67800-43-5	1 Dennhardt et al. (1978a)

Table 9. Bupivacaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
β-BUPOH	*N*-(2,6-Dimethylphenyl)-1-(2-hydroxybutyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	64013-17-8	1 Bouch & Lhoest (1976)
3«-PPXOH	3«-Hydroxy-2«,6«-pipecoloxylidide [racemic]; A(3-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 3«-Hydroxydesbutylbupivacaine	$C_{14}H_{20}N_2O_2$	247061-17-2	1 Arvidsson et al. (1999)
4«-PPXOH	4«-Hydroxy-2«,6«-pipecoloxylidide [racemic]; A(4-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 4«-Hydroxydesbutylbupivacaine	$C_{14}H_{20}N_2O_2$	51989-48-1	2 Falany et al. (1999) Goehl et al. (1973)
PrCHO	Butyraldehyde; Butanal **[A probable metabolite of a proposed metabolite (Bouch & Lhoest, 1976). No link was found between this compound and bupivacaine in Chem. Abstr.]**	C_4H_8O	123-72-8	7765 Bouch & Lhoest (1976)
PIP	Pipecolic acid; *DL*-Pipecolic acid; (±)-Pipecolic acid; a-Pipecolinic acid; (*RS*)-2-Piperidinecarboxylic acid; Piperolinic acid; Homoproline; 2-Carboxypiperidine; etc.	$C_6H_{11}NO_2$	535-75-1	518 Goehl et al. (1973)
XYL	2,6-Xylidine; 2,6-Dimethylaniline **[Has not been confirmed as a bupivacaine metabolite.]**	$C_8H_{11}N$	87-62-7	[24 with CASRN linked to metabolism] **(Conjectural)**

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxyl derivatives of xylidine and toluidine.
Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).
The lower-case Greek letter beta in a code indicates that hydroxylation is on the C-2 of the butyl moiety.

Figure 2. Metabolic Pathway for Bupivacaine in Humans and Experimental Animals



Chiral center is located on C-2 in the pipecolyl ring.
Bracketed 2,6-xylidine has not been reported, but should be formed plus its metabolites in an amount at least equal to the amount of pipecolic acid (PIP).

Table 10. Metabolites of Bupivacaine Detected *In Vivo* and Their Amounts in Humans and Experimental Animals

Metabolite Code	Range of Mean Amounts of Bupivacaine Metabolites Detected in Urine and [Plasma][a]									
	Humans		Primates		Rabbits		Rats		Sheep[c]	
BUP	X	0.13-6%[1.45] 0.09[b]	X	5.9%			X	2.8-3.4%	X	<1.0 µM
PPX	X	1.21-5% [0.17] 0.25[b]	X	3.8%			X	0.3-1.1%	X	1.4 µM
N-Bu-PIPamide*	X	n.q.					X	n.q.		
3'-BUPOH	X	3.66%			X	n.q.	X	12.1-45.3%	X	39 µM
4'-BUPOH	X	0.09-1.71% [0.02]	X	8.0%	X	n.q.	X	7.7-28.3%		3 µM
BUPOH	X	n.q.					X	n.q.		
β-BUPOH	X	n.q.			X	n.q.				
4'-PPXOH	X	4.9%	X	4.9%					X	<3 µM
3'-PPXOH									X	6 µM
PrCHO*										
PIP			X	51.7%			X	1.6-6.0%		
XYL*										
Percent of dose in urine & time				79.9% (24-hr)				27-50% (24-hr)		
Percent of dose in feces & time				6.0% (24-hr)				28-29% (24-hr)		

* These compounds have been proposed as metabolites, but they have not been confirmed.

[a] Urinary excretion is measured as the percentage of the administered dose found in the urine and are recorded here as unbracketed numbers. The plasma concentrations (µg/mL) are recorded here in brackets.

[b] Detected in breast milk (µg/mL).

[c] Concentration of bupivacaine in sheep urine was reported as molarity only.

n.q. = not quantitated

9.1.2.3 Etidocaine

9.1.2.3.1 Metabolism of Etidocaine

Etidocaine, like the other amide local anesthetics, is extensively metabolized in the liver. Only 0.17-0.33% of the dose was recovered unchanged as etidocaine (Morgan et al., 1977b). The metabolism of etidocaine may not be as extensive in neonates since the percentage of etidocaine in neonatal blood that was excreted unchanged in the 48-hour urine collections of 8 neonates was estimated to be 14% (Morgan et al., 1978).

Extraction and analysis of a 48-hour urine collection from a healthy human volunteer resulted in the determination of eight dealkylated and hydroxylated metabolites of etidocaine (Vine et al., 1978). Quantitative analysis of the metabolites was not possible because of the methods used; however, it was estimated that these metabolites accounted for approximately 10% of the total dose of etidocaine. The metabolites of etidocaine and a diagram of the metabolic pathway for etidocaine are presented in **Table 11** and **Figure 3**, respectively. Examination of 48-hour urine samples from two patients, one dosed orally with etidocaine and the other dosed by epidural injection, resulted in the isolation of nine metabolites (Thomas et al., 1976). Two of the nine metabolites isolated metabolites were unknown. A quantitative determination of the metabolites was performed on urine collected from the patient receiving the epidural dose. Six metabolites: 2-amino-2-butyroxylidide, 2-*N*-ethylamino-2-butyroxylidide, 2,6-dimethylaniline (2,6-xylidine), and 4-hydroxy-2,6-dimethylaniline (4-hydroxyxylidine) accounted for approximately 31% of the total dose of etidocaine (see **Table 12** for individual amounts).

The concentrations of the metabolites 2,6-xylidine and its metabolite, 4-hydroxyxylidine, were determined after etidocaine administration and found to be much lower than concentrations after lidocaine administration (Morgan et al, 1977a abstr.). Xylidine and 4-hydroxyxylidine accounted for only 3.0% of the dose of etidocaine, whereas the amount of the two metabolites after lidocaine administration was 75% of the dose (Keenaghan and Boyes, 1972). The authors attributed this difference to the presence of the branched alkyl side chain in the etidocaine moiety. Sixteen N-dealkylated and hydroxylated metabolites were found in this study but were not presented in the published abstract.

The placental transfer of three metabolites of etidocaine (etidocaine, 2-*N*-propylamino-2'-butyroxylidide, and 2-*N*-ethylamino-2'-butyroxylidide) were found to be related to their

hydrophobicity (Morgan et al., 1977b). The greater the lipid solubility, the greater the cord/maternal plasma ratio.

The metabolite 2-*N*-propylamino-2'-butyroxylidide was found to be more concentrated in the blood of neonates than in the blood of the mothers (Morgan et al., 1978). This pattern is also true for lidocaine and mepivacaine (Mihaly et al., 1977; Moore et al., 1975; all cited by Morgan et al., 1978).

No relationship was seen between the last dose of etidocaine to delivery and cord/maternal venous blood or plasma concentration ratios of etidocaine (Morgan et al., 1977b). 2-*N*-Propylamino-2'-butyroxylidide and 2-*N*-ethylamino-2'-butyroxylidide appeared in maternal blood at 5 minutes after dosing and in cord blood at 30 minutes post-administration. Of eight neonates born to mothers that received epidural etidocaine, three had measurable levels of 4-hydroxyxylidine and five had levels of xylidine. From 2 to 6 µg of 4-hydroxyxylidine was detected in 48-hour urine collections. The amounts of xylidine detected were between trace and 1.9 µg in the 48-hour urine of neonates. It is interesting to note that in the neonates who had excreted 4-hydroxyxylidine, no xylidine was detected, and in the ones who had excreted xylidine, no 4-hydroxyxylidine was detected.

The hydantoin metabolite 3-(2,6-dimethylphenyl)-5-ethyl-2,4-imidazolidininedione was determined to comprise 10% of the dose excreted in the urine of 2 male patients and two male volunteers (Morgan et al., 1977c). The presence of the hydantoin metabolite may contribute to the lower toxicity of etidocaine when compared to bupivacaine since hydantoins are known to have anticonvulsant properties (Scott, 1975; cited by Morgan et al., 1977c).

Table 11. Etidocaine, Its Salts, and Its Metabolites

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
ETI	Etidocaine; (α)-*N*-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide; 2-(*N*-Ethylpropylamino)-2«,6«-butyroxylidide	$C_{17}H_{28}N_2O$	36637-18-0	226
ETIÆHCl	Etidocaine hydrochloride; Duranest hydrochloride	$C_{17}H_{29}ClN_2O$	36637-19-1 (Replaced 52300-99-9)	4 (52300-99-9) 43 (36637-19-1)
EtABX	2-*N*-Ethylamino-2«-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)butanamide	$C_{14}H_{22}N_2O$	59359-47-6	3 Thomas et al. (1996)
PrABX	2-*N*-Propylamino-2«-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-(propylamino)butanamide	$C_{15}H_{24}N_2O$	59359-48-7	3 Thomas et al. (1996)
ABX	2-Amino-2«-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-aminobutanamide	$C_{12}H_{18}N_2O$	59359-46-5	15 Thomas et al. (1996)
3«-ETIOH	3-Hydroxyetidocaine; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide; 2-(Ethylpropylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide	$C_{17}H_{28}N_2O_2$	69754-76-3	1 Vine et al. (1978)
4«-ETIOH	4-Hydroxyetidocaine; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide; 2-(Ethylpropylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide	$C_{17}H_{28}N_2O_2$	69754-72-9	1 Vine et al. (1978)
3«-EtABXOH	*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-(ethylamino)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(ethylamino)butanamide; 2-(Ethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{14}H_{22}N_2O_2$	69754-70-7	1 Vine et al. (1978)

Table 11. Etidocaine, Its Salts, and Its Metabolites (Continued)

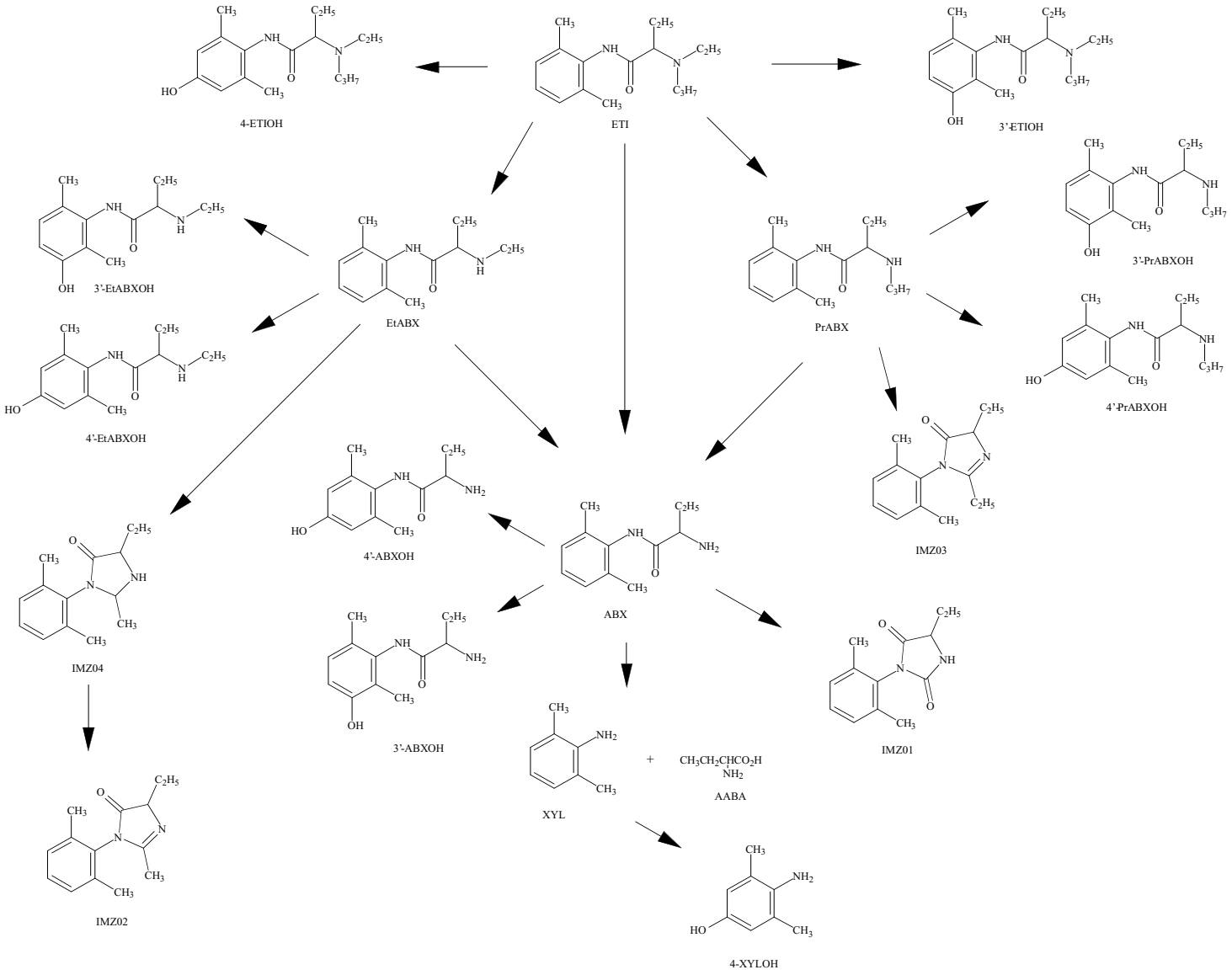
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
4«-EtABXOH	*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-(ethylamino)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(ethylamino)butanamide; 2-(Ethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{14}H_{22}N_2O_2$	69754-74-1	1 Vine et al. (1978)
3«-PrABXOH	*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-(propylamino)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(propylamino)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{15}H_{24}N_2O_2$	69754-75-2	1 Vine et al. (1978)
4«-PrABXOH	*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-(propylamino)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-propylaminobutyramide	$C_{15}H_{24}N_2O_2$	69754-71-8	1 Vine et al. (1978)
3«-ABXOH	2-Amino-*N*-(3-hydroxy-2,6-xylyl)butyramide; 2-Amino-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-aminobutyramide	$C_{12}H_{18}N_2O_2$	69754-73-0	1 Vine et al. (1978)
4«-ABXOH	2-Amino-*N*-(4-hydroxy-2,6-xylyl)butyramide; 2-Amino-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-aminobutyramide	$C_{12}H_{18}N_2O_2$	69754-69-4	1 Vine et al. (1978)
IMZ01	3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione	$C_{13}H_{16}N_2O_2$	64226-24-0 [113800-53-6 *(R)*] [113800-58-1 *(S)*]	1 Morgan et al. (1977c)
IMZ02	1-(2,6-Dimethylphenyl)-2-methyl-4-ethyl-2-imidazolin-5-one; 3-(2,6-Dimethylphenyl)-5-ethyl-3,5-dihydro-2-methyl-4*H*-imidazol-4-one	$C_{14}H_{18}N_2O$	64429-46-5	1 Morgan et al. (1977c)
IMZ03	1-(2,6-Dimethylphenyl)-2,4-diethyl-2-imidazolin-5-one; 3-(2,6-Dimethylphenyl)-2,5-diethyl-3,5-dihydro-4*H*-imidazol-4-one	$C_{15}H_{20}N_2O$	64226-25-1	1 Morgan et al. (1977c)
IMZ04	3-(2,6-Dimethylphenyl)-5-ethyl-2-methyl-4-imidazolidinone	$C_{14}H_{20}N_2O$	59359-49-8	1 Thomas et al. (1976)

Table 11. Etidocaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
AABA	α-Aminobutyric acid; 2-Aminobutanoic acid; AABA; (α)-α-Aminobutyric acid; *DL*-Aminobutyric acid; Butyrine; *DL*-Ethylglycine; Homoalanine **(Conjectural.)**	$C_4H_9NO_2$	2835-81-6 (Replaced 80-60-4)	601 (2835-81-6) 1269 (80-60-4)
XYL	2,6-Xylidine; 2,6-Dimethylaniline	$C_8H_{11}N$	87-62-7	[24 with CASRN linked to metabolism] Thomas et al. (1996) Morgan et al. (1977b)
4-XYLOH	4-Hydroxy-2,6-xylidine; 4-Amino-3,5-dimethylphenol; 4-Amino-3,5-xylenol; 4-Amino-3,5-dimethylphenol; 4-Hydroxy-2,6-dimethylaniline	$C_8H_{11}NO$	3096-70-6	75 Thomas et al. (1996) Morgan et al. (1977b)

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated metabolites of xylidine and toluidine
Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).

Figure 3. Metabolic Pathway for Etidocaine in Humans



4-XYLOH may also be produced by the hydrolysis of 4'-ETIOH, 4'-EtABXOH, 4'-PrABXOH, and 4'-ABXOH as well as by hydroxylation of xylidine, but the pathways are not shown due to figure constraints.

Table 12. Identified Metabolites of Etidocaine in Man and Their Relative Amounts Detected in Human Urine Samples

Code	Compound	Percent of Dose in Human Urine	Reference(s)
ETI	2-*N*-Ethylpropylamino-2-butyroxylidide; Etidocaine	0.21%	Thomas et al. (1996)
EtABX	2-*N*-Ethylamino-2'-butyroxylidide	0.45%	Thomas et al. (1996)
PrABX	2-*N*-Propylamino-2'-butyroxylidide		Thomas et al. (1996)
ABX	2-Amino-2'-butyroxylidide	9.5%	Thomas et al. (1996)
3'-ETIOH[a]	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide		Vine et al. (1978)
4'-ETIOH[a]	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide		Vine et al. (1978)
3'-EtABXOH[a]	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*-ethylamino)butyramide		Vine et al. (1978)
4'-EtABXOH[a]	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*-ethylamino)butyramide		Vine et al. (1978)
3'-PrABXOH[a]	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*-propylamino)butyramide		Vine et al. (1978)
4'-PrABXOH[a]	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*-propylamino)butyramide		Vine et al. (1978)
3'-ABXOH[a]	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-aminobutyramide		Vine et al. (1978)
4'-ABXOH[a]	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-aminobutyramide		Vine et al. (1978)
IMZ01	3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione	10%	Morgan et al. (1977c)
IMZ02	1-(2,6-Dimethylphenyl)-2-methyl-4-ethyl-2-imidazolin-5-one		Morgan et al. (1977c)
IMZ03	1-(2,6-Dimethylphenyl)-2,4-diethyl-2-imidazolin-5-one		Morgan et al. (1977c)
IMZ04	2-Methyl-*N*-2,6-dimethylphenyl-5-ethyl-4-imidazolidinone		Thomas et al. (1996)
AABA	α-Aminobutyric acid; 2-Aminobutanoic acid		
XYL	2,6-Dimethylaniline; 2,6-Xylidine	0.46-2.16%	Thomas et al. (1996) Morgan et al. (1977b)
4-XYLOH	4-Hydroxy-2,6-dimethylaniline; 4-Hydroxyxylidine	3.23-8.3%	Thomas et al. (1996) Morgan et al. (1977b)

[a] These metabolites were quantified in human urine and found together to comprise 10% of the administered dose.

9.1.2.3.2 Pharmacokinetics of Etidocaine

In five human male and female patients undergoing routine surgery, the protein-bound fraction of etidocaine in the blood was 93.4% to 94.8% (Morgan et al., 1977b). The *in vitro* protein binding of etidocaine is much lower in pregnant women during delivery (73.6%) than it is in pregnant women in week 35-37 of gestation (94.4%). The lower protein binding is probably due to the lower hematocrit in pregnant women (0.36) and also the fact that almost all of the etidocaine in the blood is confined to the plasma (Diem and Lentner, 1971; Assali and Brinkman, 1972; Kurata and Wilkinson, 1974; all cited by Morgan et al., 1977b). This may have important implications for fetal transfer since it is the unbound fraction of etidocaine in maternal blood that is available for transport across the placenta. The hematocrit in umbilical cord blood at delivery has been measured as 0.47, which is the same as the hematocrit in a healthy adult male (Diem and Lentner, 1971; cited by Morgan et al., 1977b; Morgan et al., 1978). This higher concentration of plasma proteins in fetal blood when compared to maternal blood may help offset the lower amount of plasma protein binding in the fetus. There was a large interpatient variation in the cord/maternal whole blood concentration ratio of etidocaine (range 0.161 to 1.38), but the cord/maternal plasma concentration ratio was less variable (range 0.234 to 0.546).

The elimination half-life of etidocaine in blood after i.v. and epidural administration was reported to be 2.6 and 6.5 to 7.7 hours , respectively (Tucker and Mather, 1975; cited by Morgan et al., 1977b). The mean elimination half-life of etidocaine in the plasma of pregnant (5.10 ± 2.58) and nonpregnant (5.46 ± 1.04) women was not found to be significantly different; however, the range of the half-life of etidocaine in plasma was significantly greater in pregnant women than in nonpregnant subjects (Morgan et al., 1977b). The mean half-life of elimination of etidocaine in neonates taken from urinary data was reported to be 6.42 hours (Morgan et al., 1978).

The mean blood/plasma ratio of etidocaine in fetal umbilical blood (1.24 ± 0.64) was much higher than seen in male and nonpregnant female adults (0.55 ± 0.03 and 0.64 ± 0.08, respectively) (Morgan et al, 1977b; Morgan et al., 1978). This indicates that even if total fetal/maternal blood concentrations of etidocaine are at equilibrium, more etidocaine may be unbound and available for absorption in the fetus. There was no significant difference observed in the elimination of etidocaine in pregnant women (14.0 ± 3.5 mL/min/kg) when compared to that of nonpregnant women (14.6 ± 4.6 mL/min/kg).

In sheep, the $t_{1/2\alpha}$ and $t_{1/2\beta}$ in the neonate and the nonpregant adult are very similar after i.v. administration of 2.5 mg/kg; however, due to the larger volume of distribution in the neonate (4.64 L/kg) when compared to that of the nonpregnant adult (1.52 L/kg), total body clearance and hepatic clearance were almost three times as much in the neonate as was seen in the nonpregnant adult sheep (Pedersen et al., 1982).

9.1.2.4 Lidocaine

9.1.2.4.1 Metabolism of Lidocaine

The metabolism of lidocaine is the most studied of all the amide local anesthetics and much information is available for interspecies comparison. The metabolism of lidocaine occurs primarily in the liver; however, extrahepatic metabolism of lidocaine has been detected *in vitro* and *in vivo* (Akerman et al., 1966). The deethylation of lidocaine to monoethylglycinexylidide (MEGX) has been shown to be mediated by cytochrome P450 isoenzyme CYP3A4 in transfected HepG2 cells and up to 60% of this deethylase activity could be inhibited by CYP3A4 antibodies in human microsomes (Bargetzi et al., 1989; Imaoka et al., 1990; both cited by Reichel et al., 1998). In rats, MEGX formation was attributed to CYP2C11 and CYP2B1 P450 isozymes. Lidocaine had no specificity for cytochrome P-448 as predicted by molecular geometrics (Parke et al., 1988). The metabolites of lidocaine as well as the metabolic pathway are presented in **Table 13** and **Figure 4**, respectively.

Lidocaine shows pronounced interspecies variability in its metabolism (Keenaghan and Boyes, 1972). **Table 14** presents data on the urinary excretion of lidocaine metabolites in various species after oral administration. Biliary excretion of reabsorbed metabolites from the intestinal tract was evident in the rat; however, biliary excretion of lidocaine and its metabolites is not as important in humans. The half-life of lidocaine disappearance was estimated to be less than 30 minutes in rats, as compared to a half-life of 45 to 60 minutes in dogs and 90 minutes in man. The primary route of metabolism in the rat was via hydroxylation. It has been shown that the metabolism of lidocaine in the rat may vary depending on age (Fujita et al., 1985; cited by Coutts et al., 1987). The primary route of metabolism in man was by hydrolysis of the amide bond in lidocaine or one of its dealkylated metabolites with subsequent hydroxylation. It has been shown that dogs and rabbits can metabolize 2,6-xylidine to 2-amino-3-methylbenzoic acid (Short et al., 1989; Kammerer and Schmitz, 1986) and that the guinea pig may also be able to

produce this metabolite from lidocaine; however it has not been detected in man (Keenaghan and Boyes, 1972). Humans appear to preferentially hydroxylate the aromatic ring of lidocaine at the 4-carbon while rats preferentially hydroxylate at the 3-carbon (Coutts et al., 1987; Keenaghan and Boyes, 1972).

The aromatic metabolite of lidocaine, 2,6-xylidine, is not a major metabolite excreted in the urine of man; however, its hydroxylated derivative, 4-hydroxyxylidine, is the predominant metabolite determined in urine and in the plasma. Xylidine can be formed from either lidocaine or its metabolite MEGX *in vitro* (Parker et al., 1996). It is thought that lidocaine may be hydroxylated prior to amide hydrolysis, resulting in little formation of xylidine but formation of large amounts of 4-hydroxyxylidine (Tam et al., 1987). The percentage of the lidocaine dose (oral dose of 250 mg or ~3.125 mg/kg bw) excreted as 2,6-xylidine in the 24-urine collection from 20 healthy human volunteers was 1.0% of the dose, but 4-hydroxyxylidine comprised 72.6 percent of the dose. After two i.v. bolus doses of 100 mg each of lidocaine hydrochloride followed immediately by i.v. infusion at a rate of 3 mg/min for 48 hours in two patients, the 72-hour urine of one patient contained predominantly 4-hydroxyxylidine (80.1% of the lidocaine dose). Xylidine was not detected in the urine of either patient (<0.2 g/mL) (Tam et al, 1987). Xylidine was not detected in the plasma; however, the concentration of 4-hydroxyxylidine in plasma was even greater than the concentration of lidocaine itself immediately after i.v. infusion (4.5 and 2.8 µg/mL, respectively) and 10 hours after infusion (1.7 and 1.0 µg/mL, respectively). Following epidural administration in four patients, as much as 75% of the dose of lidocaine was recovered as 2,6-xylidine and 4-hydroxyxylidine (Morgan et al., 1977a). All of the *in vivo* animal studies reviewed showed that xylidine was not a major metabolite in any species except guinea pigs, which excreted 16.2% of the dose as xylidine in 24-hour urine collections (Keenaghan and Boyes, 1972). Because 4-hydroxyxylidine has been shown to cause mutations in Salmonella, the toxicity of this metabolite should not be overlooked (Beardsley, 1994). Lidocaine been shown to undergo intrachannel hydrolysis (78% of the time with lidocaine) in a bovine AChE preparation using circular dichroism which was correlated with paresthesia in humans (Nickel, 1994 abstr.).

In vitro tests using human liver slices showed that the concentrations of MEGX and xylidine were similar after incubation with lidocaine (Parker et al., 1996). When liver microsomes, S9 fractions, and liver homogenates were used, relatively higher concentrations of

MEGX and relatively lower concentrations of xylidine than those seen *in vivo* were determined (Parker et al., 1996).

N-Hydroxyamides are of importance since some have been shown to be carcinogenic (e.g., *N*-hydroxy-2-acetylaminofluorene). It has been proposed that *N*-hydroxylidocaine and *N*-hydroxymonoethylglycinexylidide could be possible metabolites of lidocaine (Mather and Thomas, 1972; cited by Nelson et al., 1978). This was based on the fact that treatment of urine samples with $TiCl_3$ after lidocaine administration resulted in an increase of lidocaine and monoethylglycinexylidide when compared to untreated samples, and when urine was acidified the amount of metabolites increased suggesting oxidation at the amide nitrogen instead of the more basic amino group. However, after oral treatment with lidocaine (250 mg), no *N*-hydroxylidocaine or *N*-hydroxymonoethylglycine-xylidide was detected in human urine (Nelson et al., 1974). In another study, no *N*-hydroxylidocaine or *N*-hydroxymonoethylglycinexylidide was found in human urine after oral lidocaine administration to two subjects or after i.v. infusion of lidocaine for treatment of arrhythmia (Nelson et al., 1978).

An N-hydroxylated xylidine derivative, *N*-hydroxyxylidine, a known xylidine metabolite, forms adducts with hemoglobin (Bryant et al., 1994). This has been detected in the hemoglobin of tobacco smokers and nonsmokers (Bryant et al., 1988; cited by Bryant et al., 1994). Lidocaine has been known to induce methemoglobinemia, which may be severe in some patients (Bryant et al., 1994). The amount of xylidine-hemoglobin adducts formed after treatment with lidocaine correlates with the amount of the metabolite *N*-hydroxylidine. In nine patients receiving treatment for cardiac arrhythmia, concentrations of xylidine-hemoglobin adducts ranged from approximately 110 to 690 ng 2,6-xylidine/g hemoglobin and increases above the initial baseline concentrations ranged from 93 to 636 ng/g hemoglobin. Two patients had measurable baseline concentrations of xylidine-hemoglobin adducts prior to lidocaine treatment. One patient had an adduct concentration between 50 and 100 ng 2,6-xylidine/g hemoglobin and the other had a concentration of 423 ng 2,6-xylidine/g hemoglobin. In rats administered lidocaine and xylidine on separate occasions, 0.84% (788 µg/g hemoglobin) of the xylidine dose was bound to hemoglobin and 0.027% (1.8 µg xylidine/g hemoglobin) of the lidocaine dose was detected as hemoglobin adducts. *N*-Hydroxylidine was primarily formed from the oxidation of xylidine and not from the hydrolysis of *N*-hydroxylidocaine or *N*-hydroxymonoethylglycinexylidide, which were not found in this study. *N*-Hydroxyxylidine was

estimated to be approximately 1% of the administered dose excreted in human urine after oral administration of lidocaine hydrochloride to two subjects (Nelson et al., 1978).

The lidocaine metabolite monoethylglycinexylidide (MEGX) is at least 80% as toxic as lidocaine and contains antiarrythmic properties itself (Miyabe et al., 1998; Kakiuchi et al., 1999). In cardiac patients treated with lidocaine for more than one day (Drayer et al., 1983 abstr.), serum concentrations were readjusted for protein binding and it was determined that the plasma MEGX/lidocaine ratio was 0.68 – 0.49. GX was very low (ratio not provided). GX plasma concentration normalized to the rate of infusion of lidocaine decreased with age. It was determined that MEGX plays a greater role in the pharmacokinetics of lidocaine than GX. The metabolites MEGX and GX accumulated over time in the myocardium of dogs and humans with no time-dependent delay (Handel et al., 1982 abstr.)

In infants and children (aged 3 months to 4 years) administered lidocaine i.v. (5 mg/kg bolus, followed by infusion with 2.5 mg/kg/hr), plasma levels of lidocaine increased linearly from 2.5 µg/mL at the initiation of infusion to less than 3 µg/mL at 5 hours, while MEGX concentrations were 0.1 µg/mL at initiation of infusion to 2.5 µg/mL 5 hours later (Miyabe et al., 1998).

There is evidence of the metabolism of lidocaine in the fetus and neonate (Kuhnert et al., 1979). In a study of 25 pregnant women and their offspring it was found that lidocaine concentrations in maternal plasma were higher than concentrations in cord plasma, but the concentrations of metabolites (MEGX and GX) were equal to or greater than the concentration of metabolites in maternal plasma. MEGX was detected 10 minutes after the first lidocaine dose and GX was detected 40 minutes after the first lidocaine dose in maternal plasma. GX was found in some cord samples when it was not detectable in maternal plasma. Lidocaine, MEGX, and GX were detected in the urine of the neonates for up to three days after delivery. The urinary excretion of lidocaine in the mother was about

In cirrhotic patients dosed orally, peak plasma concentrations of lidocaine were more than twice the amount of control concentrations in healthy subjects and MEGX concentrations were about 70% of control concentrations (Munoz et al., 1999). In orally dosed patients with hepatitis, peak plasma concentrations of lidocaine were comparable to those of controls and MEGX concentrations were more than 20% higher than control concentrations. The half-life of lidocaine absorption was much longer in patients with liver cirrhosis and hepatitis when

compared to that of controls. The mean level of MEGX measured in another group of patients with liver dysfunction was about 27 mol/L at 30 minutes and about 30 mol/L one hour after i.v. administration.

Human liver slices from five donors produced xylidine in a 4-hour study when incubated *in vitro* with MEGX or LID (Parker et al., 1996). No xylidine was detected when liver homogenates, human liver microsomes, or S9 fractions were incubated with MEGX or lidocaine. It is suggested that the enzyme primarily responsible for the hydrolysis of lidocaine may be labile in subcellular fractions.

Extrahepatic formation of MEGX after lidocaine hydrochloride injection was demonstrated in an anhepatic patient awaiting a liver transplant (Sallie et al., 1992). It has been further shown *in vitro* that extrahepatic metabolism in rats may occur in the kidney and lung, but not the brain (Tanaka et al., 1994). A very slow rate of MEGX and 3-hydroxylidocaine formation (0.022-0.024 nmol/min/mg protein) was observed in rat kidney microsomes as well as a slow rate of formation of MEGX (0.87 nmol/min/mg). The rate of formation of MEGX and 3-hydroxylidocaine by rat hepatic microsomes was 4.84 and 0.64 nmol/min/mg, respectively. There is evidence that CYP2B1 may be the sole isoenzyme responsible for the de-ethylation of lidocaine in rat pulmonary and renal microsomes.

Lidocaine *N*-oxide has been proposed as a metabolite of lidocaine in humans, but has not been recovered in any *in vivo* metabolism studies reviewed. It was found *in vitro* using NADPH-supplemented rat liver microsomes (Patterson et al., 1986).

Several imidazolidinones have been proposed as metabolites of lidocaine, but only one has been detected in the blood. The mean peak concentration of N^1-ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone (0.08 µg/mL) in the plasma of two male human subjects occurred 30 minutes after lidocaine administration (Nelson et al., 1977). The other subject in this study had no detectable concentrations of N^1-ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone. The mean concentration of N^1-ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone had decreased to 0.035 µg/mL in the two subjects 180 minutes after administration.

The 3- and 4-hydroxylated metabolites of lidocaine were not glucuronide conjugates but may be sulfate conjugated (Thomas and Meffin, 1972).

Table 13. Lidocaine, Its Salts, and Its Metabolites

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	CASRN SORT	Chem. Abstr. References & References Used
LID	Lidocaine; Xylocaine; Lignocaine; 2-(Diethylamino)-2«,6«-acetoxylidide; a-Diethylamino-2,6-acetoxylidide	$C_{14}H_{22}N_2O$	137-58-6	137586	5176
LIDÆH2CO3	Lidocaine carbonate	$C_{14}H_{22}N_2O_2CH_2O_3$	56934-02-2	56934022	4
LIDÆH2SO4	Lidocaine sulfate	$C_{14}H_{24}N_2O_5$	24847-67-4	24847674	3
LIDÆHCl	Lidocaine hydrochloride	$C_{14}H_{23}ClN_2O$	73-78-9	73789	929
LIDÆHClÆH2O	Lidocaine hydrochloride monohydrate	$C_{14}H_{25}ClN_2O_2$	6108-05-0	6108050	6
MEGX	MEGX; Monoethylglycinexylidide; Monoethylglycylxylidide; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)acetamide; 2-(Ethylamino)-2«,6«-acetoxylidide; *N*-(*N*-Ethylglycyl)-2,6-xylidide; EGX; L 86; Deethyllidocaine; *N*,*N*-Ethylglycinexylidide; ω-Ethylamino-2«,6«-dimethylacetanilide	$C_{12}H_{18}N_2O$	7728-40-7	7728407	209 Keenaghan & Boyes (1972)
GX	Glycine xylidide; Glycyl xylidide; *N*-Glycyl-2,6-xylidine; GX; 2-Amino-2«,6«-acetoxylidide; ω-Amino-2,6-dimethylacetanilide; 2-Amino-2«,6«-dimethylacetanilide	$C_{10}H_{14}N_2O$	18865-38-8	18865388	106 Keenaghan & Boyes (1972)
3«-LIDOH	3-Hydroxylidocaine; 2-(Diethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide	$C_{14}H_{22}N_2O_2$	34604-55-2	34604552	46 Keenaghan & Boyes (1972)
4«-LIDOH	4-Hydroxylidocaine; 2-(Diethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide	$C_{14}H_{22}N_2O_2$	39942-41-1	39942411	8 Keenaghan & Boyes (1972)
α-LIDOH	Hydroxymethyllidocaine; 2-(Diethylamino)-*N*-[2-(hydroxymethyl)-6-methylphenyl)acetamide	$C_{14}H_{22}N_2O_2$	64585-18-8	64585188	12 Tanaka et al. (1994) Carrier et al. (1993)

Table 13. Lidocaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	CASRN SORT	Chem. Abstr. References & References Used
LID-N-Ox	Lidocaine *N*-oxide; 2-(Diethyloxidoamino)-*N*-(2,6-dimethylphenyl)acetamide; 2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide N^2-oxide; 2-(Diethylamino)-2«,6«-xylidide **[Rat liver microsomes supplemented with NADPH metabolized lidocaine to the *N*-oxide (Patterson et al., 1986). No other studies were identified that found this compound as a lidocaine metabolite.]**	$C_{14}H_{22}N_2O_2$	2903-45-9	2903459	7 Patterson et al. (1986)
	N-Hydroxylidocaine **[Synthesized by Nelson et al. (1977, 1978) as a potential metabolite, but did not match any metabolites.]**	$C_{14}H_{22}N_2O_2$	52662-13-2	52662143	3 Nelson et al. (1974, 1977, 1978)
3«-MEGXOH	3-Hydroxy-*N*-(*N*-ethylglycyl)-2,6-xylidine; 2-(Ethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide; 3«-Hydroxy-MEGX	$C_{12}H_{18}N_2O_2$	34604-56-3	34604563	20 Tam et al. (1987)
4«-MEGXOH	*p*-Hydroxy-ω-ethylamino-2,6-dimethylacetanilide; 2-(Ethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide; 4«-Hydroxy-MEGX	$C_{12}H_{18}N_2O_2$	64585-10-0	64585100	5 Tam et al. (1987)
	N-Hydroxy-MEGX; ω-(Ethylamino)-2,6-dimethylphenylacetohydroxamic acid; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)-*N*-hydroxyacetamide **[Synthesized by Nelson et al. (1977) as a potential metabolite, but did not match any metabolites.]**	$C_{12}H_{18}N_2O_2$	52662-14-3	52662143	2 Nelson et al. (1974, 1977)
3«-GXOH	3-Hydroxy-*N*-glycyl-2,6-xylidine; 2-Amino-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide; 3«-Hydroxy-GX	$C_{10}H_{14}N_2O_2$	112606-87-8	112606878	1 Coutts et al. (1987)
4«-GXOH	4-Hydroxy-*N*-glycyl-2,6-xylidine; 2-Amino-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide; 4«-Hydroxy-GX	$C_{10}H_{14}N_2O_2$	108966-35-4	108966354	2 Tam et al. (1987)

Table 13. Lidocaine, Its Salts, and Its Metabolites (Continued)

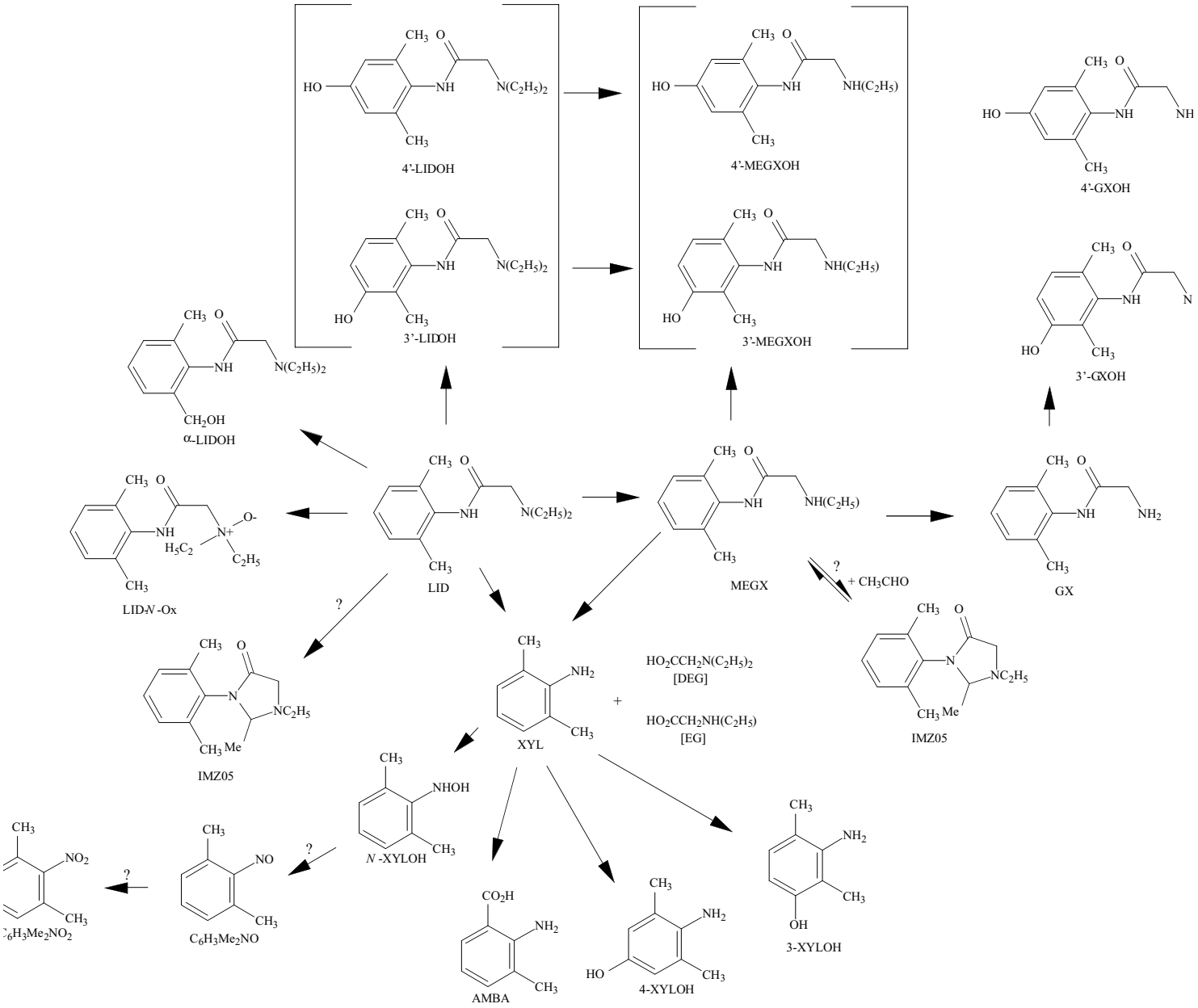
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	CASRN SORT	Chem. Abstr. References & References Used
IMZ05	N^1-Ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone; 3-(2,6-Dimethylphenyl)-1-ethyl-2-methyl-4-imidazolidinone; 1-Ethyl-2-methyl-3-(2,6-xylyl)-4-imidazolidinone **[Probable source MEGX plus acetaldehyde source (e.g., ethanol) *in vivo* (established in Rhesus monkeys) or MEGX plus acetaldehyde in urine or acetaldehyde contaminant in solvents. Might also arise through intramolecular condensation of lidocaine (Breck and Trager, 1971; Nelson et al., 1973; Carrier et al., 1993).]**	$C_{14}H_{20}N_2O$	32845-42-4	32845424	3 Breck & Trager (1971) Nelson et al. (1977) Carrier et al. (1993)
IMZ06	3-(2,6-Dimethylphenyl)-1,2-diethyl-4-imidazolidinone **[Formed by lidocaine oxidation by biomimetic systems (Carrier et al., 1993).]**	$C_{15}H_{22}N_2O$	152361-30-3	152361303	1 Carrier et al. (1993)
IMZ07	3-(2,6-Dimethylphenyl)-1-ethyl-4-imidazolidinone **[Possible formation from MEGX and endogenous or contaminant formaldehyde (Nelson et al., 1973).]**	$C_{13}H_{18}N_2O$	51044-98-5	51044985	1 Nelson et al. (1973)
XYL	2,6-Xylidine; 2,6-Dimethylaniline	$C_8H_{11}N$	87-62-7	87627	[24 with CASRN linked to metabolism] Keenaghan & Boyes (1972)
DEG	*N*,*N*-Diethylglycine; (Diethylamino)acetic acid	$C_6H_{13}NO_2$	1606-01-5	1606015	63 Nelson et al. (1977)
EG	*N*-Ethylglycine; (Ethylamino)acetic acid	$C_4H_9NO_2$	627-01-0	627010	47
3-XYLOH	3-Hydroxy-2,6-xylidine; 3-Amino-2,4-dimethylphenol	$C_8H_{11}NO$	100445-96-3	100445963	4 Coutts et al. (1987)

Table 13. Lidocaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	CASRN SORT	Chem. Abstr. References & References Used
4-XYLOH	4-Hydroxy-2,6-xylidine; 4-Amino-3,5-dimethylphenol	$C_8H_{11}NO$	3096-70-6	3096706	75 Tam et al. (1987)
AMBA	2-Amino-3-methylbenzoic acid; 2-Amino-*m*-toluic acid; 3-Methyl-2-aminobenzoic acid; 3-Methylanthranilic acid	$C_8H_9NO_2$	4389-45-1	4389451	141 Kammerer & Schmitz (1986)
N-XYLOH	*N*-Hydroxy-2,6-xylidine; 2,6-Dimethylphenylhydroxylamine	$C_{14}H_{22}N_2O_2$	3096-63-7	3096637	0 [See Nelson et al. (1977, 1978).]
$C_6H_3Me_2NO$	1,3-Dimethyl-2-nitrosobenzene; 2-Nitroso-*m*-xylene; 2,6-Dimethylnitrosobenzene **[Possible metabolite, but no evidence (Kammerer and Schmitz (1986).]**	C_8H_9NO	19519-71-2	19519712	18 Kammerer & Schmitz (1986)
$C_6H_3Me_2NO_2$	1,3-Dimethyl-2-nitrobenzene; 2-Nitro-*m*-xylene; 2,6-Dimethylnitrobenzene; 2-Nitro-1,3-dimethylbenzene; 2-Nitro-1,3-xylene **[Possible metabolite, but no evidence (Kammerer and Schmitz (1986).]**	$C_8H_9NO_2$	81-20-9	81209	190 Kammerer & Schmitz (1986)

[a] Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated metabolites of xylidine and toluidine.
Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).
The lower-case Greek letter alpha in a code indicates that hydroxylation is on a xylidine methyl group.

Figure 4. Proposed Metabolic Pathway for Lidocaine in Humans and Experimental Animals



Question marks indicate pathways that have been suggested by IR spectral analysis only.

Table 14. Metabolites of Lidocaine Detected *In Vivo* and Their Amounts in Human Urine and [Plasma]

Metabolite Code	Range of Mean Amounts of Lidocaine Metabolites Detected in Urine and [Plasma][a]							
	Humans		Dogs		Guinea Pig		Rats	
LID	X	2.1-4.76%	X	2.0%	X	0.5%	X	0.2%
MEGX	X	1.7-12.68%	X	2.3%	X	14.9%	X	0.7%
GX	X	0.55-2.3%	X	12.6%	X	3.3%	X	2.1%
3'-LIDOH	X	0.1-1.3%	X	6.7%	X	0.5%	X	6.0-31.2%
4'-LIDOH	X	0.1-0.28%					X	3-5%
α-LIDOH[b]								
N-XYLOH	X	1.0%						
LID-*N*-Ox[d]								
3'-MEGXOH	X	0.04-0.3%	X	3.1%	X	2.0%	X	Minute-36.9%
4'-MEGXOH	X	0.06%						
3'-GXOH							X	Appreciable amounts
4'-GXOH	X	0.24%						
EG	X	n.q.						
DEG	X	35%						
IMZ05	X	[0.04-0.08]						
AMBA[c]								
$C_6H_3Me_2NO$[d]								
$C_6H_3Me_2NO_2$[d]								
XYL	X	0.84-1.0%	X	1.6%	X	16.2%	X	1.5%
3-XYLOH							X	Trace amounts
4-XYLOH	X	60.5-80.1%	X	25.2%	X	16.4%	X	Minor quantities 12.4%
Percent of dose in urine & time		50% (72-hr); 69.07-88.9% (24-hr)						
Percent of dose in feces & time								

[a] Urinary excretion is measured as the percentage of the administered dose found in the urine and the plasma concentrations are measured in micrograms per milliliter.
[b] Only detected *in vitro* using rat liver microsomes (Tanaka et al., 1994).
[c] Only detected *in vitro* using rabbit liver homogenates (Kammerer and Schmitz, 1986).
[d] Proposed as possible metabolites but were not detected (Kammerer and Schmitz, 1986).

9.1.2.4.2 Pharmacokinetics of Lidocaine

Lidocaine s use is favored because of its low incidence of side effects, especially cardiovascular toxicity (Berlin-Wahlen et al., 1977). Lidocaine is used extensively as an i.v. anti-arrhythmic agent. Lidocaine is not an effective oral treatment for arrhythmia due to its low oral availability and short elimination half-life. The vasodilatory effect of lidocaine cannot be overlooked when discussing pharmacokinetics. The vasodilatory effect contributes to lidocaine s rapid onset of action when compared to the other local anesthetics and also causes its short analgesic effect.

The plasma protein-bound concentration of lidocaine was determined to be 51% (Williams et al., 1976). Protein binding of lidocaine (44%) is reduced during viral hepatitis. It was proposed in one study that protein-bound lidocaine can enter the liver and that protein-bound lidocaine may enter peripheral tissues via a free intermediate mechanism (Pardridge et al., 1983).

The venous/arterial blood concentration ratio of lidocaine (0.73) is higher than that of prilocaine (0.47) and this may contribute to the greater toxicity of lidocaine when compared to prilocaine (Eriksson, 1966).

Lidocaine may remain at the site of topical application for prolonged periods of time, depending on the location, being slowly released into the bloodstream and resulting in a longer half-life than after i.v. administration . When 250 mg was applied to the forearm of human volunteers, mean lidocaine concentrations peaked (~9 ng/mL) 24 hours after dermal application and lidocaine persisted in plasma for over 32 hours (Dal Bo et al., 1999). However, there was a wide deviation (1-28 hours) in the time to peak concentration. The peak plasma concentration of lidocaine after application of a lidocaine patch to the gingiva of human volunteers ranged from 16.5 to 27.2 ng/mL, 29-45 minutes after application (Noven Pharmaceuticals, 1997). Peak plasma concentrations after application of lidocaine ointment (location not provided) was 9 times higher than with the patch. In studies with EMLA cream, which contains lidocaine (2.5%) base, it was shown that the site of application can greatly affect plasma concentrations and the elimination half-life of lidocaine (Juhlin et al., 1989).

After topical application of the patch to the gingiva, elimination half-lives were similar to half-lives seen after i.v. administration of lidocaine (Noven Pharmaceuticals, 1997).

Lidocaine had a much higher affinity for accumulation in the heart than bupivacaine in rabbits, contributing to lidocaine s affect on the heart (Hollm n et al., 1973).

The umbilical vein/maternal vein concentration ratio of lidocaine after i.v. administration in a pregnant mother was 0.51, which was similar to ratios between 0.48 and 0.69 obtained in other placental transfer studies (Banzai et al., 1995). The transfer of lidocaine across the placenta by passive diffusion is rapid with equilibrium also being reached rapidly. Lidocaine does not accumulate in the amniotic fluid; however, amniotic fluid concentrations of lidocaine were found to be higher than concentrations in fetal plasma.

When lidocaine (30%) is used for male circumcision in infants, mean peak plasma concentrations are 0.27 ± 19 µg/mL (Weatherstone et al., 1993; cited by Woodman, 1999).

Certain conditions have been shown to affect the pharmacokinetics of lidocaine. Since rapid metabolism of the local anesthetics is important for detoxification, any illness that affects the liver will result in increased plasma concentrations of lidocaine and reduced amounts of metabolites.

Cerebrospinal fluid concentrations of lidocaine have been measured at 75% of plasma concentrations after i.v. administration (Glazer and Portenoy, 1991).

9.1.2.5 Mepivacaine

9.1.2.5.1 Metabolism of Mepivacaine

The metabolism of mepivacaine, like that of the other local anesthetics, is extensive. The urinary excretion of unchanged drug after adminstration of mepivacaine was usually very low (trace amounts to 1.6%); however, one study found concentrations of mepivacaine in four healthy male volunteers that represented 16% of the dose in acidified (pH=5.0) 24-hour urine samples (Thomas and Meffin, 1972; Reynolds, 1971). Although the excretion of mepivacaine in the urine was found to be pH-dependent, the excretion of its metabolites was determined to be pH-independent (Meffin et al., 1973b). The metabolites of mepivacaine are excreted primarily as glucuronide conjugates in the urine of rats and man (76-85% and 99%, respectively) (Hansson et al., 1965; Meffin et al., 1973b). The biliary excretion of mepivacaine is significantly higher in rats than in man (Hansson et al., 1965; Ryrfeldt and Hansson, 1971; Meffin and Thomas, 1973). As much as 51-56% of the dose in rats was excreted in the bile within 6 hours of administration (mostly hydroxylated mepivacaine), while no hydroxylated mepivacaine was found in the bile of a human female subject. The mepivacaine excreted in bile is probably reabsorbed into the blood stream from the digestive tract due to the low concentration of metabolites found in the feces. The metabolites of mepivacaine and metabolic pathway are presented in **Table 15** and **Figure 5**, respectively.

In studies with rats, 55-60% of the dose was excreted in the urine after 24 hours and 59.1-68.1% of the dose was excreted in the urine during the following 48 hours (Thomas and Meffin, 1972; Hansson et al., 1965). The feces from rats contained between 4.3 and 15.6% of the mepivacaine dose. In mice, the respired CO_2 was found to contain between 10.5 and 11.4% of the dose (Hansson et al., 1965).

In rats, the predominant metabolite found in the urine is 3'-hydroxymepivacaine (~60%) (Thomas and Meffin, 1972). Little or no 4'-hydroxymepivacaine was found in the rat. This is in contrast to the almost equal excretion of both 3'-hydroxy- and 4'-hydroxymepivacaine in the urine of human subjects. The presence of hydroxylated mepivacaine in the 24-hour urine of rats (~60% of the mepivacaine dose) is greater than that seen in the urine of humans (18-35% of the dose) (Meffin and Thomas, 1973).

Mepivacaine, like bupivacaine and ropivacaine, contains an alkylated pipecolyl moiety whose dealkylation results in the formation of pipecoloxylidide (PPX) as a metabolic product. In

humans, between 1.0 and 1.2% of the dose of mepivacaine has been found as PPX in the 24-hour urine collections (Thomas and Meffin, 1972; Reynolds, 1971). This concentration is equal to or lower than concentrations of PPX found in the urine after bupivacaine administration (Lindberg et al., 1986; Pihlajam ki et al., 1990; Reynolds, 1971; Goehl et al., 1973). No plasma PPX concentrations were determined in any of the studies reviewed.

The tissue distribution of mepivacaine and its metabolites was determined in mice after i.v. injection (Kristerson et al., 1965). It was found that mepivacaine, but not its metabolites, enters the brain. Liver and kidney extracts revealed rapid metabolism as was evident from less lipid-soluble metabolites. Sixty minutes after injection, the amount of metabolites were 10 times as high as that of mepivacaine in the kidney. Four metabolites were detected, but were not quantitated. The submaxillary glands contained metabolic products equal to 0.3% of the radioactive mepivacaine dose twenty minutes after i.v. injection, but had decreased to 0.1% sixty minutes after injection.

In mice it was found that 10.5-11.4% of the ^{14}C-labeled mepivacaine dose is exhaled in the expired CO_2 (Hansson et al., 1965).

No studies were found that attempted to determine the presence of 2,6-xylidine or its derivatives in urine or plasma after mepivacaine administration. The fate of more than 50% of the dose of mepivacaine in humans is yet undetermined.

Table 15. Mepivacaine, Its Salts, and Its Metabolites

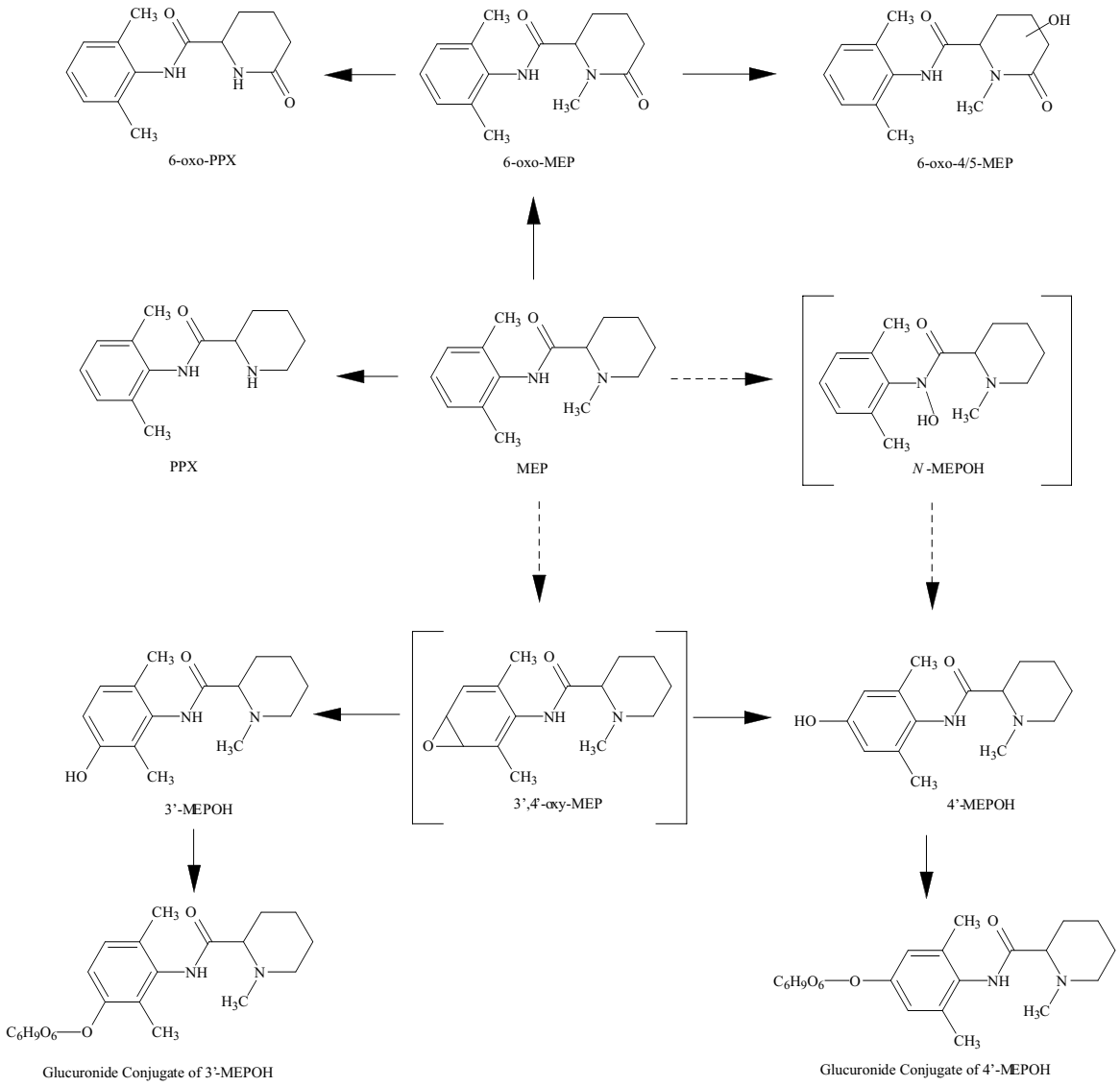
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
MEP	Mepivacaine; (±)-Mepivacaine; *DL*-Mepivacaine; Carbocaine; 1-Methyl-2«,6«-pipecoloxylidide; *N*(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide	$C_{15}H_{22}N_2O$	96-88-8	547
MEPÆHCl	Mepivacaine hydrochloride; Carbocaine hydrochloride; Scandonest	$C_{15}H_{22}N_2O$¥HCl	1722-62-9	107
PPX	2«,6«-Pipecoloxylidide [racemic]; 2«,6«-Pipecolylxylidide; PPX; *N*-Desbutylbupivacaine; Mono-*N*-demethylmepivacaine; *N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	15883-20-2	45 Hansson et al. (1965)
3«,4«-oxy-MEP	1-Methylpipecolo-3«,4«-dihydro-3«,4«-epoxy-2«,6«-xylidide; 1-Methylpipecolo-3«,4«-dihydro-3«,4«-oxy-2«,6«-xylidide	$C_{15}H_{22}N_2O_2$	Not identified	Meffin and Thomas (1973)
N-MEPOH	1-Methylpipecolo-*N*-hydroxy-2«,6«-xylidide; *N*-Hydroxymepivacaine **[Authors suggested possible rearrangement of the N-hydroxy group to the 4«-position. CAS did not index the abstract for this compound.]**	$C_{15}H_{22}N_2O_2$	Not identified	Meffin and Thomas (1973)
3«-MEPOH	3«-Hydroxymepivacaine; *N*-(3-Hydroxy-2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 3«-Hydroxy-1-methyl-2«,6«-pipecoloxylidide; 1-Methylpipecolo-3«-hydroxy-2«,6«-xylidide **[Major mepivacaine metabolite in horses (Harkins, 1999)]**	$C_{15}H_{22}N_2O_2$	37055-90-6	4 Harkins (1999) Meffin & Thomas (1973) Meffin et al. (1973a)
4«-MEPOH	4«-Hydroxymepivacaine; *N*-(4-Hydroxy-2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 4«-Hydroxy-1-methyl-2«,6«-pipecoloxylidide; 1-Methylpipecolo-4«-hydroxy-2«,6«-xylidide	$C_{15}H_{22}N_2O_2$	616-66-0	4 Meffin & Thomas (1973) Meffin et al. (1973a)
6-oxo-MEP	*N*-(2,6-Dimethylphenyl)-1-methyl-6-oxo-1-piperidinecarboxamide; 1-Methyl-6-oxo-2«,6«-pipecoloxylidide; 1-Methyl-6-oxopipecolo-2«,6«-xylidide	$C_{15}H_{20}N_2O_2$	43063-89-4	1 Meffin et al. (1973b)
6-oxo-PPX	*N*-(2,6-Dimethylphenyl)-6-oxo-2-pyridinecarboxamide; 6-Oxopipecolo-2«,6«-xylidide; 6-Oxopipecolo-2«,6«-xylide	$C_{14}H_{18}N_2O_2$	43063-88-3	1 Meffin et al. (1973b)

Table 15. Mepivacaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
6-oxo-4/5-MEPOH	*N*-(2,6-Dimethylphenyl)hydroxy-1-methyl-6-oxo-2-piperidinecarboxamide; Hydroxy-1-methyl-6-oxo-2«,6«-pipecoloxylidide; Hydroxy-1-methyl-6-oxopipecolo-2«,6«-xylidide **[The author presumed a hydroxy group was on position 4 or 5 of the 6-oxo-2-piperidinecarboxamide ring.]**	$C_{15}H_{20}N_2O_3$	50306-98-4	1 Meffin et al. (1973b)
	N-(2,6-Dimethylphenyl)-1-(hydroxymethyl)-6-oxo-2-pyridinecarboxamide; 1-Hydroxymethyl-6-oxo-2«,6«-pipecoloxylidide **[Examination of the original article (Meffin et al., 1973) provided no evidence for this compound. Apparently, the CASRN assignment was an indexing mistake for the abstract Chem. Abstr. 80:10211.]**	$C_{15}H_{20}N_2O_3$	43063-90-7	1 [Chemical Abstracts Service attributed to Meffin et al. (1973b).]

[a] Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated metabolites of xylidine and toluidine. Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).

Figure 5. Metabolic Pathway for Mepivacaine in Humans and Experimental Animals



* Proposed intermediates

Table 16. Metabolites of Mepivacaine Detected *In Vivo* and Their Amounts in Human Urine and [Plasma]

Metabolite Code	Range of Mean Amounts of Mepivacaine Metabolites Detected in Urine and [Plasma][a]			
	Humans		Rats	
MEP	X	<5% [3.8-5.50 µg/mL]		
PPX	X	1.0-1.2% [0.20-0.38 µg/mL]		
3'-MEPOH	X	9.9-17%	X	50.0-59.2%
4'-MEPOH	X	7.6-12.5%	X	n.d.
6-oxo-MEP	X	These three were found to represent not more than 10% of the administered dose of mepivacaine in a 12-hour urine sample.		
6-oxo-4/5-MEP	X			
6-oxo-PPX	X			
3',4'-oxy-MEP[b]				
N-MEPOH[b]				

[a] Urinary excretion is measured as the percentage of the administered dose found in the urine and the plasma concentrations are measured in micrograms per milliliter.
[b] These are proposed intermediates, but were not detected (Meffin and Thomas, 1973).
n.d. = not detected (Thomas and Meffin, 1972)

9.1.2.5.2 Pharmacokinetics of Mepivacaine

Mepivacaine is a mixture of (S)- and (R)-enantiomers. The median (*S*)-mepivacaine concentration in the blood of 150 pregnant mothers given 50 mL of 1% mepivacaine was 1.18 µg/mL without epinephrine and 0.86 µg/mL with epinephrine immediately after birth (Schierup et al., 1988). The median (*S*)-mepivacaine concentrations in umbilical venous blood of mothers with and without epinephrine were 0.42 µg/mL and 0.37 µg/mL, respectively.

In a study of five healthy male volunteers, mean plasma concentrations of mepivacaine after i.v. infusion of mepivacaine hydrochloride (250 mg) was 3.5 µg/mL 10 minutes after adminstration and 1.0 µg/mL after 4 hours (Arthur et al., 1979).

The mean total body clearance of mepivacaine in five healthy male volunteers was 0.70 L/min and the terminal half-life was 125 min (Arthur et al., 1979). These data were similar to data provided by Tucker and Mather (1975), who calculated a terminal half-life of 114 minutes and a clearance of 0.78 L/min.

In a study of 12 pregnant women administered between 200 to 400 mg mepivacaine in a single injection and their fetuses, the mean maternal plasma concentrations were 4.47 µg/mL in the 400-mg-dose group and 1.86 µg/mL in the 200-mg-dose group (Teramo and Rajamaki, 1971). The fetuses of women dosed with 300-400 mg mepivacaine experienced a decrease in plasma pH (mean of —0.115). Six fetuses (5 in the 400-mg-dose group and one whose mother received 300 mg) experienced bradycardia. The mean plasma mepivacaine concentration in the fetuses that experienced bradycardia was 3.07 µg/mL. The mean plasma mepivacaine concentration in the fetuses that did not experience bradycardia was 1.52 µg/mL. The mean maximum mepivacaine concentration in the six fetuses that experienced bradycardia was 3.07 µg/mL. One fetus had a mepivacaine concentration of 8.3 g/mL 12 min after block with 300 mg mepivacaine, while the corresponding maternal concentration was was 2.2 g/mL. The fetal pH in this fetus was 7.20 at about 10 minutes. No signs of toxicity were evident in the mother. A correlation exists between the severity of bradycardia and the extent of the decrease in fetal pH after paracervical block (Teramo, 1969; cited by Teramo and Rajam ki, 1971). In nonpregnant female adult and neonatal rats injected with mepivacaine hydrochloride at a dose of 25 or 50 mg/kg body weight, blood and brain concentrations of mepivacaine were higher in neonates than in adult rats; but the blood-to-brain ratios were not significantly different (Gans et al., 1980). For example, in the adult group dosed with 25 mg/kg body weight, blood and brain concentrations were 2.61 ± 0.30 µg/g and 5.16 ± 0.54 µg/g, respectively, 15 minutes after administration. While blood and brain concentrations of mepivacaine in neonates, also dosed with 25 mg mepivacaine /kg body weight, were 8.76 ± 1.5 µg/g and 15.50 ± 2.2 µg/g, respectively, 15 minutes after administration. The adult and neonatal blood-to-brain ratios in the 25-mg/kg-dose groups were 2.58 ± 0.39 and 2.01 ± 0.26, respectively.

During obstetric blocks, mepivacaine may be used with epinephrine to achieve a longer and more intense anesthesia; however, a prolongation of the second stage of labor was found in one study and may increase the risk of fetal acidosis (Zador et al., 1974; cited by Schierup et al. 1988).

The accumulation of radiolabeled mepivacaine (labeled on the pipecoloyl *N*-methyl) in tissues of mice was studied after i.v. and s.c. administration (Kristerson et al., 1965). The tissues with the highest concentration 5 and 20 minutes following administration were the brain, salivary glands, liver, kidney, bone marrow, and gastric and intestinal mucosa. One or more hours after

injection, the highest concentrations of radioactivity were found in the excretory organs, such as kidney, urinary bladder, liver, and gall bladder. Radioactivity was taken up more rapidly in the brain (2-5 minutes post-administration), but also cleared more quickly than any other tissue. After 1 hour, the brain concentration was equal to that of the blood. The rapid decrease in concentrations of mepivacaine in the liver and the high activity in the gastrointestinal tract was probably due to biliary excretion. Four hours after injection, most of the radioactivity was present in the intestinal contents. Twenty-four hours after administration, most radiation was found in the intestinal tract and urinary bladder. Absorption to the tissue after s.c. administration was much slower than after i.v. administration. The distribution 20 and 60 minutes after s.c. injection was similar to that 5 minutes after i.v. administration; however, most of the radioactivity was still at the site of s.c. injection. Four hours after s.c. administration, the highest concentrations were found in the intestinal contents and the kidney.

The possibility of monitoring mepivacaine concentrations in the blood by determining saliva concentrations was studied in 29 female Sprague-Dawley rats (Gans et al., 1980). When mepivacaine was administered for 30 minutes (1 mg/mL; 1 mL/min), saliva and blood concentrations of mepivacaine were 4.79 ± 0.84 μg/g and 8.57 ± 1.07 μg/g, respectively. When mepivacaine was administered for 45 minutes (1 mg/mL; 1 mL/min), saliva and blood concentrations of mepivacaine were 14.30 ± 4.64 μg/g and 8.10 ± 0.85 μg/g, respectively. There was no clear relationship between plasma and saliva concentrations of mepivacaine; however, the accumulation of mepivacaine in the saliva over time was evident.

9.1.2.6 Prilocaine

9.1.2.6.1 Metabolism of Prilocaine

The metabolites of prilocaine as well as metabolic pathway in humans is presented in **Table 17** and **Figure 6**, respectively. The metabolism of prilocaine *in vitro* was primarily due to the hydrolysis of the amide bond (Akerman et al., 1966). The structure of prilocaine differs slightly from the other amide local anesthetics in this report due to the presence of a toluidine moiety (only one ortho-methyl group), rather than a xylidine moiety, and the unbranched alkyl chain on the amine group. Prilocaine metabolizes to *o*-toluidine instead of xylidine upon hydrolysis of the amide bound. The hydrolysis of prilocaine to *o*-toluidine is thought to proceed more readily than the hydrolysis of 2,6-xylidine after lidocaine administration due to less steric hindrance (one ortho-vs. two ortho-methyl groups) (Geddes, 1965, 1967). Even though hydrolysis is the primary means of metabolizing prilocaine, subsequent hydroxylation of *o*-toluidine and hydroxylation of prilocaine results in the greater formation of hydroxylated derivatives, similar to what is observed with xylidine after lidocaine administration (kerman et al., 1966; Hjelm et al., 1962). The *in vivo* metabolism of prilocaine in rats or *in vitro* metabolism using mouse liver slices was not affected by pre-treatment with SKF 525, a microsomal enzyme inhibitor shown to affect the dealkylation of *N*-alkylamines (Axelrod et al., 1954; cited by kerman et al., 1966; Hargreaves, 1968). This is in contrast to significant inhibition of MEGX formation from lidocaine *in vitro* after pretreatment of liver homogenates and slices from several species (kerman et al., 1966).

In humans, the primary metabolite excreted in 24-hour urine samples is *p*-hydroxytoluidine (34.2% of the dose), followed by *o*-hydroxytoluidine (2.7%), and *o*-toluidine (0.75%) (Hjelm et al., 1972). The hydroxylated metabolites are probably excreted almost entirely as conjugates since only 0.08% of the excreted *p*-hydroxytoluidine was unconjugated.

In a female rat, 23% of the radioactive dose of ^{14}C-labeled prilocaine was excreted in the urine and 5% was recovered in expired air in a 54-hour collection period (Geddes et al, 1965 and 1967).

The formation of methemoglobin in serum after prilocaine administration has been correlated with the concentration of its metabolite o-toluidine. Methemoglobin is formed when ferrous iron (Fe^{2+}) in the blood is converted to ferric iron (Fe^{3+}), which reduces the blood s ability to transport oxygen to tissues. Methemoglobin concentrations are kept low (2%) in adults

and children by enzymatic reduction (metHb reductase or cytochrome b5 reductase) coupled with NADH (Nilsson et al., 1990; Conroy et al., 1993; Hjelt et al., 1995; all cited by Brisman et al., 1998). Another pathway utilizes NADPH reductase, whose reaction rate is increased by methylene blue, which is used to treat methemoglobinemia. One study observed peak concentrations of *o*-toluidine (243 ng/mL) and prilocaine (632 ng/mL) 30 minutes after i.v. administration of prilocaine plus lidocaine (both 25 mg) in six full-term male newborn piglets (Klein et al., 1994). Topical application of EMLA cream to the penile area of the piglets resulted in a peak plasma concentration of 39 ng/mL prilocaine at 30 minutes post-application, and no formation of *o*-toluidine. In piglets dosed both i.v. (25 mg of lidocaine and 25 mg prilocaine) and topically with 1 g of EMLA cream, methemoglobin concentrations were 0.9-3.0% in the i.v. group and 0.7-2.0% in the topically dosed group (Taddio et al., 1994 abstr.). In preterm neonates that received 0.5 g EMLA cream for heel lances, methemoglobin concentrations were not much different from baseline (0.2-1.1% and 0.1-0.7%, respectively) and plasma *o*-toluidine was below the limit of detection (0.025 mg/L) (Essink-Tebbes et al., 1999).

One study correlated the serum concentration of methemoglobin with the plasma concentration of *p*-hydroxytoluidine (Hjelm et al. 1972). When the plasma concentration of *p*-hydroxytoluidine was 4 µg/mL in 4 out of 5 healthy volunteers, concentrations of methemoglobin were between 10 and 15%. Methemoglobin concentration peaked 1 hour after the peak in plasma concentration of *p*-hydroxytoluidine.

The use of EMLA (2.5% lidocaine, 2.5% prilocaine) cream in neonates is not recommended and use in adults should be monitored because of the risk of methemoglobinemia following the administration of prilocaine (Brisman et al., 1998). The enzymes that reduce methemoglobin are not fully developed in neonates until 3 months of age (Nilsson et al., 1990; Tse et al., 1995; Jackobson and Nilsson, 1985; all cited by Brisman et al., 1998). In studies of the use of EMLA cream in neonates, concentrations of methemoglobin in plasma were always within safe limits (<5%) (Essink-Tjebbes, 1999; Brisman et al., 1998). Methemoglobin concentrations of 5-6% have been detected in other studies after the administration of EMLA cream but were considered to be within safe limits (Brisman et al, 1998).

The rate of methemoglobin formation was more rapid after administration of (*D*)-(−)-prilocaine than with (*L*)-(+)-prilocaine *in vivo* in cats and *in vitro* (kerman and Ross, 1970). The rate of *o*-toluidine formation after the administration of the racemic mixture in cats was

between that of the two isomers. Peak methemoglobin concentrations after administration of (*D*)-(−)-prilocaine, (*L*)-(+)-prilocaine, and (*DL*)-(±)-prilocaine were approximately 14.5, 12, and 10%, respectively.

Prilocaine has been shown to undergo intrachannel hydrolysis (40% of the time) to *o*-toluidine in a bovine AChE preparation using circular dichroism which was correlated with paresthesia in humans (Nickel, 1994 abstr.).

The *in vitro* hydrolysis of prilocaine in several animal species was due solely to constituents of the microsomal fraction; no hydrolytic activity was seen in the soluble fraction of liver homogenates, with a higher selectivity for (*D*)-(−)-prilocaine (kerman and Ross, 1970). Rabbit liver homogenates appeared to have the greatest metabolic activity for prilocaine, as well as lidocaine, followed by guinea pig, mouse, rat, and cat liver homogenates.

The evidence for extrahepatic metabolism of prilocaine in humans and animals is based on pharmacokinetics and *in vitro* studies. The rate of prilocaine clearance (2.84 L/min) is much higher than the calculated hepatic blood flow rate (1.7 L/min). Results of *in vitro* studies indicate extrahepatic metabolism (Arthur et al., 1979; kerman et al., 1966; Geng et al., 1995; van der Meer et al., 1999). Metabolism of prilocaine occurred in lung and kidney homogenates of cats, but not from kidney and lung homogenates of rabbits (kerman et al., 1966). It is unlikely that the lungs are the site of extrahepatic metabolism in humans (van der Meer et al., 1999).

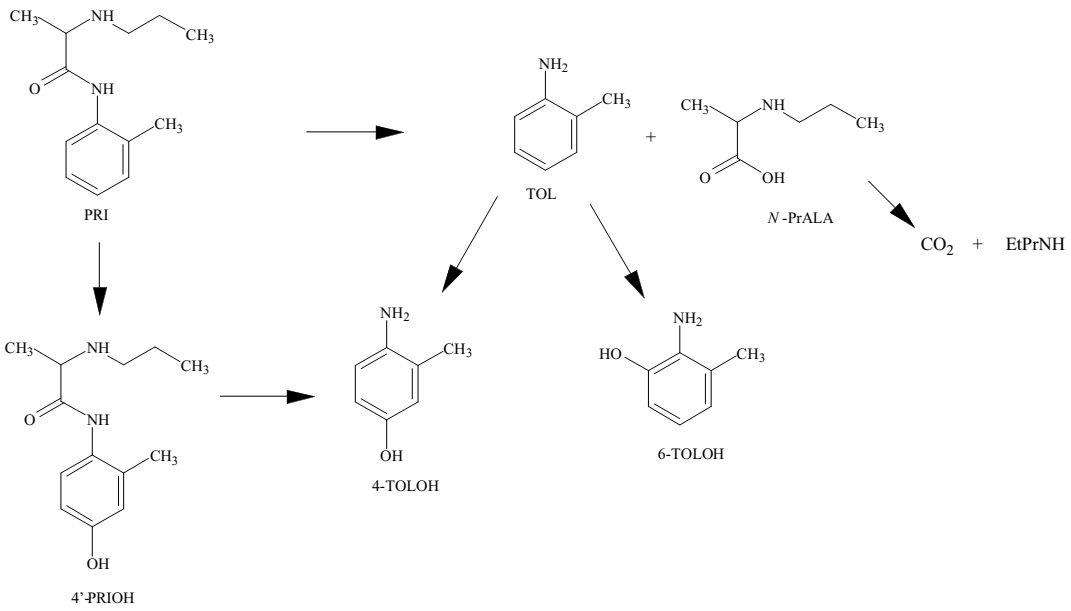
Metabolism of prilocaine should result in the formation of *N*-*n*-propylalanine in man (Geddes, 1965). *N*-*n*-Propylalanine has been determined *in vitro* with rat liver slices (kerman et al., 1966).

Table 17. Prilocaine, Its Salts, and Its Metabolites

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
PRI	Prilocaine; *DL*-(±)-Prilocaine; Citanest; *N*-(2-Methylphenyl)-2-(propylamino)propanamide; *o*-Methyl-2-propylaminopropionanilide; 2-Methyl-α-propylaminopropionanilide; α-Propylamino-2-methylpropionanilide	$C_{13}H_{20}N_2O$	721-50-6	391
(+)-PRI	*L*-(+)-Prilocaine; (+)-Prilocaine; (*S*)-Prilocaine; (2*S*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide; *L*-(+)-2-(Propylamino)-*o*-propionotoluidide;	$C_{13}H_{20}N_2O$	14289-31-7	20
(-)-PRI	*D*-(-)-Prilocaine; (-)-Prilocaine; (*R*)-Prilocaine; (2*R*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide; *D*-(-)-2-(Propylamino)-*o*-propionotoluidide	$C_{13}H_{20}N_2O$	14289-32-8	21
PRIÆHCl	Prilocaine hydrochloride; Xylonest	$C_{13}H_{21}ClN_2O$	1786-81-8	75
4«-PRIOH	*p*-Hydroxyprilocaine; 4-Hydroxyprilocaine	$C_{13}H_{21}N_2O_2$	Not identified	Hjelm et al. (1972)
TOL	*o*-Toluidine; 2-Methylaniline; 2-Methylbenzeneamine; *o*-Tolylamine; 1-Amino-2-methylbenzene [Potential metabolites, including hydroxylamine and nitroso derivatives, and their CASRNs are listed in the EMICBACK records for Gupta et al. (1987, 1989).]	C_7H_9N	95-53-4	4739
6-TOLOH	*o*-Hydroxytoluidine; 6-Hydroxy-*o*-toluidine; 2-Amino-3-methylphenol; 3-Methyl-2-aminophenol; 2-Amino-*m*-cresol; 6-Hydroxy-2-methylaniline	C_7H_9NO	2835-97-4	44 Hjelm et al. (1972)
4-TOLOH	*p*-Hydroxytoluidine; 4-Hydroxy-*o*-toluidine; 4-Amino-3-methylphenol; 4-Amino-*m*-cresol; 4-Hydroxy-2-methylaniline	C_7H_9NO	2835-99-6	326 Hjelm et al. (1972)
N-PrALA	*N*-*n*-Propylalanine; *N*-Propyl-*L*-alanine	$C_6H_{13}NO_2$	13013-28-0	3 Geddes (1965, 1967)

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated derivatives of xylidine and toluidine. Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).

Figure 6. Metabolic Pathway for Prilocaine in Humans



9.1.2.6.2 Pharmacokinetics of Prilocaine

Prilocaine, like the other amide local anesthetics in this report, except for ropivacaine, is a racemic mixture. After separate i.v. injections of 2.0% solutions of equal amounts of (*D*)-(−)-prilocaine and (*L*)-(+)-prilocaine into cats, the concentration of (*D*)-(−)-prilocaine (peak: ~9.5 µg at 5 min) was lower than that of (*L*)-(+)-prilocaine (peak: ~15.5 at 10 min) during the entire 80-minute test period (kerman and Ross, 1970). In rabbits, the enantiomers and racemate of prilocaine did not exhibit any significant difference in toxicity (LD_{50}); however, the cumulative anesthetic effect of (*L*)-(+)-prilocaine was more pronounced than that of (*D*)-(−)-prilocaine after repeated slow i.v. injections every 15 minutes (kerman and Ross, 1970). At infusion rates of 0.12 and 0.30 mg/min of 2.0% solutions, (*D*)-(−)-prilocaine was significantly less toxic than (*L*)-(+)-prilocaine, but when infused with 0.72 mg/min there was no significant difference between toxicity of the enantiomers. In 10 healthy human male volunteers, the unbound fraction of (*D*)-(−)-prilocaine in plasma was lower than the fraction of (*L*)-(+)-prilocaine (van der Meer et al., 1999). The total plasma clearance of (*D*)-(−)-prilocaine (2.57 ± 0.46 L/min) was greater than that of (*L*)-(+)-prilocaine (1.91 ± 0.30 L/min), and the terminal half-lives of elimination were 87 ± 27 minutes and 124 ± 64 minutes, respectively. Because prilocaine is administered as a single

injection due to the risk of methemoglobinemia, the importance of the enantioselectivity in the pharmacokinetics of prilocaine are probably small.

Like lidocaine, prilocaine is extensively used as a topical local anesthetic. The hydrophobicity of prilocaine may enhance its anesthetic quality by allowing more prilocaine to remain at the topical site of application for an extended period of time (Woodman et al., 1999). The pharmacokinetics of prilocaine is often compared to that of lidocaine. When prilocaine is administered with lidocaine in EMLA (2.5% lidocaine, 2.5% prilocaine) preparations, the pharmacokinetics of both drugs must be considered. In this section, the pharmacokinetics of prilocaine administered alone will be presented first, followed by the pharmacokinetics of lidocaine and prilocaine administered as EMLA.

9.1.2.6.2.1 Prilocaine

The urinary excretion of prilocaine in humans was found to be dependent on urinary pH; the lower the pH, the greater the rate of diffusion into the urine (Erikson, 1966).

After i.v. injection of prilocaine (50 mg) in five healthy male volunteers, the mean peak plasma concentration of prilocaine was 2.0 µg/mL ten minutes after administration and decreased to <0.1 µg/mL two hours after administration (Arthur et al., 1979). The mean total body clearance of prilocaine was 2.84 L/min and the terminal elimination half-life was 93 min.

When ^{14}C-labeled prilocaine was injected i.v. in near-term pregnant rats, the whole-body radiograms and scintillation counting revealed that the distribution of prilocaine was similar to the distribution of lidocaine except that the concentration of prilocaine was higher in all tissues (Katz, 1969). The highest concentrations were found in the kidney, liver, lung, heart, bowel wall, bone marrow, brain, and salivary glands. This distribution is similar to that seen in rats with peak concentrations of radioactivity occurring in the lungs (37.0 µg prilocaine/g tissue) 10 minutes after administration of prilocaine, and kidney (28.0 µg/g), spleen (19.3 µg/g), brain (18.1 µg), heart (10.9 µg/g), and liver (7.3 µg/g) 30 minutes after dosing (kerman et al., 1966). The concentrations of prilocaine in the placenta and fetus were higher than in maternal blood with maternal blood/fetal and maternal blood/placenta ratios of 0.31 and 0.26, respectively. The placenta/fetus ratios of prilocaine were constant throughout the test period, indicating early equilibrium of prilocaine in the fetus, which does not vary with maternal blood concentrations.

9.1.2.6.2.2 EMLA

In a recent study, topical application of EMLA cream (1 mL) was found to be more therapeutic than application of 30% lidocaine cream for male circumcision (Woodman, 1999). In addition, the plasma concentrations of lidocaine and prilocaine were 7.5 times lower than with 30% lidocaine. When 0.5 g EMLA was applied topically to a 5-cm^2 area of the heel in 25 human neonates for 30 minutes, low concentrations of lidocaine and prilocaine in plasma were observed (0.230 and 0.223 mg/L, respectively) six hours after administration (Essink-Tebbes et al., 1999). Eighteen hours after application, low concentrations of lidocaine and prilocaine were found in one and six neonates, respectively. Thirty hours after administration, lidocaine and prilocaine concentrations in all neonates were below 0.10 mg/L. When EMLA cream (10 g) was applied topically to the face of 10 healthy volunteers for 2 hours, the mean concentrations of lidocaine and prilocaine peaked at 150 ng/mL and 58 ng/mL, respectively, 2 to 2.5 hours after dermal application under occlusion (Juhlin et al., 1989). However, when the same amount was applied to the forearm of the same volunteers under the same conditions, concentrations of lidocaine (18 ng/mL) and prilocaine (<5 ng/mL) peaked 5 hours after application. This clearly shows that the location of dermal application of EMLA plays a large role in the resulting plasma concentrations of lidocaine and prilocaine.

The elimination half-lives of lidocaine, prilocaine, and *o*-toluidine after i.v. injection (25 mg lidocaine, 25 mg prilocaine) in 15 healthy full-term male piglets were 1.9, 1.4, and 5.4 hours, respectively (Gazarian et al., 1995). Clearance after i.v. injection was 26.6 mL/min/kg for lidocaine and 111.4 mL/min/kg for prilocaine.

Although concentrations of lidocaine and prilocaine may be low in the general circulation, they may be higher in the draining veins near the site of topical application of EMLA cream, especially in individuals that have skin conditions with lesions such as psoriasis or dermatitis (Juhlin et al., 1989). These conditions appear to cause more rapid diffusion of anesthetics through the skin causing plasma concentrations of prilocaine and lidocaine in the vein draining the topical site to be 2 to 90 times higher than concentrations in the general circulation. The application of EMLA on lesional skin resulted in more rapid onset and termination of anesthesia in the applied area. The draining vein concentrations seen in patients with atopic dermatitis (9,560-13,070 ng/mL) that were 90 times higher than general circulation concentrations would be toxic if in the general circulation. The authors also found that the

location of the draining vein in relation to the site of topical application influenced the results. Lower concentrations were observed when EMLA was applied to the dorsal rather than the ventral aspect of the forearm.

After topical application of EMLA cream, prilocaine concentrations in plasma are 10-20% lower than that of lidocaine (Juhlin et al., 1989). This may be due to the more rapid metabolism of prilocaine, prilocaine s low plasma binding, or its higher tissue absorption and affinity when compared to lidocaine (Juhlin et al., 1989). When lidocaine and prilocaine were administered together i.m. in 60 female rats, the amount of prilocaine in tissue at the site of injection (tongue) was less than if prilocaine was administered alone (kerman et al., 1966). This is probably due to the vasodilatory action of lidocaine, causing more rapid movement of anesthetic away from the area of administration and into the blood.

9.1.2.7 Ropivacaine

9.1.2.7.1 Metabolism of Ropivacaine

Since ropivacaine is relatively new compared to the other amide local anesthetics in this report, the metabolism studies are fairly recent. The metabolism of ropivacaine is similar to that of bupivacaine and mepivacaine in that dealkylation results in the formation of PPX; however, the common metabolites after ropivacaine and bupivacaine administration do show quantitative differences that will be discussed later. Ropivacaine used clinically is the (*S*)-(−)-enantiomer. The cytochrome P450 enzymes involved in ropivacaine metabolism have been well studied both *in vivo* and *in vitro*. The metabolites of ropivacaine and metabolic pathway are presented in **Table 19** and **Figure 7**, respectively. The *in vitro* and *in vivo* metabolism of ropivacaine is compared in **Table 20**. **Table 18** lists the human and rat isozymes involved in the *in vitro* metabolism of ropivacaine.

Ropivacaine is extensively metabolized in humans since only ≤1.0-1.4% of the ropivacaine dose is excreted in the urine unchanged (Halldin et al., 1996; Arlander et al., 1998; Scott et al., 1997). The metabolism of ropivacaine was found to be mediated *in vivo* by human P450 enzymes CYP1A2 and CYP3A4 (Arlander et al., 1998; Ekstr m and Gunnarsson, 1996). Inhibition of CYP1A2 by fluvoxamine strongly enhanced the urinary excretion of (*S*)-PPX and inhibited (*S*)-3'-hydroxyropivacaine excretion while inhibition of CYP3A4 with ketoconazole increased excretion of (*S*)-3'-hydroxyropivacaine and decreased urinary excretion of PPX

(Arlander, 1998). *In vitro* metabolism by dealkylation followed by hydroxylation at position 3'- and 4'- of the xylidine moiety by selected rat and human hepatic P450 enzymes resulted in the formation of PPX, 4'-hydroxyropivacaine, and 3'-hydroxyropivacaine (see**Table 12**) (Oda et al., 1995). The human P450 isozymes CYP3A4 and CYP1A2 are also involved in the metabolism of other drugs, such as nifedipine, alfentanil, midazolam, and quinidine, that are commonly administered during anesthesia. This may result in the pharmacokinetic interaction of ropivacaine with other pharmaceuticals metabolized by CYP1A; however, the lower affinity of ropivacaine for CYP3A and the large amount of the enzyme in the liver most probably make it less likely that drug interactions would occur (Ekstr m and Gunnarsson, 1996).

The metabolites detected in the 96-hour urine collection from six healthy volunteers that received ropivacaine hydrochloride monohydrate (50 mg) i.v. were 3'-hydroxyropivacaine (36.9% of the total dose), 2'-hydroxymethylropivacaine (18.5%), PPX (2.8%), 3'-hydroxypipecoloxylidide (2.2%), ropivacaine (1.0%), and 4'-hydroxyropivacaine (0.4%) (Halldin et al., 1996). The relative amounts of metabolites in this study were representative of amounts detected in urine in other human metabolism studies with ropivacaine (Arlander, 1998; Arvidsson et al., 1999). No 4'-hydroxypipecoloxylidide was detected in any *in vitro* studies with human and rat microsomes or *in vivo* studies with humans and rabbits. This is in contrast to the presence of 4'-hydroxypipecoloxylidide (4.9% of the dose) detected in human urine after bupivacaine administration.

Only trace amounts of PPX were detected in urine *in vivo*, compared to the major amounts found to be metabolized *in vitro* with human liver microsomes in the presence of ropivacaine (Ekstrom and Gunnarsson, 1996; Oda et al., 1995). In one patient with liver disease, the recovery of PPX (20% of the dose) in the urine was three times greater than the recovery of 3'-hydroxyropivacaine (7%) (Scott et al., 1997). The mean terminal elimination half-life of PPX in the plasma of 12 healthy volunteers was 8.8 ± 2.8 hours (Arlander, 1998), much longer than the elimination half-life of ropivacaine itself (1.7-2.0 hours) (Emanuelsson et al., 1997; Halldin et al., 1996). The mean PPX concentration in plasma was 16.6 mg/L 8 hours after ropivacaine administration, but was 77.1 and 4.1 mg/L with concomitant administration of fluvoxamine and ketoconazole, respectively (Arlander et al., 1998).

Table 18. The Ropivacaine Metabolic Activity of Purified Rat and Human Cytochrome P450 Enzymes

Purified Rat Hepatic P450s	Purified Human Hepatic P450s	Ropivacaine Metabolites (nmol Æ min^{-1} Æ nmol P450^{-1})		
		PPX	4'-Hydroxyropivacaine	3'-Hydroxyropivacaine
	CYP1A1	0.10	0.09	0.05
	CYP1A2		0.04	1.46
CYP1A2		0.09	0.04	0.34
CYP2A2		0.09		
	CYP2A6			
CYP2B1		0.04		0.03
CYP2B2				
	CYP2B6	0.42		0.01
CYP2C11		0.40		0.02
CYP2D1		0.04		0.14
	CYP2D6		0.08	0.01
	CYP2E1			
CYP2E1				0.04
CYP3A2		0.04		
CYP3A2*		0.31		
	CYP3A4	3.20	0.09	

Taken from Oda et al. (1995).
* Mixture of phospholipids: dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, and phosphatidylserine (1:1:1) were used instead of dilauroylphosphatidylcholine.

No 2,6-xylidine was detected in the 96-hour urine collection from six healthy males given an i.v. infusion of ^{14}C-labeled ropivacaine hydrochloride monohydrate (50 mg) using GC and HPLC methods with a limit of quantification of 0.3 µM (Halldin et al., 1996).

The phenolic metabolites of ropivacaine can be sulfonated by liver sulfotransferases. The sulfotransferases that are capable of sulfonating ropivacaine metabolites most efficiently were M-PST, P-PST-1, and EST (Falany et al., 1999). DHEA-ST and ST1B2 showed no sulfation activity for ropivacaine metabolites. M-PST does circulate in the blood and it is suggested that some sulfation could occur throughout the body (Heroux and Roth, 1988; Wang et al., 1998; both cited by Falany et al., 1999).

No racemization of ropivacaine metabolites occurred in 22 male human volunteers dosed i.v. and intrarectally or in intravenously infused dogs, sheep, or rats (Arvidsson et al., 1994; Halldin et al., 1996).

Some drugs affect the metabolism of ropivacaine *in vitro*. Cimetidine (1 mM), a non-competitive P450 inhibitor, has been shown to inhibit the formation of 4'-hydroxyropivacaine and 2-hydroxymethylropivacaine by 40-50% with human liver microsomes incubated for 30 minutes (Ekstr m and Gunnarsson, 1996). Addition of high concentrations of sulfaphenazole (100 mM) in the medium inhibited formation of 4'-hydroxyropivacaine, 2-hydroxymethyropivacaine, and PPX by 20-27%. The addition of naphthoflavone or furafylline almost completely inhibited the formation of 3'-hydroxyropivacaine, but did not affect formation of 4'-hydroxyropivacaine, 2-hydroxymethylropivacaine, and PPX.

In vitro studies of ropivacaine metabolism do not accurately reflect *in vivo* metabolism. In all *in vitro* studies, PPX and 4'-hydroxyropivacaine were the major metabolites detected, and 3'-hydroxyropivacaine was a minor metabolite when human and rat hepatic microsomes were incubated with ropivacaine (Oda et al., 1995; Ekstr m and Gunnarsson, 1996). However, in humans PPX and 4'-hydroxyropivacaine are minor metabolites and 3'-hydroxyropivacaine is the major metabolite (Halldin et al., 1996; Arlander, 1998).

Table 19. Ropivacaine, Its Salts, and Its Metabolites

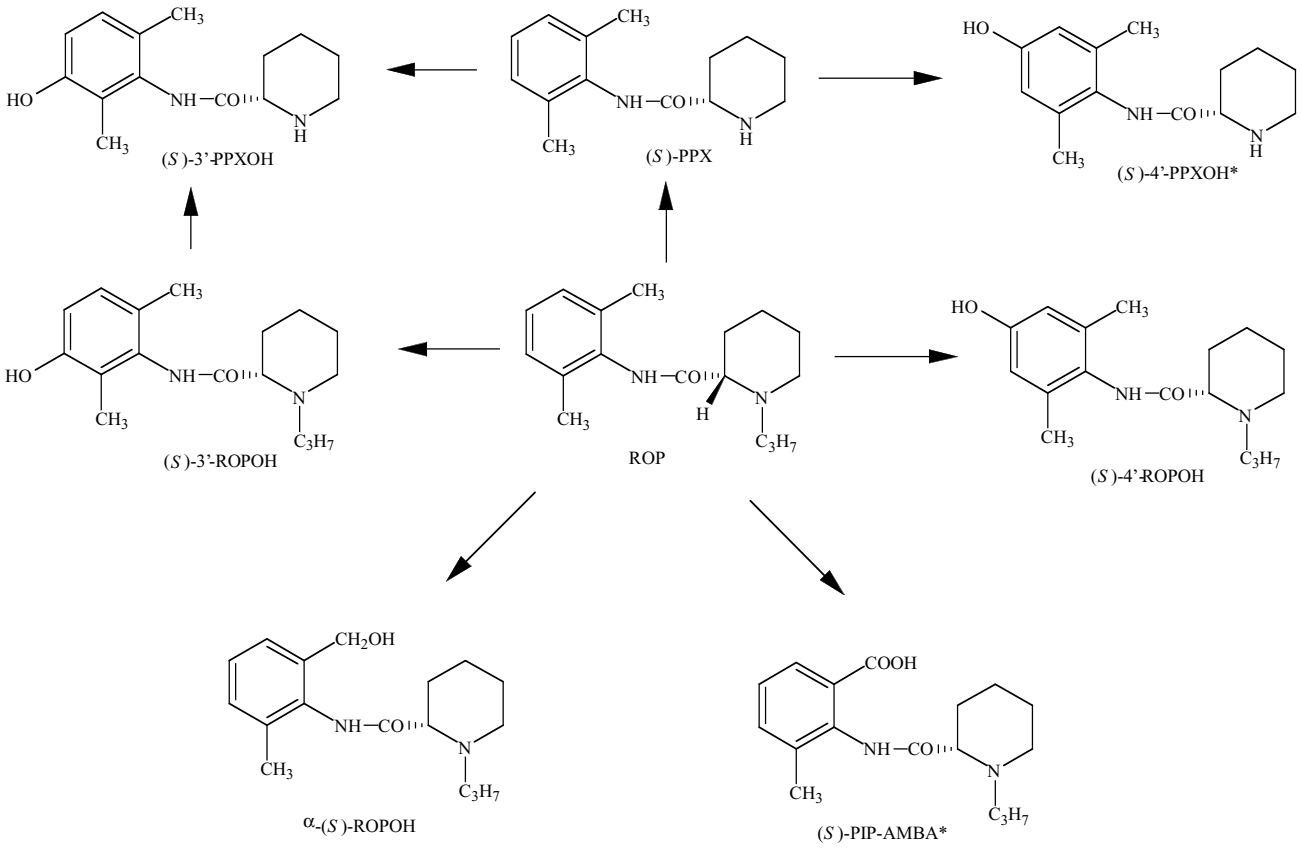
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
(S)-ROP	Ropivacaine; (*S*)-(-)-Ropivacaine; (-)-Ropivacaine; (-)-LEA; (2*S*)-*N*-(2,6-Dimethylphenyl)-1-propyl-2-piperidinecarboxamide; (-)-1-Propyl-2«,6«-pipecoloxylidide	$C_{17}H_{26}N_2O$	84057-95-4	162
(S)-ROPÆHCl	Ropivacaine hydrochloride	$C_{17}H_{27}ClN_2O$	98717-15-8	11
(S)-ROPÆHClÆH2O	Ropivacaine hydrochloride monohydrate	$C_{17}H_{29}ClN_2O_2$	132112-35-7	6
(R)-PPX	(*R*)-2«,6«-Pipecoloxylidide; (*R*)-Desbutylbupivacaine; (-)-2«,6«-Pipecoloxylidide **[Very minor.]**	$C_{14}H_{20}N_2O$	27262-43-7	Arvidsson et al. (1995)
(S)-PPX	(*S*)-2«,6«-Pipecoloxylidide; (*S*)-Desbutylbupivacaine; (+)-2«,6«-Pipecoloxylidide; (2*S*)-*N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	27262-40-4	20 Arlander et al. (1998) Arvidsson et al. (1995)
PPX	2«,6«-Pipecoloxylidide [racemic]; 2«,6«-Pipecolylxylidide; PPX; *N*-Desbutylbupivacaine; Mono-*N*-demethylmepivacaine; *N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	15883-20-2	45 (Frequently indexed as a ropivacaine metabolite when (S)-PPX [27262-40-4] is meant.)
(S)-3«-ROPOH	(-)-3«-Hydroxyropivacaine; 3«-Hydroxyropivacaine; (*S*)-3«-Hydroxy-1-propyl-2«,6«-pipecoloxylidide; (2*S*)-*N*-(3-Hydroxy-2,6-dimethylphenyl)-1-propyl-2-piperidinecarboxamide	$C_{17}H_{26}N_2O_2$	163589-30-8	8 Halldin et al. (1996)
(S)-4«-ROPOH	(-)-4«-Hydroxyropivacaine; (*S*)-4«-Hydroxy-1-propyl-2«,6«-pipecoloxylidide; (2*S*)-*N*-(4-Hydroxy-2,6-dimethylphenyl)-1-propyl-2-piperidinecarboxamide	$C_{17}H_{26}N_2O_2$	163589-31-9	5 Halldin et al. (1996)

Table 19. Ropivacaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
(S)-α-ROPOH	(2*S*)-*N*-[2-(Hydroxymethyl)-6-methylphenyl]-1-propyl-2-piperidinecarboxamide; 2-OH-methyl-ropivacaine [*sic*, Ekstrom & Gunnarsson (1996)]	$C_{17}H_{26}N_2O_2$	182703-01-1	2 Halldin et al. (1996)
(S)-PIP-AMBA	"(*S*)-2-Carboxyropivacaine;" 3-Methyl-2-[(1-propylpiperidine-2-carbonyl)amino]benzoic acid; (2*S*)-*N*-[(2-Carboxy)-6-methylphenyl]-1-propyl-2-piperidinecarboxamide **[Falany et al. (1999) conducted *in vitro* sulfation of synthesized known and suspected ropivacaine metabolites. Not derived as a metabolite. Not found in references cited.]**	$C_{17}H_{24}N_2O_4$	Not identified	Falany et al. (1999)
(S)-3«-PPXOH	(*S*)-3«-Hydroxy-2«,6«-pipecoloxylidide; (*S*)-3«-Hydroxy-2«,6«-PPX; (2*S*)-*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide **[Has not been reported as a bupivacaine metabolite.]**	$C_{14}H_{20}N_2O_2$	182878-70-2	2 Halldin et al. (1996) Arvidsson et al. (1999)
(S)-4«-PPXOH	(*S*)-4«-Hydroxy-2«,6«-pipecoloxylidide; (*S*)-4«-Hydroxy-2«,6«-PPX; (2*S*)-*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide **[Proposed ropivacaine metabolite, but no evidence for this compound as a human metabolite.]**	$C_{14}H_{20}N_2O_2$	243989-47-1	1 Arvidsson et al. (1999)

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated derivatives of xylidine and toluidine.
Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).
The lower-case Greek letter alpha in a code indicates that hydroxylation is on a xylidine methyl group.

Figure 7. Metabolic Pathway of Ropivacaine in Humans and Experimental Animals



* conjectural metabolites were not detected in any studies reviewed

Table 20. Metabolites of Ropivacaine Detected *In Vivo* and *In Vitro* and Their Amounts in Human Urine and [Plasma]

Metabolite Code	Range of Mean Amounts of Ropivacaine Metabolites Detected in Urine and [Plasma][a]			
	In Vivo		*In Vitro*	
ROP	X	4.7 µM [4.9 µM] 1.0%		
(*S*)-PPX	X	23.2 µM [1.5 µM] 2.8%	X	1847 pmol/mg/min
(*S*)-PIP-AMBA			X	n.q.
(*S*)-3'-ROPOH	X	118 µM; 36.9%	X	46 pmol/mg/min
(*S*)-3'-ROPOH	X	0.4%	X	105 pmol/mg/min
α-(*S*)-ROPOH	X	trace-18.5%	X	9 pmol/mg/min
(*S*)-3-PPXOH	X	10 0 µM; 2.2%		

[a] Urinary excretion = percentage of the administered dose found in the urine. Plasma concentrations are given in micrograms per milliliter.

9.1.2.7.2 Pharmacokinetics of Ropivacaine

The pharmacokinetics of ropivacaine is similar to bupivacaine except that the neuro- and cardiotoxicity of ropivacaine is less, probably associated with the fact that ropivacaine is used as the (S)-enantiomer only and no racemization of ropivacaine or its metabolites occurs after administration. This means that at the same dose or infusion rate, ropivacaine concentrations in the blood are less than those of bupivacaine (Gustorff et al., 1999). Ropivacaine (0.5%) results in less motor block than bupivacaine (0.5%).

The protein-bound fraction of ropivacaine in plasma was observed to be about 95%. In one study of 11 patients undergoing elective orthopedic surgery, the bound fraction of ropivacaine ranged from 85.9% to 98.8% (Scott et al., 1997). Protein binding was observed to increase from the initiation of infusion to the end of the observation period, which was due to increases in the concentration of α-acid glycoprotein during infusion (Erichson et al., 1996; Scott et al., 1997).

The urinary excretion of radioactivity from ^{14}C-labeled ropivacaine hydrochloride was 86% of the dose in 96-hour urine collections from nine healthy human males, which was higher than excretion in rats (~41%) and dogs (63%), but similar to urinary excretion in pregnant rabbits (92%) (Halldin et al., 1996).

The elimination half-life of ropivacaine from venous plasma after epidural infusion (4.2 hours) is much longer than the half-life after i.v. administration, again due to the slow absorption from the epidural space (1.7-2.0 hours) (Emmanuelsson et al., 1995, 1997; Halldin et al, 1996). The plasma concentrations of ropivacaine may or may not plateau during continuous epidural infusion.

After i.v. administration, mean peak plasma concentrations of ropivacaine were 1.23 ± 0.21 mg/L immediately after infusion in 12 healthy human subjects.

It has been suggested that monitoring arterial plasma concentrations of ropivacaine would be better than monitoring venous concentrations since arterial concentrations are higher than venous (Emanuelsson et al., 1997).

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