

Mepivacaine: a closer look at its properties and current utility

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The use of mepivacaine in dentistry has remained strong since its introduction in the 1960s. It has retained its place as a valuable local anesthetic, either as a primary agent or as an alternative to lidocaine or articaine. Mepivacaine is commonly used in medically compromised patients—for whom elevations in blood pressure or heart rate are not advisable—in a formulation with a vasoconstrictor, or in pediatric populations in a formulation without a vasoconstrictor. Pharmacologically, these are the 2 groups most susceptible to side effects and toxicity, thus mepivacaine is commonly indicated. Most often the decision to

use mepivacaine is based on its vasoconstrictor effect or lack thereof (depending on the formulation). However, the pharmacokinetics of mepivacaine are not well understood or assumed to be similar to that of other local anesthetics. It is important to understand the unique pharmacologic characteristics of mepivacaine in order to minimize the potential for inadvertent toxicity.

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Currently used local anesthetics and their formulations each have individual characteristics that allow them to claim clinically useful niches to validate their continued market presence. While the introduction of articaine—in 1982 in Canada and in 2000 in the US—has gained much of the market share in North America, lidocaine and mepivacaine have remained commonly used agents.¹ In Canada, where articaine is the most used agent, a survey of general dentists showed that from 1993 to 2007, mepivacaine usage declined but remained the third most used agent.² Mepivacaine's niche has been considered by many dentists to be the “safer” lidocaine alternative, to be used in elderly or cardiovascular disease patients, because it not only comes without a vasoconstrictor, but it is available with levonordefrin, which is assumed to have less vasopressor potency and 25% of the direct beta effects on the heart.³ It is now known, however, that levonordefrin acts similarly to norepinephrine, as it elevates not only systolic blood pressure, but diastolic and mean arterial pressures as well. Used at 5 times the concentration of epinephrine, it possesses relatively the same or more potential for cardiac stimulation, especially elevations in blood pressure.⁴ Mepivacaine is also commonly used—in a formulation without levonordefrin—for children, as it is available without a vasoconstrictor for shorter postoperative duration, whereas articaine and lidocaine have longer durations and must have vasoconstrictors for their efficacy. Many general and pediatric practices use mepivacaine

formulations exclusively with these characterizations in mind. Whereas the 2 different vasoconstrictors used in local anesthetics bear many similarities to each other with similar clinical limitations, it is worthwhile to look at mepivacaine by itself.

Rather than being a lidocaine substitute, mepivacaine possesses distinct pharmacokinetic characteristics of its own that are important for the clinician to understand. This article reviews the unique pharmacology of mepivacaine and the potential clinical implications involved with its use.

History and chemistry: pipechoyl xyliidines

In the years immediately after the development of the xyliidine derivative, lidocaine, there followed a series of chemical syntheses based upon the same

successful 2,6-xyliidine-amide structure, with emphasis on increasing the duration of action. In 1957, af Ekenstam et al synthesized (along with many other structures with anesthetic properties) mepivacaine and bupivacaine, both very similar in structure and with longer durations than lidocaine.⁵ Each preserved the 2,6-xyliidine group on the aromatic ring, but each had a shortened intermediate chain, and replaced the terminal tertiary amine with a less basic methyl-piperidine ring. Homologous local anesthetics that share the mepivacaine structure, such as bupivacaine and ropivacaine, are referred to as *pipechoyl xyliidines* due to the presence of this pipechoyl acid moiety (Fig. 1). Bupivacaine differs from mepivacaine only by substitution of the methyl group on the piperidine ring by a

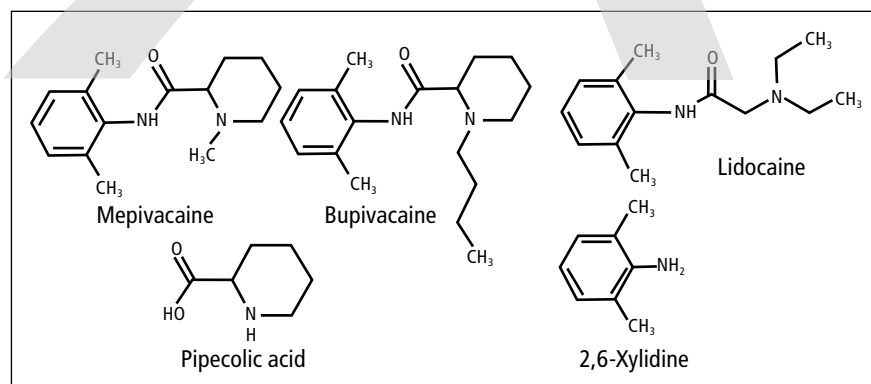


Fig. 1. Pipechoyl xyliidines compared to lidocaine.

Table. Physicochemical properties and relative in vitro conduction blocking potency of the intermediate-acting amide local anesthetics.¹⁵

Anesthetic	MW base (g/mol)	pKa (36°C)	Hydrophobicity ^a (mol/L)	Lipid solubility (distribution coefficient Q _{7.4}) ^b	Relative conduction blocking potency (in vitro, isolated nerve fibers)
Lidocaine	234	7.8	304 (366)	43 (110)	2.0
Prilocaine	220	8.0	129	25	1.8
Mepivacaine	246	7.7	90 (130)	21 (42)	1.5

^aOctanol/buffer partition coefficients for unprotonated species only: 25°C. Values in parentheses: 36°C.

^bQ_{7.4} = (total drug/ml octanol)/(total drug/ml buffer) at pH 7.4. Includes ionized and unionized partition coefficients.

Margins of error not shown.

more lipid soluble butyl (C₄H₉) group. It was not until the late 1970s, however, that bupivacaine was approved for clinical use as a nerve blocker in dentistry.⁶⁻⁸

Mepivacaine, being less toxic than bupivacaine, was immediately evaluated for clinical use in various types of regional and dental anesthesia and was identified as having a faster onset and longer duration than lidocaine without a vasoconstrictor.⁹⁻¹² Approved by the FDA in 1960, it was subsequently studied in many dental trials, where it rapidly established its dual utility in dentistry when used in a formulation without a vasoconstrictor or in a formulation with 1:20,000 levonordefrin (Neo-Cobefrin, Novocol Pharmaceutical of Canada, Inc.) which markedly increased its duration.^{13,14}

Lipid solubility and potency

Mepivacaine, lidocaine, and prilocaine are considered to be “intermediate” in terms of their lipid solubility and anesthetic potencies (Table).¹⁵ The correlation of lipid solubility, and the ability to penetrate membranes with increased affinity for hydrophobic binding sites are the main determinants of anesthetic potency.¹⁶ The lipid solubility and hydrophobicity (tendency to be readily soluble in nonpolar solvents but only sparingly in water) is lowest in mepivacaine compared to the other local anesthetics.

Hydrophobicity correlates with in vitro methods that measure conduction blocking (anesthetic) potency on isolated nerve fibers, such as rabbit vagus and sciatic.

These methods showed mepivacaine to have a correspondingly lower anesthetic potency than lidocaine or prilocaine under in vitro conditions.¹⁷ However, these measurements were derived under controlled conditions and do not directly reflect in vivo anesthetic potency. They also do not correctly reflect the clinical end-points of mepivacaine use, where success is measured by an adequate conduction block, and the physiologic variables that affect tissue concentration, diffusion, and ionization are more complex. Animal studies with live nerve blocks have shown the potency of mepivacaine to be equivalent or greater, with a faster onset time, and longer duration of anesthesia than lidocaine and prilocaine.¹⁸ Mepivacaine, lidocaine, and prilocaine have all been shown in numerous clinical studies to have similar intermediate anesthetic efficacy, regardless of differences in their lipid solubility.¹⁹⁻²¹

Effectiveness in infected tissues

The ionization constant, or pKa, of mepivacaine is also the lowest of the intermediate agents (articaine and lidocaine have the same pKa). At 36°C, the pKa's of the intermediate-acting agents are all close enough to make onset times roughly equivalent under normal physiologic conditions.²² Estimates of the effects of acidic conditions such as those found in infected tissue—using quantitative structure-activity relationship modeling (QSAR) calculations—have shown the relative anesthetic potency of lidocaine drops 72.8% from a normalized 100 (at pH 7.4)

to 27.2 (at pH 6.5).²² In comparison, the relative anesthetic potency of prilocaine decreases by 66.5%, and mepivacaine decreases by 64.7%. Theoretically, mepivacaine would lose less potency when injected into areas of reduced pH and this may be considered an advantage. However, realistically, this is a rare occurrence if a regional block is available.

Hypersensitivity and cross reactivity

For patients who are known to be allergic to sulphites, the availability of mepivacaine without vasoconstrictor and sodium metabisulphite is a highly valuable clinical asset, since articaine and lidocaine must have vasoconstrictors added for their efficacy. Allergy to mepivacaine itself, as well as any of the amide local anesthetics is very rare, but does occur.²³ Most case reports of mepivacaine allergic reactions prior to the mid-1980s were related to the methylparaben used as antimicrobials in the cartridges; these were subsequently removed by FDA mandate.²⁴

A large 2009 study that analyzed the French Pharmacovigilance database over a 12-year period (1995-2006) found 16 cases of allergic reactions to amide local anesthetics, of which 11 were immediate Type I reactions occurring within 1 hour with severe symptoms.²⁵ Of the Type 1 reactions, 6 were due to lidocaine, 2 to mepivacaine, 2 to articaine, and 1 to bupivacaine. Of the other 5 reactions, which were delayed-type skin reactions, 4 were due to lidocaine and 1 to mepivacaine.²⁵

Cross-reactivity among the amides, previously thought to be rare, was found in 6 cases (38%) and all were between lidocaine and mepivacaine. In patients with a true lidocaine or mepivacaine allergy, neither lidocaine nor mepivacaine should be used as a substitute due to very possible cross-allergenicity.²⁵

A 2006 report in Spain published a similar case of a patient with confirmed lidocaine and mepivacaine allergies who was not allergic to bupivacaine, despite its structural similarity.²⁶ No cross-allergenicity to articaine was found in either study. The findings in these and other studies suggest that articaine may have rare cross-allergenicity with other members of the amide class, including delayed-type reactions.^{27,28}

Systemic absorption

At therapeutic concentrations, mepivacaine has an intrinsic vasodilating activity intermediate between lidocaine and prilocaine.²⁹ In various arterial blood flow studies, lidocaine markedly increased blood flow whereas mepivacaine and prilocaine tended to either maintain or decrease peripheral blood flow.³⁰⁻³² This would appear to be an additional safety factor, by keeping systemic levels low. However, in maxillary infiltration studies conducted by Goebel et al, serum levels of the mepivacaine formulation without vasoconstrictors were always higher and more persistent than lidocaine.^{33,34} Complimentary studies by Goebel et al comparing lidocaine and mepivacaine with their respective vasoconstrictors, epinephrine and levonordefrin, also showed that mepivacaine produced significantly higher and more variable serum levels than lidocaine at all time intervals.^{34,35} Medical studies comparing lidocaine and mepivacaine in regional blocks also indicate that mepivacaine, even in the vasoconstrictor formulation, produce higher and more sustained systemic blood levels on the order of 35% to 38%.^{36,37}

The studies by Goebel et al showed that mepivacaine displays mean peak levels at about 30 minutes, with or without a vasoconstrictor, while lidocaine with epinephrine produces peak levels earlier, at approximately 15 minutes.³³⁻³⁵ Since the duration of mepivacaine without a vasoconstrictor is about 30 minutes, reinjection at that time occurs at peaking serum levels. In addition, at all later time intervals, differences in mepivacaine serum levels are not significantly different whether or not vasoconstrictor is used. Serum levels at time intervals beyond 30 minutes in maxillary infiltration studies are essentially the same regardless of whether or not the vasoconstrictor formulation was used.³⁸ The mean peak (Cmax) percentage difference between plain 2% mepivacaine and 2% mepivacaine with levonordefrin was only 8%, while the peak difference between lidocaine with and without epinephrine was 29%.³² Systemic levels of mepivacaine decrease less when compared to lidocaine in the presence of a vasoconstrictor. A formulation with 3% mepivacaine (no vasoconstrictor) produces the highest

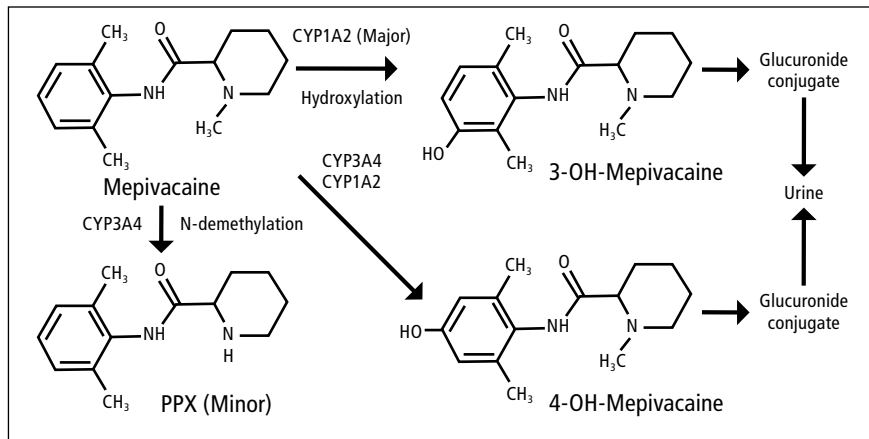


Fig. 2. Mepivacaine metabolism.

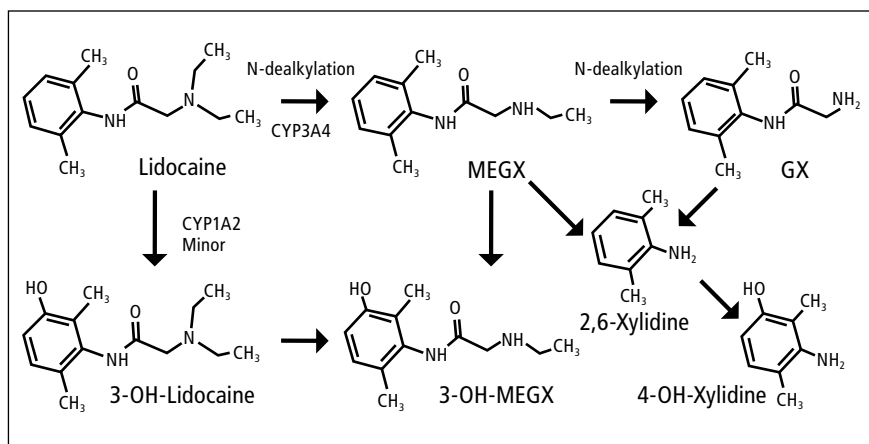


Fig. 3. Lidocaine metabolism.

systemic levels of local anesthetic, which are 1.5 times higher than 2% mepivacaine with levonordefrin, and thus has the most potential for chronic accumulation.³⁵

Metabolism and disposition compared to other local anesthetics

Mepivacaine, like the other amide local anesthetics, undergoes extensive hepatic biotransformation with <5% urinary excretion of the unchanged drug. Metabolism is primarily through hydroxylation of the parent compound to inactive 3-OH-mepivacaine and 4-OH-mepivacaine by CYP1A2 (Fig. 2). CYP1A2 is constitutive, and CYP1A1 is the inducible isoform which also participates in metabolism. CYP3A

also contributes to the formation of 4-OH-mepivacaine.³⁹ All these hydroxyl (OH) metabolites are excreted as glucuronide conjugates and comprise >50% of the total mepivacaine dose. Urinary sampling shows the 3-OH-mepivacaine to be the major metabolite earlier in the process, with the 4-hydroxy compound produced later in smaller amounts, indicating the predominance of CYP1A metabolism.⁴⁰ Demethylation by CYP3A produces pipercolonylidide, a minor metabolite accounting for about 1% of the urinary output.

Lidocaine metabolism involves similar enzymatic activities, but CYP3A4 plays the larger role in dealkylation to the major metabolite monoethylglycinexylidide (MEGX), an active metabolite that still retains central nervous system

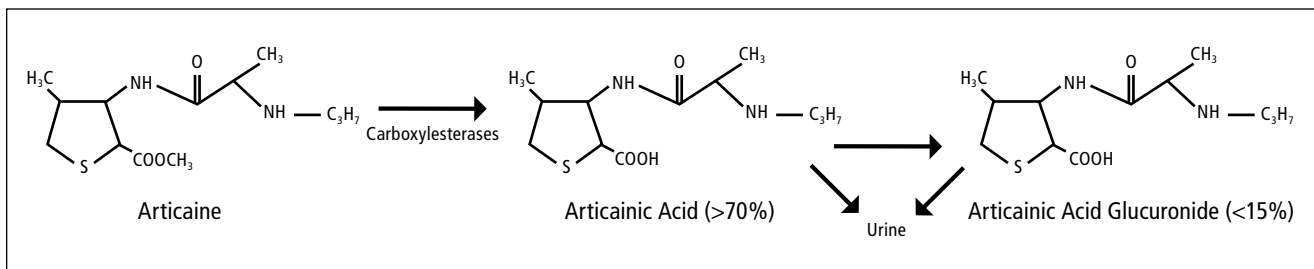


Fig. 4. Articaine metabolism.

(CNS) toxicity. CYP1A contributes to forming MEGX in addition to generating 3-OH-lidocaine which is converted to 3-OH-MEGX.⁴¹ These are all eventually eliminated as glucuronide conjugates. MEGX is metabolized to inactive glycinexylidide (GX) and excreted for the most part renally.⁴² The remaining MEGX and GX is further broken down to 2,6-xylylidine metabolites when the xylylidine ring is removed by hydrolytic reactions involving hepatic carboxylesterases or amidases (Fig. 3).⁴³

Prilocaine metabolism occurs in the liver and kidney by carboxylesterases and CYP3A4 that generate *o*-toluidine. CYP2E1 produces hydroxylated toluidine metabolites that represent more than 40% of the urinary metabolites of prilocaine. *O*-toluidine and its hydroxylated variants can oxidize hemoglobin to methemoglobin, a critical dose-limiting restriction for prilocaine use.⁴⁴ Drug interactions with prilocaine mainly involve inducers of CYP3A4 (carbamazepine, phenytoin, rifampin), or other drugs that contribute to methemoglobinemia, such as benzocaine, nitrates, or acetaminophen.⁴⁵

Articaine has the simplest and most rapid metabolism of the amides due to its carboxyl group ester linkage. Articaine is metabolized rapidly into articaic acid by plasma carboxylesterases with a plasma half-life of 20 minutes.⁴⁶ Forty percent to 70% is excreted as articaic acid, and 4% to 15% as articaic acid glucuronide (Fig. 4). Almost all major P450 cytochromes participate in the remaining metabolism of articaine, but only 10% of the total dose is metabolized by cytochromes, making articaine relatively resistant to pharmacokinetic drug interactions.⁴⁷

Lidocaine clearance is reduced metabolically by inhibitors of CYP3A4, such as cimetidine, erythromycin, and azole antifungals. Antidepressants and benzodiazepines that heavily utilize CYP3A4 have also been associated with serious lidocaine toxicities, including sertraline (Zoloft), escitalopram (Lexapro), desipramine (Norpramin), and flurazepam (Dalmane).⁴⁸ Because of the high hepatic extraction ratio of lidocaine, drugs that reduce hepatic blood flow also reduce its metabolism significantly. Beta-blockers that decrease cardiac output, especially propranolol, decrease lidocaine elimination by decreasing hepatic blood flow.⁴⁹ Propranolol also prolongs mepivacaine blood levels, but mepivacaine is not as dependent on hepatic blood flow since it has a lower hepatic clearance (extraction ratio) of 0.51 compared to 0.72 for lidocaine.⁵⁰⁻⁵²

Pharmacokinetic drug interactions with mepivacaine are more likely to involve inhibitors of CYP1A2. Potent inhibition of CYP1A2 occurs with selective serotonin receptor inhibitors fluvoxamine (Luvox) and fluoxetine (Prozac) and moderate inhibition with paroxetine (Paxil) and sertraline (Zoloft).⁵² Other strong inhibitors of CYP1A2 and drugs known to interfere with mepivacaine metabolism include caffeine, grapefruit juice, fluoroquinolone antibiotics, and verapamil (Calan), mexiletine (Mexitil), and zileuton (Zyflo).⁵³ Lastly, significant hepatic CYP1A2 levels are not present in infancy (<1 year), and may not be fully functional before the age of 3 years, which prolongs metabolism of mepivacaine in infancy, whereas fetal CYP3A7 and immature CYP3A are present at birth.^{54,55}

The main difference in pharmacokinetic safety levels between local anesthetics is the *total clearance* rate (Cl_{tot}). Local anesthetic

duration of activity is determined by vascular redistribution from the local site and is only indirectly and weakly correlated with final elimination of the drug from the body. Total clearance (expressed in volume/time) is the removal of a drug from a volume of plasma in a given unit of time as the sum of all clearances by all the various elimination mechanisms, such as renal and hepatic. Of the currently used intermediate-acting agents, mepivacaine has the slowest total clearance. In comparison, the total body clearance of lidocaine is 3 times higher than that of mepivacaine (0.95-1.1 l/min vs 0.45 l/min).³⁶ Medical studies examining systemic levels of mepivacaine after caudal or regional blocks have clinically demonstrated the drug's relatively long persistence.^{56,57} The typically slower total clearance of mepivacaine is a factor that can lead to potential accumulation in cases of repetitive dosing over time or excessive doses, especially when children are involved.⁵⁸⁻⁶⁰ In neonates, the lidocaine total plasma clearance normalized to body weight is not significantly different than adults because more lidocaine is excreted renally and unchanged.⁶¹ The neonatal capacity for aromatic hydroxylation, however, is very limited, thus the total plasma clearance of mepivacaine is <50% the adult clearance rate, coupled with a hepatic clearance that is approximately 25% that of adults.⁶² Concomitant drug interaction from CYP1A inhibition would also contribute to prolonged or toxic blood levels. Prilocaine has a notably fast total clearance—almost 2.5 times that of lidocaine—which not only indicates high hepatic extraction but also extrahepatic metabolism.^{63,64} This hydrolysis of the amide bond occurs very efficiently, considering only 5% of prilocaine is excreted

unchanged. Articaine has the fastest total body clearance of all amide local anesthetics, ranging from 3.9 l/min for intraoral injections to 8.9 l/min for IV injections.⁴⁶

In dentistry, local anesthetic toxicity occurs more frequently in children, most often with mepivacaine.⁶⁵ Plain mepivacaine is favored and useful in pediatric dentistry for its shorter duration of activity, but plain mepivacaine leads to higher systemic levels which are subject to a slow total clearance rate. Even with levonordefrin, serum levels are not decreased as they are with lidocaine and a vasoconstrictor. Mepivacaine—especially 3% mepivacaine without a vasoconstrictor—has been implicated in most reported fatalities due to excessive dosing.^{66,67} Factors that contribute include practitioners not understanding fully the implications of injecting additional anesthetic in low body weight children, basing the dosage on the number of carpules rather than the patient's weight, and in many instances not understanding the synergistic effects of concomitant opioids or CNS depressants in pediatric sedation protocols. For example, opioids such as meperidine can decrease convulsant thresholds by producing respiratory acidosis and elevating arterial carbon dioxide, which increase the CNS toxicity of local anesthetics.⁶⁸ All these factors can contribute to toxicity due to mepivacaine's inherent characteristic of maintaining prolonged and relatively high serum levels even when used with a vasoconstrictor.

Conclusion

Mepivacaine is an efficacious and useful intermediate-acting local anesthetic for use in dentistry as it can be used when required and without a vasoconstrictor. The presence of a vasoconstrictor increases the duration of action but has little effect on systemic blood levels. The slower total clearance of mepivacaine makes it more susceptible to the various mechanisms that can lead to chronic toxicity, such as the lack of fully functional enzymes in infants, inadvertent excessive dosing of 3% mepivacaine, or repeated dosing in conjunction with long appointments, renal failure, or drug inhibition of CYP1A (in elderly patients). Children <5 years of age are most susceptible to overdose and are also often given sedation that can increase toxicity. Weight-based dosing

in children should be used as a matter of course, and the maximum recommended dose should never be exceeded, especially when using 3% mepivacaine. It has been recommended by many other authors that, since the 3% formulation is potentially 1.5 times more toxic than the 2% formulation, mepivacaine use in children be restricted to smaller volumes, and that its use be limited to supraperiosteal injections whenever possible.⁶⁰

Author information

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