

3 Continuing Dental Education Credits

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HOW TO USE LOCAL ANESTHETICS AT THEIR MAXIMUM EFFECTIVENESS; WITH SPECIAL EMPHASIS ON ARTICAININE

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The Academy of Dental Therapeutics and Stomatology
Continuing Dental Education Series

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EDUCATIONAL OBJECTIVES

- Upon completion of this course you will:
- * Have a better understanding of the history of anesthetics.
 - * Have a better understanding of the mechanism of action of anesthetics.
 - * Be able to maximize the effectiveness of anesthetics using the chemical properties.
 - * Review the pharmacokinetics of anesthetics.
 - * Review how many anesthetic cartridges to use during an office visit.
 - * Discuss the newest anesthetic launched in the United States: Articaine.

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Local Anesthetics

are fascinating compounds. Dentists rely on their ability to allow treatment to be performed painlessly. It is obvious that without these wonderful drugs, people would be less likely to attend a dental visit. A survey study done in Ontario, Canada in 1995 indicated that, on average, each dentist gave around 1750 injections in that year¹. Doing something so many times, over and over, allows one to become an expert. However, expertise may harbor the danger of complacency. Because local anesthetics are so effective at providing anesthesia and because dentists use them in such a repetitive fashion with rarely a complication, there is the potential to use them as if they were water.

If one takes a careful look at the actual success rates of profound anesthesia, they are anything but 100%. Any dentist will admit to the difficulty of anesthetizing a “hot” tooth. Also, it is widely accepted that the ability to obtain profound and complete anesthesia in the hemimandible using a conventional mandibular nerve block is only around 85%. Despite these universal problems, very close to 100% success in obtaining profound local anesthesia is possible.

A sound knowledge of anatomy, the ability to use accessory techniques, and an understanding the pharmacology of local anesthetics are necessary in order to be most proficient at achieving reliable anesthesia. This course will focus on the pharmacology of local anesthetics and how to use the pharmacological characteristics to maximize anesthesia. In addition, we will take a careful look at a local anesthetic that has just been introduced into the American marketplace—that is articaine.

HISTORY

The first local anesthetic discovered was cocaine. It was initially isolated by Niemann who observed that it caused numbness in his tongue. He wrote, “it benumbs the nerves of the tongue, depriving it of feeling and taste”². In 1880, Von Anrep discovered that when cocaine was injected into his finger, it became insensitive to a pinprick. This led him to suggest that cocaine be used as a local anesthetic. The first clinical use of cocaine was by Sigmund Freud and Karl Kollar in 1884. While using cocaine to wean a patient from a morphine addiction, they also recognized cocaine’s anesthetizing ability. Kollar then introduced cocaine to the practice of surgical ophthalmology as an anesthetic agent. Finally, also in 1884, Hall first used cocaine as an injectable anesthetic in dentistry.

In 1905, the first synthetic local anesthetic, procaine, was formulated. Procaine (generically known as Novocain is classified as an ester, and as a result, has some undesirable properties compared to the amide type local anesthetics that dentists use today. Esters have the potential for increased allergenicity, have a longer onset of action, a shorter duration of action, and are less potent as compared to amides. This is why, in the mid 1940’s, the synthesis of the first amide local anesthetic, lidocaine, was such an important step towards better local anesthesia. In fact, lidocaine was so highly regarded in the 1940’s and 50’s and its enhanced properties were so universally recognized that the use of nitrous oxide decreased tremendously due the vast improvement in pain control.

Over the next 30 years, a number of other amide local anesthetics were synthesized with no major difference in clinical action when compared to the standard lidocaine. The only real advancement was that the synthesis of mepivacaine and prilocaine allowed for the first time the ability to use a local anesthetic without a vasoconstrictor. Lidocaine is too great a vasodilator on its own to be used as a “plain” local anesthetic. The same holds true for articaine. It would vasodilate the vasculature in the area of injection enough to be largely taken up into the blood stream, rendering itself ineffective and more toxic. Mepivacaine and prilocaine do not vasodilate to the same degree as lidocaine and as such can be used without a vasoconstrictor. This is of obvious advantage for cardiac patients who do not require quick procedures. However, the ability to use a plain solution has huge pharmacological advantages in areas of infection and in areas where large volumes of

anesthetic have been injected. This will be discussed later.

In 1973, a new local anesthetic, articaine, was introduced in Germany and Switzerland and over the course of 12 years became the most widely used local anesthetic in dentistry in a number of European countries and in Canada. The companies manufacturing articaine claim that it has enhanced local anesthetic properties as do many of the dentists who have converted to this product. This issue will also be addressed later in this course.

STRUCTURE

Local anesthetics are all weak bases, classified as tertiary amines. They have three structures in common: an aromatic group, an intermediate chain, and an amine. Each of these components is responsible for different properties and local anesthetics differ according to the variability of these components. The aromatic portion allows for lipid solubility, that is, for the penetration of barriers such as the nerve membrane. The amino terminal contributes water solubility thus allowing the solution to remain in the nerve cell. The intermediate chain differentiates an anesthetic as an ester or an amide as well as creating a physical space between the lipophilic and hydrophilic ends, allowing each to exhibit a distinctive role³.

pK_a of Local Anesthetics

	pK _a	% RN at pH 7.4	Approx. onset in min.
Mepivacaine	7.6	40	2 to 4
Etidocaine	7.7	33	2 to 4
Articaine	7.8	29	2 to 4
Lidocaine	7.9	25	2 to 4
Prilocaine	7.9	25	2 to 4
Bupivacaine	8.1	18	5 to 8
Procaine	9.1	2	14 to 18

Figure 1: Dissociation constants (pKa) of local anesthetics related to onset of action.

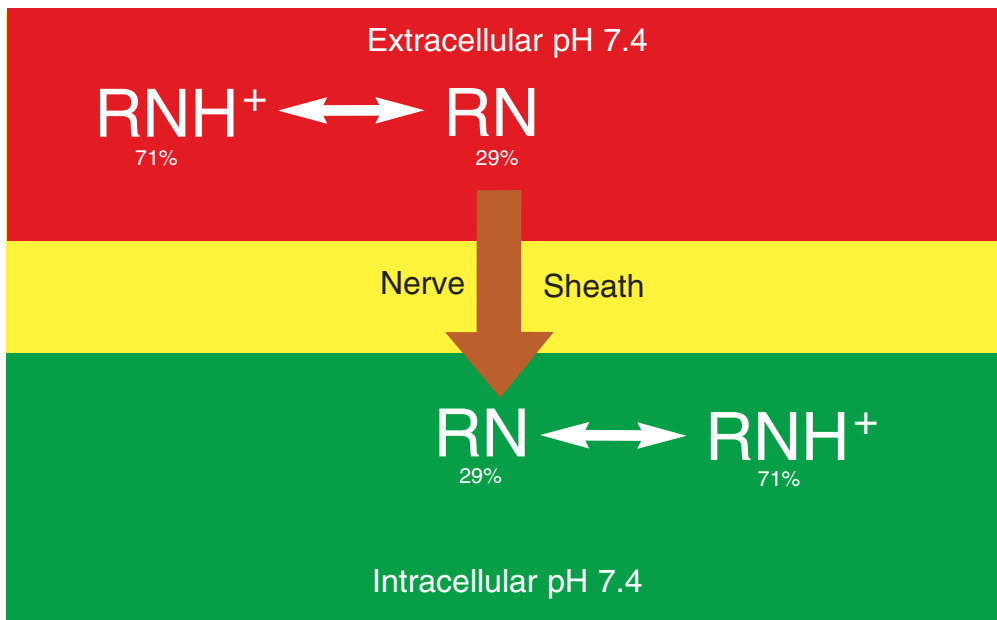


Figure 2: The mechanism of action for local anesthetic molecules with pKa of 7.8. 29% of lipophilic RN molecules are available to cross the nerve membrane and once inside, where the pH is still 7.4, the RN molecules re-equilibrate to the original 71% - 29% ratio⁷.

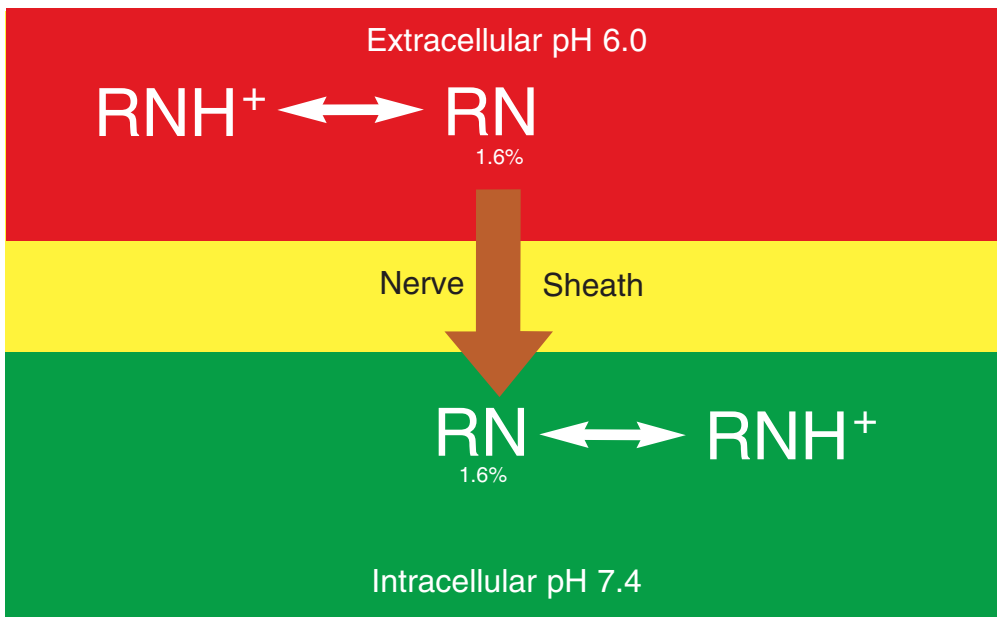


Figure 3: The pKa of the local anesthetic is still 7.8 as in Figure 2, but in this case, the tissue pH is 6. As a result, the relative proportion of cation to base is 98.4% to 1.6%. There is relatively less base available to cross into the nerve. As a result, there is significantly less cation available intracellularly to exert the desired effect of local anesthesia⁷.

MECHANISM OF ACTION

It is well known that local anesthetics block nerve conduction when administered close to a nerve. They can act on any nerve fiber and cause sensory and motor paralysis to the innervated

area. Their action is totally reversible, leaving no structural damage to nerve tissue or surrounding structures. The question is - how do they do this?

Just prior to a normal action potential within a nerve fiber, one of the major changes that occur is an influx of positively charged sodium ions from the interstitial surroundings. This influx

raises the electrical charge inside the nerve and if this increase in electrical charge is sufficient enough to reach a critical threshold level, a self-propagating action potential will occur along the whole length of an intact nerve. The primary effect of local anesthetics is to block the nerve action potential by decreasing the permeability of the nerve membrane to sodium ions. This disallows the influx of sodium ions into the cell thereby creating a negatively charged environment intracellularly in relation to the extracellular fluid. The exact mechanism of this has not yet been definitively proven; however, there are several theories.

The most accepted theory, the so-called specific receptor theory, postulates that local anesthetics bind to specific receptor sites on or within the sodium channels, thereby altering the configuration of the channel. This new configuration does not allow the passage of sodium ions into the cell^{4,5}. A second theory, the membrane fluidization theory, suggests that local anesthetics become engaged within the cell membrane, thereby changing the cell membrane's organization. This in turn reduces the compressibility exerted on the sodium channel by the cell membrane, thus not allowing the channel to open⁶. In both theories, no action potential is possible.

USING CHEMISTRY TO MAXIMIZE EFFECTIVENESS:

The synthetic preparation of a local anesthetic as a weak base is not stable in air and poorly soluble in water. It is therefore combined with an acid to form a salt, HCl, which is hydrophilic and now stable. This salt is dissolved in sterile water or saline and in this form, the solution is stable and injectable.

The pH of both the solution and the tissue results in a clinical effect. The salt within the local anesthetic solution exists simultaneously in two forms: uncharged base molecules (RN) and positively charged cation) molecules (RNH⁺).



The pH of the local anesthetic and the tissue determines the relative proportion of base to cation molecules. For example, at low tissue or anesthetic pH (i.e. many H⁺ ions present and therefore more acidic) the above equation shifts to the left. This means that there will be more cation molecules present. This is an undesirable situation noted by the equation.



At a higher tissue or anesthetic pH (i.e. less H⁺ ions and therefore more basic), the formula shifts to the right. In this case there are more basic molecules present. This is an advantageous situation.



The ratio of base to cation also depends on the dissociation constant, or pKa, of the local anesthetic. The pKa of a solution is the pH at which half of the molecules exist in the cation form and half exist in the base form. This matters because having different proportions of these two entities will allow the local anesthetic to be more or less effective. It is most advantageous to have as many base (RN) molecules present when the local anesthetic is initially injected into the tissue because it is this molecule that carries lipid solubility and therefore the ability to cross the nerve membrane. The percentage of cation to base can be determined by the Henderson-Hasselbalch equation:

$$\log_{10} \frac{[\text{base}]}{[\text{acid}]} = \text{pH} - \text{pK}_a$$

That is, the log of the ratio for concentration of base (RN) to the concentration of the acid (RNH⁺) for a given local anesthetic is equal to the pH of the tissue being injected, minus the pKa of the particular local anesthetic.

Let's look at this according to realistic situations and see how the proportion of base to cation changes according to tissue pH and local

anesthetic pKa.

If both the pH of the tissue and the pKa of the local anesthetic were to be 7.4 (normal tissue pH), the inverse log of zero (7.4 minus 7.4) is one. This means that the amount of base equals the amount of acid. This would be an excellent local anesthetic since there would be an initial high proportion of base molecules present and able to cross the lipid nerve membrane. Unfortunately, all local anesthetics have pKa values above 7.4 (Figure 1). If the pH of the tissue remains at 7.4 but the pKa of the local anesthetic is 7.8 (as is the case for articaine) then the inverse log of -0.4 equates to 0.398. This means that for every 39.8 molecules of base, there are 100 molecules of acid. Therefore, out of 139.8 molecules in total, 29% are base and 71% are acid (Figure 2). Finally, if the tissue pH remains at 7.4 but this time the pKa of the local anesthetic is 8.1 (as is the case for bupivacaine) then the inverse log of -0.7 equals 0.20. That is for every 20 molecules of base, there are 100 molecules of acid. Therefore, out of 120 total molecules, 17% are base and 83% are acid.

Let us look again at why these ratios matter. The base, or RN portion of the equilibrium is responsible for diffusion of the local anesthetic through the lipid barrier of the nerve cell membrane. Local anesthetic solutions with a lower pKa value, and thus more molecules in the RN form, tend to diffuse through the lipid wall faster and therefore have a faster onset of action. Therefore, in the above example, and in a perfect world, bupivacaine will have a longer onset of action than articaine since it has relatively less RN available initially. Simply put, the more molecules that are available in the RN form, the more effectively the local anesthetic is able to permeate through the cell membrane (29% versus 17% in the above two examples). The remaining local anesthetic on the outside of the cell reorganizes its equilibrium such that 29% or 17% (as in the above examples) of these leftover molecules become RN and they then diffuse intracellularly. This process continues until there is no more local anesthetic solution left outside the

nerve or until it is taken up by the vasculature (Figure 2).

The pH inside the nerve is 7.4. Once intracellular, the RN form reorganizes itself into equilibrium according to its pKa. So in our above example, 29% or 17% will exist as RN and 71% or 83% will exist as RNH⁺. It is this component, the RNH⁺, that is responsible for "binding" to the receptor site and thereby blocking the influx of sodium into the nerve, thus inhibiting the action potential. Again in this example, articaine has a lower pKa than bupivacaine and so has more molecules to cross the nerve membrane and therefore has a faster onset of action.

Why then does one experience poor local anesthesia if the solution is injected into infected or inflamed tissue? The pH of infected or inflamed tissue could be as low as 5.0 to 6.0. The lower pH of the tissue causes the equilibrium to shift away from the RN side of the equilibrium and so there are less available RN molecules to initially diffuse into the nerve. Once inside the nerve (where the pH will remain stable at 7.4) there are fewer RN molecules available to re-equilibrate and so there are also fewer RNH⁺ molecules on hand to bind to the receptor sites. With the local anesthetic not diffusing into the nerve, it is instead taken up by blood vessels, which to make matters worse, are dilated in this situation. This may be encountered when one attempts to anesthetize a tooth with a periapical infection (Figure 3).

This phenomenon may also occur during what may be termed as an iatrogenic lowering of the tissue pH or the "sterile abscess theory"⁸. In solution, the most common local anesthetics have a pH in the acidic range. Despite the body's tissue buffering capacity (making an acidic compound more neutral) the deposition of an excess amount of acidic local anesthetic into a confined zone could potentially render the local anesthetic ineffective, for example during repeated mandibular blocks.

Another factor that relates to successful chemical delivery of local anesthetic is the addition of a vasoconstrictor. Solutions that do not contain vasoconstrictors have a pH

MAXIMUM DOSES

	Max. Dose mg/kg	Max. Dose mg
Articaine	7.0	500
Mepivacaine	6.6(4.5)	400(300)
Etidocaine	8.0	400
Lidocaine	7.0* (4.4)	500(300)
Prilocaine	8.0(6.0)	600(400)
Bupivacaine	1.3 ⁺	90

Figure 4: Dosages given are for healthy adults taken from officially approved product information⁹⁻¹¹. Values in parentheses are more conservative values^{5,7}. Note that all cartridges contain 1.8 ml of solution except articaine cartridges, which contain 1.7 ml.

*with vasoconstrictor

+ from Malamed, S.F. Handbook of Local Anesthesia, 2nd Ed.

buffered to between 5.0 to 7.0. When vasoconstrictors are added to local anesthetic cartridges, they must be acidified with a preservative to avoid oxidation and thereby becoming ineffective. Sodium metabisulphite is an example of a preservative used to avoid this oxidation process. However, the addition of this preservative lowers the pH of the local anesthetic solution to a range of 3.8 to 5.0 as is the case for lidocaine with 1:100,000 epinephrine. A lower pH means that it will take the body's extracellular fluid longer to buffer the solution. This lower pH shifts the initial equilibrium away from the lipid soluble molecule and there are therefore less of these lipid-soluble molecules available initially to exert an effect.

Therefore in areas of infection or inflammation, one might consider using a solution with the lowest pKa and without any vasoconstrictor (e.g. mepivacaine). One may also consider the following: After two attempts at a mandibular block with a local anesthetic containing vasoconstrictor, if the dentist still requires more anesthetic to achieve anesthesia, he/she should

switch to a "plain" solution. This will help to minimize the acidity in the pterygomandibular triangle and thus maximize the amount of lipid-soluble RN molecules. This will greatly increase the chance of obtaining the block after two or three failed attempts.

Consider the duration of action of local anesthetics. This is partially dependent on the protein binding of the drug. Agents that bind strongly will have a longer duration of action as compared to those that do not bind as firmly. For example, bupivacaine is more protein

Local Anesthetic Half-Lives	
Local Anesthetic	Half-Life(min)
Articaine	20
Prilocaine	90
Lidocaine	90
Mepivacaine	115
Etidocaine	155
Bupivacaine	210

Figure 5: The biological half-life of local anesthetics.

bound than lidocaine and therefore will have a longer effect. Other factors that affect duration are the vascularity of the tissue and the amount of vasoconstrictor in the solution. In general, decreased vascularity and increased vasoconstrictor will increase the duration of anesthesia.

PHARMACOKINETICS

As with any drug injected into the body, local anesthetics are distributed according to various biological factors. Once absorbed into the blood stream, they are transported throughout the body and exert specific effects. First, let us examine the fate of local anesthetics themselves.

The amount of local anesthetic that is initially absorbed into the blood stream is dependent on two factors as mentioned above: the amount of vasoconstrictor in the solution and the perfusion of the tissues. Increased vasoconstrictor and poorly perfused tissue will allow lower concentrations of local anesthetic into the blood and hence decrease toxicity. However, the opposite is also true. That is that no vasoconstrictor and well perfused tissues may contribute to increased local anesthetic toxicity.

Once inside the circulatory system, levels of anesthetic depend on the rate of distribution to other tissues and the elimination or metabolism of the agent through excretory processes. The half-life, or time required to remove 50% of the drug from the blood, varies between 70 to 120 minutes depending on the local anesthetic⁷. Articaine is an exception to this as it has a half-life of approximately 20 minutes (this will be explored later on in this course).

The location of metabolism for local anesthetics depends on the type of solution. Ester local anesthetics are biotransformed in the plasma by an enzyme called pseudocholinesterase. Patients with atypical pseudocholinesterase (1 in 3,000 people)⁵ should not be given ester type anesthetics since their LD50 (lethal dose for 50% of the population) will be much lower. This

Toxicity: Lidocaine vs. Articaine

	Lidocaine 1.8 ml	Articaine 1.7 ml
% Solution	2	4
mg/ml	20	40
mg of drug per cartridge	$1.8 \text{ ml} \times 20 \text{ mg/ml} = 36 \text{ mg}$	$1.7 \text{ ml} \times 40 \text{ mg/ml} = 68 \text{ mg}$
Maximum dose	500 mg	500 mg
# of cartridges allowed	$\frac{500 \text{ mg}}{36 \text{ mg}} = 13.8$	$\frac{500 \text{ mg}}{68 \text{ mg}} = 7.3$

Figure 6: Values are for a healthy 70-kg adult and do not take into account the toxicity of the vasoconstrictor.

Figure 6: The number of cartridges tolerated before the maximum dose is reached for the average 70-kg (154 lb) adult comparing 2% lidocaine with 4% articaine, both with epinephrine.

is yet another downfall for the ester local anesthetics. Amide type agents are mainly metabolized by the liver microsomal enzyme system. Therefore, patients with decreased liver function (e.g. chronic alcoholism, hepatitis, or other liver ailments) will have a lower threshold for toxicity. All local anesthetics are excreted through the kidney and so renal disease is another potential contributor to local anesthetic toxicity. The metabolism of articaine is different from other amides. This will be discussed in more detail later.

These agents have various systemic effects, all dose dependent. In the central nervous system, local anesthetics easily cross the blood brain barrier. At low concentrations, these drugs act as anticonvulsants and have a depressant type of action. However, at higher toxic levels, these solutions can cause tonic-clonic seizures. Initial signs and symptoms of CNS toxicity include slurred speech, shivering and twitching, warm flushed feeling, lightheadedness, visual and/or auditory impairment, pleasant sleepy feeling, or, in some people, apprehension⁵.

The cardiovascular system is affected in a variety of ways. In the surrounding venostructure, these agents are mostly vasodilatory. On the myocardium, local anesthetics also carry a

depressant action. The electrical excitability, the conduction rate and the force of contraction of the heart muscle are all decreased. This is why lidocaine is such an important drug in the treatment of some cardiac emergencies. As a result of peripheral vasodilation and decreased myocardial action, the overall effect of local anesthetics is hypotension. This however is clinically not significant when recommended doses are used in dentistry.

Patient factors that affect the dose of local anesthetics are: age (the elderly may have decreased liver, renal and protein-binding functions, thereby increasing potential toxicity), weight, and liver or kidney pathology. Drug factors include the rate of injection, vascularity of the site, the use of a vasoconstrictor, and the concentration of the local anesthetic used.

HOW MANY CARTRIDGES CAN BE USED

Local anesthetics are manufactured in concentrations between 0.5 to 4%. The maximum dose for these drugs is somewhere between 70 mg to 500 mg, depending on the age and health of the patient and on the type of solution used (Figure 4). Simple arithmetic can be used to calculate the number of cartridges

that it would take to reach the maximum toxic dose. For example, let's use a 2% solution of lidocaine with a maximum safe amount of 300 mg of drug for an average, healthy, 70-kg adult. One cartridge contains 1.8 ml of solution, and at 2% this means that there are 0.036 g or 36 mg of local anesthetic per cartridge. This would allow for 8.3 cartridges to be used in order to stay below a toxic level for this particular patient.

The maximum dose for lidocaine could be considered as 2.0 mg/lb or 4.4 mg/kg. Some literature quotes a more liberal dose range maximum of 7.0 mg/kg for lidocaine (Figure 4). This however should act only as a guideline since other factors such as rate of absorption, tissue conditions, human variability, absorption, pediatric and geriatric age groups must be considered.

ARTICAINE

In April 2000, the Food and Drug Administration approved articaine for use in the United States. Articaine is a 4% solution and has an epinephrine concentration of 1:100,000. The formulation that contains 1:200,000 epinephrine, which is available in Canada and many European countries, has yet to be approved in the U.S.

Articaine was initially synthesized in Germany in 1969. They called the drug carticaine and in 1976, the name was changed to articaine when it was approved for use in dentistry for the first time in Germany and Switzerland¹². Health Canada approved articaine in 1983, and in the United Kingdom, articaine was approved in 1998.

The reason that it took so long for articaine to be approved in the United States has mostly to do with a preservative called methylparaben. This antibacterial, antioxidant and antifungal used to be included in all dental local anesthetic cartridges. It however served no purpose in dental cartridges since they are single-use products. Methylparaben does serve an important function in multi-use vials of local anesthetic as is used in medicine. In the mid 1980's the FDA

reported that all dental local anesthetics must have methylparaben removed due to its relatively high allergenicity and its uselessness in this realm. Following this mandate, all dental cartridges had methylparaben removed except Ultracaine, manufactured by Hoechst, which at that time was the only formulation of articaine available. This drug was not sold in the U.S. and therefore the German company did not have to comply with FDA requests. Finally in the mid 1990's Septodont Inc. based in France, decided to seek approval for articaine in the U.S. and in doing so, removed methylparaben from their articaine formulation. Septodont's articaine is called Septocaine(in the United States and Septanest(in Canada. The rigorous approval process began in 1995 and was granted in April 2000.

THE PHARMACOLOGY OF ARTICAININE

Articaine differs from other amide local anesthetics because it is derived from thiophene. It therefore does not contain a benzene ring like the other amide local anesthetics, but instead, has a thiophene ring. This allows for increased lipid solubility and therefore a better ability to cross lipid barriers such the nerve membrane. It has been suggested that it is this mechanism that accounts in part for the possible enhanced action of articaine when compared to other local anesthetics.

A second molecular difference between articaine and other amide local anesthetics is that articaine has an extra ester linkage. This causes articaine to be hydrolyzed by plasma esterase. In fact, 90-95% of articaine is metabolized in the blood; the liver breaks down only 5-10%. The major metabolite of articaine is articainic acid. It is unclear how much activity, if any, this biproduct has.

In a study by Van Oss et al, one subject was given articainic acid intravenously and no change was found in electroencephalography, electrocardiography, blood pressure, or heart rate¹³. The question regarding

articainic acid's activity is important since an active metabolite may affect toxicity and may exert undesirable side effects. Lidocaine, in comparison, has active metabolites. Only cautious conclusions can be drawn from this because Van Oss reported results from only one study subject. In fact, current research may suggest that articaine's metabolite will have some biological activity.

Articaine is excreted by the kidneys, 2 to 5% unchanged, 40 to 70% as articainic acid, and 4 to 15% as articainic acid glucuronide, which appears to be inactive¹⁴.

The half-life of articaine is approximately 20 minutes¹⁵ as compared to lidocaine, which is in the 90-minute range. Articaine's shorter half-life is due to the fact that it is primarily metabolized by plasma esterases. As other amides are metabolized by the liver, which is a much longer process, their resultant half-life is longer (Figure 5).

The comparatively rapid metabolism of articaine indicates that articaine may be a safer drug to re-inject later on during a dental visit. This would be especially true if articaine's metabolites were found to be inactive or even only slightly active. For example if after 30 minutes have elapsed since the initial injection of articaine and the operator deems it necessary to inject more articaine, he/she can do so knowing that at least half of the initial dose will have been metabolized. This lowers the risk of toxicity. If this same injection sequence is done using a different local anesthetic, the dentist will be directly adding to the initial dose since all other local anesthetics have half-lives longer than 30 minutes.

Despite the short half-life, the clinician must be aware of one very important fact. Articaine is a 4% solution with a toxic dose of 7 mg/kg for the average healthy adult. (In Canada, there is a separate pediatric maximum dose of 5 mg/kg the rationale of which will be explored later.) The dentist must know how to convert these numbers to realize the maximum number of cartridges allowed. Since lidocaine has the same

maximum dose of 7 mg/kg but is only a 2% solution as opposed to a 4% solution, the average patient will tolerate approximately twice as much lidocaine as compared to articaine before the maximum dose is reached (Figure 6).

PRECAUTIONS AND CONTRAINDICATIONS

Articaine, the vasoconstrictor and the vasoconstrictor preservative (sodium metabisulphite), has the same precautions and contraindications as those that occur for all other amide local anesthetics. One additional caution for articaine is that, like prilocaine, a very high dose may cause methemoglobinemia. When used in the range of maximum dosages for dentistry, this side effect is highly unlikely. In fact, no cases of methemoglobinemia have been reported following the use of articaine within recommended dosages for dental local anesthesia.

Although articaine is not recommended for children under the age of 4 years¹⁶, studies have shown that articaine is likely safe for children under 4 years^{17,18}. In the first study, Jakobs et al looked at serum concentrations of articaine at different time intervals for children 3 to 12 years and showed that pharmacologically, articaine acts very similarly for these children as compared to adults. In the second paper cited, Wright et al administered articaine to 211 children aged 12 to 48 months and did not observe any adverse effects. Jakobs therefore recommended that there is no need to have a lower mg/kg dose limit for children as is the case in Canada where 7 mg/kg is the maximum dose for adults and 5 mg/kg is the maximum for children. This is why in the U.S. there is only the 7 mg/kg dose limit for both children and adults. However the dentist must be aware that if treating a small child, for example one who weighs in the 15-kg or 30-lb range, the maximum dose can be reached with less than two cartridges of 4% articaine.

A final precaution with respect to articaine also applies to prilocaine. Both are 4% solutions. Haas et al published a 21-year retrospective study showing that there was a significantly higher risk of

causing a parasthesia following a mandibular block when a 4% solution was used. In 1993 in Ontario, Canada, 14 cases were out of an estimated 11,000,000 injections given by dentists in that year. This translates to 1 in 785,714 injections¹⁹.

IS ARTICAINA BETTER THAN OTHER LOCAL ANESTHETICS?

Articaine has become the most widely used local anesthetic in just about every country that it has been introduced into. Many studies have demonstrated that articaine is an effective local anesthetic. In scientific controlled studies, articaine performed as well as any local anesthetic it was compared to. Most interesting, is whether or not the scientific literature confirms the belief that articaine is a more effective local anesthetic. Many dentists who use articaine claim that it is a more effective drug. For example some believe that an infiltration of articaine around mandibular premolars will provide profound anesthesia of these teeth. The scientific literature is quite uniform in its results with respect to articaine action compared to other local anesthetics. No study has significantly shown articaine to be a better local anesthetic²⁰⁻²⁷. However despite the lack of significant differences, each of the papers cited do show articaine to slightly (but again not scientifically significant) outperform the local anesthetics that it is compared to.

CONCLUSION:

There is a wide range of local anesthetics for dentists to choose from. Different percent solutions, different vasoconstrictor concentrations and different products can be utilized to maximize the effectiveness of local anesthesia. This course has attempted to highlight these differences as well as to show when and how to apply them. Also, the characteristics of articaine, the new local anesthetic in the American marketplace, have been described. With this knowledge at hand, the reader can decide if it is worth giving this product a try in their offices.

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Continuing Education Questions:

1. Dentists give, on average, how many injections per year?

- a) 750
- b) 1000
- c) 1500
- d) 1750

2. Conventional mandibular block anesthesia has which of the following success rates?

- a) 100%
- b) 85%
- c) 80%
- d) 75%

3. The first local anesthesia discovered was

- a) Lidocaine
- b) Procaine
- c) Novocain
- d) Cocaine

4. The first use of a local anesthetic in medicine was for the practice of?

- a) Dentistry
- b) Obstetrics
- c) Ophthalmology
- d) General surgery

5. A local anesthetic was first used in dentistry in which year?

- a) 1776
- b) 1884
- c) 1904
- d) 1910

6. Which of the following is not an undesirable property of an ester local anesthetic?

- a) **Increased allergenicity**
- b) **Longer onset of action**
- c) **Longer duration of action**
- d) **Poor lipid solubility**

7. Lidocaine and articaine are not available as non-vasoconstrictor containing solutions because?

- a) **They would burn too much when injected**
- b) **They are potent vasodilators and are therefore taken up into the vasculature that they are ineffective anesthetics**
- c) **It is not possible to synthesize these local anesthetics without a vasoconstrictor**
- d) **They would not be able to cross the nerve membrane without the vasoconstrictor**

8. Local anesthetics are all classified as:

- a) **Weak bases**
- b) **Strong bases**
- c) **Weak acids**
- d) **Strong acids**

9. Which of the following is not a structural component common to all amide local anesthetics?

- a) **Aromatic group**
- b) **Terminal amine**
- c) **Intermediate chain**
- d) **Benzene ring**

10. The major mechanism by which local anesthetics block an action potential is to?

- a) **Block the influx of sodium ions**
- b) **Block to efflux of sodium ions**
- c) **Block the influx of potassium ions**
- d) **Block the efflux of potassium ions**

11. The most likely method by which local anesthetics block the movement of ions across the nerve membrane is to?

- a) **Alter the configuration of the ion channel**
- b) **Repel the ion electrically**
- c) **Physically blocks the channel**
- d) **Stimulate the release of a repellent**

12. Local anesthetics are more lipid soluble in which environment?

- a) **Salt**
- b) **pH < 7.4**
- c) **pH > 7.4**
- d) **pH = 7.4**

13. The higher the pKa of the local anesthetic:

- a) **The shorter its onset of action**
- b) **The longer its onset of action**
- c) **pKa does not affect onset**

14. In areas of infection, in order to obtain maximum anesthesia, the dentist should use which type of local anesthetic?

- a) **One without a vasoconstrictor**
- b) **One with 1:200,000 epinephrine**
- c) **One with 1:100,000 epinephrine**
- d) **One with 1:50,000 epinephrine**

15. Local anesthetics with a vasoconstrictor must have which of the following?

- a) **A preservative such as sodium metabisulphite**
- b) **A salt**
- c) **Methylparaben**
- d) **Sterile water**

16. Which of the following affect the duration of local anesthesia?

- a) **The vascularity of the tissue**
- b) **The degree of protein binding capable by the local anesthetic**
- c) **The amount of vasoconstrictor in the local anesthetic**
- d) **All of the above**

17. Local anesthetics are metabolized :

- a) **In the liver by pseudocholinesterase**
- b) **In the liver by microsomal enzymes**
- c) **In the blood by microsomal enzymes**
- d) **In the kidneys by pseudocholinesterase**

18. Which of the following is not an initial sign of local anesthetic toxicity?

- a) **Slurred speech**
- b) **Sleepy feeling**
- c) **Metallic taste**
- d) **Coma**

19. If a dentist is using a 1.8-ml cartridge of a 3% solution that has a maximum dose of 300 mg, how many cartridges can the dentist use before the maximum dose is reached?

- a) **10**
- b) **7.5**
- c) **5.5**
- d) **4.5**

20. Which of the following is true regarding the local anesthetic drug?

- a) **It is more toxic with the addition of a vasoconstrictor**
- b) **It is less toxic with the addition of a vasoconstrictor**

21. Articaine was first used for dentistry:

- a) **In 1976 in Germany**
- b) **In 1976 in Canada**
- c) **In 1983 in Germany**
- d) **In 1983 in Canada**

22. Articaine differs chemically from all other amide local anesthetics because:

- a) **It has a benzene ring and one less ester linkage**
- b) **It has a thiophene ring and one less ester linkage**
- c) **It has a benzene ring and one more ester linkage**
- d) **It has a thiophene ring and one more ester linkage**

23. Articaine has a:

- a) **Shorter half-life than other local anesthetics**
- b) **Longer half-life than other local anesthetics**
- c) **An equivalent half-life to other local anesthetics**

24. Articaine is a

- a) **1% solution**
- b) **2% solution**
- c) **3% solution**
- d) **4% solution**

25. Which of the following are possible advantages of articaine?

- a) **A shorter half-life**
- b) **Increased lipid solubility**
- c) **Increased ability to cross the nerve membrane**
- d) **All of the above**

26. In the United States, articaine has a vasoconstrictor concentration of :

- a) **1:50,000**
- b) **1:100,000**
- c) **1:200,000**
- d) **No vasoconstrictor**

27. Articaine has a maximum dose of:

- a) **7 mg/kg**
- b) **10 mg/kg**
- c) **5 mg/kg**
- d) **6 mg/kg**

28. Knowing the maximum dose, if a dentist was treating a 15-kg child, how many cartridges would be needed to reach the maximum dose?

- a) **2.1**
- b) **1.5**
- c) **3.0**
- d) **2.5**

29. Which of the following is true regarding possible side effects of articaine?

- a) **There is no document of a dental dose of articaine causing methemoglobinemia**
- b) **One study showed articaine and prilocaine to have an incidence of approximately 1:750,000 injections causing lip or tongue paresthesia**
- c) **Because of articaine's short half-life, it may be safer to re-inject later on during a dental procedure**
- d) **All of the above**

30. Which of the following is false regarding articaine?

- a) **A dental cartridge of articaine contains methylparaben**
- b) **A dental cartridge of articaine contains sodium metabisulphite**
- c) **It is manufactured by Septodont Inc.**
- d) **It is the most widely used local anesthetic in many countries**

Septocaine™ (articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 injection)

BRIEF SUMMARY. [See Package Insert For Full Prescribing Information]

INDICATIONS AND USAGE

Septocaine™ is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures.

CONTRAINDICATIONS

Septocaine™ is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type, or in patients with known hypersensitivity to sodium metabisulfite.

WARNINGS

ACCIDENTAL INTRAVASCULAR INJECTION MAY BE ASSOCIATED WITH CONVULSIONS, FOLLOWED BY CENTRAL NERVOUS SYSTEM OR CARDIORESPIRATORY DEPRESSION AND COMA, PROGRESSING ULTIMATELY TO RESPIRATORY ARREST. DENTAL PRACTITIONERS AND/OR CLINICIANS WHO EMPLOY LOCAL ANESTHETIC AGENTS SHOULD BE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF EMERGENCIES THAT MAY ARISE FROM THEIR USE. RESUSCITATIVE EQUIPMENT, OXYGEN, AND OTHER RESUSCITATIVE DRUGS SHOULD BE AVAILABLE FOR IMMEDIATE USE.

Intravascular injections should be avoided. To avoid intravascular injection, aspiration should be performed before Septocaine™ is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Septocaine™ contains epinephrine that can cause local tissue necrosis or systemic toxicity. Usual precautions for epinephrine administration should be observed.

Septocaine™ contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

General: Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use (See WARNINGS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of Septocaine™ may cause significant increases in blood levels with each repeated dose because of possible accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated patients, elderly patients, acutely ill patients and pediatric patients should be given reduced doses commensurate with their age and physical condition. Septocaine™ should also be used with caution in patients with heart block.

Local anesthetic solutions, such as Septocaine™ containing a vasoconstrictor should be used cautiously. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Septocaine™ should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac condition and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and patient's state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity.

In vitro studies show that about 5% to 10% of articaine is metabolized by the human liver microsomal P450 isoenzyme system. However, because no studies have been performed in patients with liver dysfunction, caution should be used in patients with severe hepatic disease. Septocaine™ should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Small doses of local anesthetics injected in dental blocks may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should be observed constantly. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (See DOSAGE and ADMINISTRATION).

Information for Patients: The patient should be informed in advance of the possibility of temporary loss of sensation and muscle function following infiltration and nerve block injections.

Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies to evaluate the carcinogenic potential of articaine HCl in animals have not been conducted. Five standard mutagenicity tests, including three in vitro tests (the nonmammalian Ames test, the mammalian Chinese hamster ovary chromosomal aberration test and a mammalian gene mutation test with articaine HCl) and two in vivo mouse micronucleous tests (one with Septocaine™ and one with articaine HCl alone) showed no mutagenic effects. No effects on male or female fertility were observed in rats for Septocaine™ administered subcutaneously in doses up to 80 mg/kg/day (approximately two times the maximum male and female recommended human dose on a mg/m² basis).

Pregnancy: Teratogenic Effects-Pregnancy Category C.

In developmental studies, no embryofetal toxicities were observed when Septocaine™ was administered subcutaneously throughout organogenesis at doses up to 40 mg/kg in rabbits and 80 mg/kg in rats (approximately 2 times the maximum recommended human dose on a mg/m² basis). In rabbits, 80 mg/kg (approximately 4 times the maximum recommended human dose on a mg/m² basis) did cause fetal death and increase fetal skeletal variations, but these effects may be attributable to the severe maternal toxicity, including seizures, observed at this dose.

When articaine hydrochloride was administered subcutaneously to rats throughout gestation and lactation, 80 mg/kg (approximately 2 times the maximum recommended human dose on a mg/m² basis) increased the number of stillbirths and adversely affected passive avoidance, a measure of learning, in pups. This dose also produced severe maternal toxicity in some animals. A dose of 40 mg/kg (approximately equal to the maximum recommended human dose on a mg/m² basis) did not produce these effects. A similar study using Septocaine™ (articaine hydrochloride and epinephrine 1:100,000) rather than articaine hydrochloride alone produced maternal toxicity, but no effects of offspring.

There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. Septocaine™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether articaine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Septocaine™ is administered to a nursing woman.

Pediatric Use: In clinical trials, 61 pediatric patients between the ages of 4 and 16 years received Septocaine™. Among these pediatric patients, doses from 0.76 mg/kg to 5.65 mg/kg (0.9 to 5.1 mL) were administered safely to 51 patients for simple procedures and doses between 0.37 mg/kg and 7.48 mg/kg (0.7 to 3.9 mL) were administered safely to 10 patients for complex procedures. However, there was insufficient exposure to Septocaine™ at doses greater than 7.00 mg/kg in order to assess its safety in pediatric patients. No unusual adverse events were noted in these patients. Approximately 13% of these pediatric patients required additional injections of anesthetic for complete anesthesia. Safety and effectiveness in pediatric patients below the age of 4 years have not been established. Dosages in pediatric patients should be reduced, commensurate with age, body weight, and physical condition. See DOSAGE AND ADMINISTRATION.

Geriatric Use: In clinical trials, 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received Septocaine™. Among all patients between 65 and 75 years, doses from 0.43 mg/kg to 4.76 mg/kg (0.9 to 11.9 mL) were administered safely to 35 patients for simple procedures and doses from 1.05 mg/kg to 4.27 mg/kg (1.3 to 6.8 mL) were administered safely to 19 patients for complex procedures. Among the 11 patients ≥75 years old, doses from 0.78 mg/kg to 4.76 mg/kg (1.3 to 11.9 mL) were administered safely to 7 patients for simple procedures and doses of 1.12 mg/kg to 2.17 mg/kg (1.3 to 5.1 mL) were administered to 4 patients for complex procedures. No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Approximately 6% of patients between the ages of 65 and 75 years and none of the 11 patients 75 years of age or older required additional injections of anesthetic for complete anesthesia compared with 11% of patients between 17 and 65 years old who required additional injections.

ADVERSE REACTIONS

Reactions to Septocaine™ are characteristic of those associated with other amide-type local anesthetics. Adverse reactions to this group of drugs may also result from excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

The reported adverse events are derived from clinical trials in the US and UK. Of the 1325 patients treated in the primary clinical trials, 882 were exposed to Septocaine™.

Table 2
Adverse Events in controlled trials with an incidence of 1% or greater in patients administered Septocaine™ (articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 injection)

Body System	Septocaine™ N (%)
Number of Patients	882 (100%)
Body As A Whole	
Face Edema	13 (1%)
Headache	31 (4%)
Infection	10 (1%)
Pain	114 (13%)
Digestive System	
Gingivitis	13 (1%)
Nervous System	
Parasthesia	11 (1%)

The following list includes adverse and intercurrent events that were recorded in 1 or more patients, but occurred at an overall rate of less than one percent, and were considered clinically relevant.

Body as a Whole - abdominal pain, accidental injury, asthenia, back pain, injection site pain, malaise, neck pain.

Cardiovascular System - hemorrhage, migraine, syncope, tachycardia.

Digestive System - constipation, diarrhea, dyspepsia, Glossitis, gum hemorrhage, mouth ulceration, nausea, stomatitis, tongue edemas, tooth disorder, vomiting.

Hemic and Lymphatic System - ecchymosis, lymphadenopathy.

Metabolic and Nutritional System - edema, thirst.

Musculoskeletal System - arthralgia, myalgia, osteomyelitis.

Nervous System - dizziness, dry mouth, facial paralysis, hyperesthesia, increased salivation, nervousness, neuropathy, parasthesia, somnolence.

Respiratory System - pharyngitis, rhinitis.

Skin and Appendages - pruritis, skin disorder.

Special Senses - ear pain, taste perversion.

Urogenital System - dysmenorrhea.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during the therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution (see WARNINGS, PRECAUTIONS, **General**, and ADVERSE REACTIONS).

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as hypoventilation, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation as needed. The adequacy of the circulation should be assessed. Should convulsions persist despite adequate respiratory support, treatment with appropriate anticonvulsant therapy is indicated. The practitioner should be familiar, prior to the use of local anesthetics, with the use of anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor.

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

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