

# LOCAL ANESTHETIC CONSIDERATIONS IN PODIATRIC SURGERY

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## INTRODUCTION

Local anesthetic (LA) infiltration, first introduced by Karl Schleich in 1892, has allowed surgeons to develop safe operative techniques (1). Local anesthesia offers many benefits and is routinely recommended regardless of whether surgery is performed under monitored anesthetic care or general anesthesia (2). LA provides patient safety and analgesia, optimal operating conditions, control of intra-operative and postoperative pain and decreased demand of intravenous sedation (2). Although LA toxicity is rarely reported, it is important to understand properties of LAs and the signs of LA toxicity. Prevention of toxicity has been based upon manufacturer warnings and vague recommendations. In this review, toxic dose formulas will be simplified and the importance of these values will be clarified.

## LOCAL ANESTHESIA

Of the many commercially available LA agents, lidocaine and marcaine are most commonly used in podiatric surgery (3). These drugs are both amides but have specific chemical properties that make them very different and suitable in certain conditions (Table 1).

Lidocaine has a faster onset of action than marcaine. Onset of action is determined by molecular properties that define how easily LA molecules can penetrate the neuron cell membrane. Non-charged, lipid soluble molecules have greater permeability across the cell membrane's phospholipid bilayer; therefore, they can work quicker and have more potent effects (4, 5). LAs that have pKa values close to the physiologic pH of the injected tissues (7.35-7.45) will exist primarily in the non-charged state, allowing for membrane permeability and rapid onset of anesthesia (1, 5). Once LA molecules enter the neuron, they bind cell membrane sodium channels to block membrane depolarization and ultimately nerve signal conduction (5). In areas of inflammation or infection, a decrease in pH shifts the acid-base equilibrium so that LA molecules are largely in the charged form (1, 4, 5). Under these acidic conditions, LA entry into the nerve is impaired and less effective anesthesia is achieved (1).

Marcaine offers a longer duration of anesthesia than lidocaine. Duration of LA depends on degree of protein binding and LA-induced vasodilation. When bound by protein, LA molecules are inactive, but in this form, they serve as a reservoir of LA. As LA is metabolized, LA molecules bound to proteins are released in an active form and anesthesia is maintained over long periods (5-7). The degree that LA relaxes smooth muscle and causes

**Table 1**

## CHARACTERISTICS OF LIDOCAINE AND MARCAINE

The concentration of non-charged LA molecules at a particular pH environment (represented by pKa values) and LA lipid solubility determine onset of action. Duration of LA effect and drug half life are dependent on the degree of protein binding and LA-induced vasodilation. Ribotsky's experimental data for 1:1 mixtures of 1% lidocaine plain and 0.25% marcaine plain is presented.

LA	Onset (min)	pKa	Lipid Solubility	Duration (hr)	Half Life (hr)	% Bound
Lidocaine 1% or 2 %	1-3	7.86	43	3.17	1.6	64
Marcaine 0.25 or 0.5%	2-10	8.05	346	9.38	2.7	84-95
<b>1:1 Mixture of 1% Lidocaine : 0.25% Marcaine</b>	1.4			3.75		

(Table modified from Chen AH. Toxicity and allergy to local anesthesia. Journal of the California Dental Association. 1998;26:683-92 and Ribotsky BM, et al. Local anesthetics: is there an advantage to mixing solutions? J Am Podiatric Med Assoc 1996;86:487-91.)

vasodilation correlates to rate of LA systemic absorption. When absorbed systemically, LA is removed from the infiltrated area and it cannot produce anesthesia locally (6). Lidocaine causes more vasodilation than marcaine, partially explaining its shorter duration. Vasodilation-induced effects of LA can be negated by adding vasoconstrictive agents to the LA that slow systemic absorption and allow for longer blocks (4). Epinephrine addition to LA, first described by Heinrich F. W. Braunn in 1903, serves as a “chemical tourniquet” (8). Epinephrine provides surgical hemostasis, which at times can eliminate the demand for a surgical tourniquet. By decreasing systemic absorption of LA, epinephrine also increases dose limits of LAs and can prolong the post-analgesic effect of LA (6, 9). Use of epinephrine in patients with vascular compromise, severe hypertension, and cardiac disease is contraindicated; however, with careful patient selection and monitoring, epinephrine use has proven to be a safe practice even in digital foot surgery (10-13).

Neuronal sensitivity to LA depends on nerve size, location and myelination. Larger nerves and highly myelinated nerves are more difficult to anesthetize (10). Small A $\delta$  nerve fibers (thinly myelinated sensory fibers that transmit cold and pressure information associated with nociceptive stimuli) and unmyelinated C fibers (nociceptors) are most sensitive to LAs whereas A $\beta$  (sensory non-nociceptors) and large myelinated motor fibers are most resistant (4). Therefore, signal blockade progresses from loss of temperature and pain, loss of proprioception, loss of touch and pressure, and eventually motor paralysis (4).

## LOCAL ANESTHESIA TOXICITY

Incidence of LA toxicity has drastically declined over the past 25 years with the development of safer anesthetics and package insert warnings; however, LA toxicity remains an important concept that must still be appreciated (7, 14-23). Current incidence of LA toxicity may be under-reported, but is estimated to range from 7.5-20/10,000 peripheral nerve blocks (14). Although rarely reported, LA toxicity can be lethal. A Japanese study, published in 2005 by Irita, reviewed 4,291,925 operative cases with LA infiltration and reported LA toxicity in 1.17/100,000 and LA-induced fatality in 0.023/100,000 (15). Mild LA toxicity is not uncommon and according to Mather’s 2005 review, there are many incidents of mild toxicity that are safely treated before becoming more serious problems (16). This requires identification of early signs and symptoms attributed to LA toxicity.

Systemic LA toxicity typically manifests as central nervous system (CNS) excitation followed by depression (1). CNS excitation results when LA inhibits the cerebral

cortex’s inhibitory pathways (1). Lightheadedness, dizziness, visual and auditory disturbances, tinnitus, and drowsiness are common symptoms (17, 18). Objective findings of CNS excitation include shivering, muscle twitches, and tremors typically seen in the face or distal aspects of the extremities (1). CNS excitation can be quickly followed by CNS depression when LA levels become high enough to inhibit the cerebral cortex’s inhibitory and excitatory pathways (1). CNS depression manifests as respiratory depression that can potentially lead to respiratory arrest and death (1, 5, 17, 18). Higher LA blood concentrations can result in direct cardiac effects.

Toxicity affects the cardiovascular system when LA, primarily marcaine, blocks sodium channels of the fast-conducting Purkinje fibers and ventricular muscle (1). Conduction times are prolonged as evidenced by an increase in PR intervals and duration of QRS complexes (1, 14). Extremely high LA levels can depress the spontaneous pacemaker activity of the sinoatrial node and cause bradycardia and death (1, 17, 18).

Early identification of these symptoms can be made by monitoring pulse oximetry, blood pressure, and electrocardiogram changes. Although recognized by the American Society of Anesthesiologists to be the standard monitoring protocol for all cases undergoing LA, only 69% of anesthesiology departments use these three monitors in cases with peripheral nerve blockade (14). Objective findings are necessary and can be lifesaving, especially since patients in the anesthetized state may not be capable of verbalizing subjective symptoms. In addition to monitoring equipment, it is recommended to also have an oxygen tank, airway equipment, and anti-convulsant medications available for treatment of LA toxicity (1,14). No consensus for optimum management of systemic LA toxicity exists, but the basic principles of cardiopulmonary life support are essential (1, 14).

## TOXIC DOSE LIMITS

Implicit in LA dose recommendations is the duality of needing enough LA to produce neural blockade while not using too much LA as to cause toxicity (16). Recommendations for maximum LA doses have gone unchallenged since human recommendations were originally extrapolated from animal studies over 50 years ago (6). Originally, maximum amounts were recommended as endpoint values: 300 mg of lidocaine plain, 500 mg of lidocaine with epinephrine, 175 mg of marcaine plain, and 225 mg of marcaine with epinephrine (6,17,18). These maximum total doses are still recommended; however, manufacturer package inserts now also include LA dose recommendations that take into consideration patient body mass: 4.5 mg/kg of lidocaine plain, 7 mg/kg of lidocaine with epinephrine, 2.0 mg/kg

<b>A. Toxic Dose = [1/(LA Concentration)] x (Weight-Based Toxic Dose) x (Weight)</b>
<b>B. Toxic Dose of 1% Lidocaine for 175lb Patient = <math>\frac{1\text{ml}}{10\text{mg}} \times \frac{4.5\text{mg}}{1\text{kg}} \times \frac{1\text{kg}}{2.2\text{lb}} \times 175\text{lb} = 35.8\text{ml}</math></b>
<b>C. Toxic Dose of 1% Lidocaine for 175lb Patient = <math>\frac{1\text{ml}}{10\text{mg}} \times \frac{4.5\text{mg}}{1\text{kg}} \times \frac{1\text{kg}}{2.2\text{lb}} \times 175\text{lb} = 35.8\text{ml}</math></b>
<b>D. Toxic Dose of 1% Lidocaine for 175lb Patient = <math>\frac{1\text{ml}}{10\text{mg}} \times \frac{4.5\text{mg}}{1\text{kg}} \times \frac{1\text{kg}}{2.2\text{lb}} \times 175\text{lb} = 35.8\text{ml}</math></b>
<b>E. Toxic Dose of 1% Lidocaine for 175lb Patient = <math>(0.20) \times (175\text{lb}) = 35\text{ml}</math></b>
<b>F. Toxic Dose of 1% Lidocaine for (X)lb Patient = <math>(0.20) \times (X)\text{lb}</math></b>

Figure 1. Local anesthesia weight-based toxic dose calculation and simplification. (A) Weight-based equation to calculate LA toxic dose. (B) Example. Note, LA concentration listed as a percent is in terms of g/100ml and must be converted to mg/ml. For example, for a 1% solution: 1%=10mg/ml. (C) This equation allows for dimensional analysis in which units are canceled via multiplication and the answer is given in desired units. (D) For any toxic dose calculation of a 1% lidocaine solution, the concentration will be 10mg/ml and the weight-based toxic limit will be 4.5mg/kg. The pound to kilogram conversion also remains the same. By reducing all unchanging values into a single constant value (with units of ml/lb), this formula can be simplified as shown in (E). A close approximation is obtained. When calculating weight-based toxic doses, also be mindful of maximum total dose recommendations. Here, the 35ml weight-based dose exceeds the maximum total dose of 300mg of lidocaine plain (30ml). (F) Simplified equation for a 1% lidocaine plain solution.

Table 2

### SIMPLIFIED EQUATIONS FOR LA TOXIC DOSE

It is assumed that weight-based toxic limits are 4.5mg/kg for lidocaine plain, 7mg/kg of lidocaine with epinephrine and 2mg/kg of marcaine plain. Note, these recommended limits may vary depending on country and LA manufacturer. Weight-based recommendations are not offered for marcaine with epinephrine. Manufacturer's recommended total maximum doses are also listed for each LA (300mg of lidocaine plain, 500mg of lidocaine with epinephrine, 175mg of marcaine plain and 225mg of marcaine with epinephrine).

LA	Weight-Based Toxic Dose	Maximum Dose (ml)
2% Lidocaine	$\text{TD}=(0.10)\times(\text{lbs})$	15
2% Lidocaine with Epi	$\text{TD}=(0.16)\times(\text{lbs})$	25
1% Lidocaine	$\text{TD}=(0.20)\times(\text{lbs})$	30
1% Lidocaine with Epi	$\text{TD}=(0.32)\times(\text{lbs})$	50
0.5% Marcaine	$\text{TD}=(0.18)\times(\text{lbs})$	35
0.5% Marcaine with Epi		45
0.25% Marcaine	$\text{TD}=(0.36)\times(\text{lbs})$	70
0.25% Marcaine with Epi		90

of marcaine plain (6, 17, 18). Using these limits and the patient's weight, toxic doses can be calculated for specific LA concentrations (Figure 1). Package inserts do not offer a weight-based toxic limit for marcaine with epinephrine. Assuming a maximum total limit of 225 mg of marcaine with epinephrine, the dose limit is reached with 45 ml of 0.5% marcaine with epinephrine and 90 ml of 0.25% marcaine with epinephrine.

For a given LA concentration (mg/ml), the weight-

based limit in (mg/kg) is known and the only variable remaining in the toxic dose equation is the patient's weight. Known terms can be reduced into a constant value to provide a simplified toxic dose equation for any particular LA. This is demonstrated in Figure 1 and Table 2. Relative toxicities for a specific patient weight can be assessed as demonstrated in Figure 2. Although LA toxic dose calculations should be routinely performed, often times they are not. Simplified equations in Table 2 are offered in

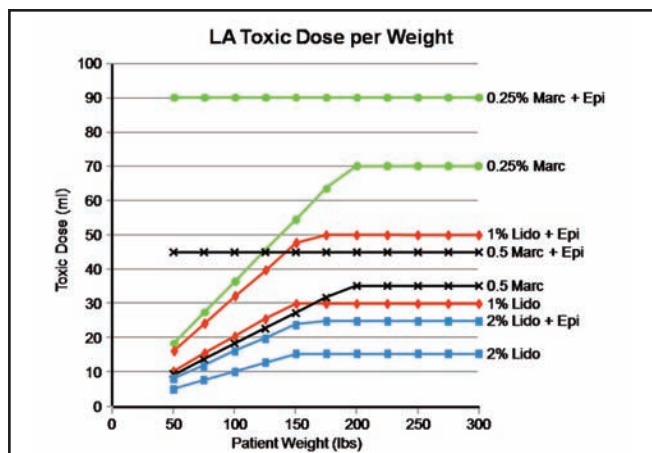


Figure 2. LA-specific display of toxic doses for patients of different weights. Weight-based recommendations are shown for each LA. Manufacturer's recommended maximum total doses are also accounted for. Adjustments for patient age, metabolism, etc. must be made as described.

hopes that an easier and quicker approach to determine toxic limits will aid in potentially preventing LA overdose in our patients.

It is important to note that the manufacturer weight-based limits used in the US are not universal (24). Furthermore, the US Food and Drug Administration and drug manufacturers recognize that recommended LA doses are for normal, healthy adults and these doses serve only as a guide to the amount of anesthetic required for most routine procedures (17, 18). It cannot be assumed that recommended doses are exact limits for all patients undergoing any procedure. The vague recommendations do not specify how long to wait before additional LA can be infiltrated. In general, a second dose of LA can usually be safely injected after two drug half lives (6, 25).

## MANY FACTORS OF TOXICITY

Toxicity limits cannot be accurately determined solely on drug concentration, LA manufacturer's weight-based recommendations and patient weight. The vascularity and composition of the site of infiltration, patient's age and metabolism must be considered (6, 16-19). Systemic LA absorption depends on the vascularity of the area being injected and the amount of adipose in surrounding tissues (6). Studies demonstrate that the same systemic concentrations of lidocaine are achieved following a 300 mg intercostal nerve block, 500 mg epidural block, 600 mg brachial plexus block and 1,000 mg subcutaneous leg infiltration (6,24). More accurate toxicity recommendations would account for the high variability of LA absorption at different sites of infiltration (16).

Metabolic factors should also be accounted for on a patient-specific basis. For a single infiltration of LA, toxic doses are not significantly altered for patients with deficient

hepatic metabolism or renal clearance (6). A 10-20% LA dose reduction is recommended in patients with renal dysfunction (6). Patients with mild hepatic dysfunction have almost no alteration in LA clearance; however, a 10-50% LA dose reduction is recommended in patients with severe liver dysfunction (6). Heart failure patients with reduced liver and kidney perfusion should also have a reduced LA dose. Patients who are very young, old, or pregnant are more susceptible to LA toxicity due to reduced LA protein binding (1,17). General anesthesia may alter LA elimination, prolonging LA effects and can contribute to toxicity (19). Copeland et al report that LA blood concentrations are twice as high in patients under general anesthesia than in a conscious state (16).

## LA MIXTURES AND TOXICITY

The majority of podiatric surgeons routinely infiltrate a mixture of lidocaine and marcaine to take advantage of a quick-acting and long-lasting anesthesia (Table 1). However, there are no manufacturer or evidence-based guidelines that safely predict toxicity of LA mixtures in humans (3, 20, 25, 26). Animal research, studying various LA agents and mixtures, provides conflicting results and suggests that LA mixtures can have synergistic, additive, invariable, or antagonistic toxic effects (21). A rat study described mixtures of lidocaine and marcaine to have an additive toxic effect (7). Lidocaine and marcaine mixtures are also believed to have additive toxicity in humans (6, 7, 23, 28). This means that a LA mixture will have the same toxicity as the more toxic agent. Further research is necessary to better understand the multifactorial concept of toxicity and predict toxic doses of LA mixtures in humans (25, 26).

## SUMMARY

Chemical properties of LA agents determine onset of action, duration and safety profiles. Although LA toxicity is rare, close monitoring and identification of the signs and symptoms of LA toxicity are necessary for initiation of treatment. Prevention of LA toxicity is paramount. Podiatrists should use the lowest effective LA concentrations and lowest effective doses. Toxic limits should be considered on a patient-specific, block-specific and site-specific basis. Simplified weight-based LA toxic dose formulas have been presented to provide an easier and faster approach for calculating toxic limits. A weight-based LA toxicity dose calculator is also available on the Podiatry Institute website. However, further research with anesthesiologist-pharmacologist collaboration is needed to better understand the multifactorial concept of LA toxicity in humans. Until then, LA toxic dose recommendations will remain vague.

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