

**COMPARISON OF ARTICHAINE AND LIDOCAINE USED AS
DENTAL LOCAL ANESTHETICS**

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	Page
Contents	2
Preface	3
Introduction	3
The basic properties of articaine and lidocaine	4
Factors affecting local anesthetic action	5
Pharmacokinetics	6
Uptake	6
Distribution	7
Metabolism (Biotransformation)	7
Excretion	8
Pharmacodynamics	8
Clinical comparison of articaine versus lidocaine	9
Safety	9
Efficacy	10
Use in pediatric dentistry	13
Use in geriatric patients	15
Complications	16
Why is articaine delivered as a 4 % solution?	20
Discussion	20
References	22

Preface

This paper is submitted as partial fulfillment of the requirements for the degree Candidatus/Candidata Odontologiae (DDS) by the Faculty of Dentistry, University of Oslo, Norway.

Introduction

Local anesthesia is an important part of the daily routines for a dentist. In Norway alone a significant number of carpules (cartridges) of local anesthesia is injected every year. The first substance that was used for this purpose was cocaine, as far back as in 1884. In 1903, Braun suggested using adrenaline as a “chemical tourniquet” to prolong the duration of local anesthetics. In 1904 Einhorn synthesized procaine, an ether anesthesia. In the 1940’s a new group of local anesthetic compounds, the amides, were introduced. The initial amide local anesthetic, lidocaine, was synthesized by the Swede chemist Nils Løfgren in 1943. Lidocaine revolutionized pain control in dentistry worldwide, as it was both more potent and less allergenic than procaine. In the succeeding years, other amide local anaesthetics (prilocaine in 1953 by Løfgren and Tegner, bupivacaine and mepivacaine in 1957 by A. F. Ekenstam, etidocaine in 1971 by Takman) were introduced.

These researchers gave the dental practitioner a local anesthetic armamentarium which provided pulpal anesthesia for periods lasting from 20 minutes (mepivacaine) to as long as three hours (bupivacaine and etidocaine with adrenaline). In addition, these popular drugs proved to be more rapid-acting than the older ester-type drugs and, at least from the perspective of allergenicity, safer. In 1969, Rusching et al. prepared a new drug, articaine. It differed from the previous amide local anesthetics in that it was derived from thiophene, and because of that contained a thiophene ring in its molecule in stead of the usual benzene ring. It was first named carticaine, but its generic name was changed to articaine in 1984. It was introduced onto the German market in 1969. (Malamed 1997)

For time being, articaine combined with adrenaline 1:100 000 and 1:200 000 has a market share in Norway of approximately 50 % per January 2004 (personal communication T. Stjernesund), while lidocaine, prilocaine and mepivacaine constitute the rest. In other countries like Canada, Italy, France and the Netherlands, articaine is the number one choice, and in Germany more than 90 percent of the local anesthesia used by dentists is articaine (Isen 2000).

The purpose of this article is to present a brief comparison of articaine and lidocaine as used in dentistry.

The basic properties of articaine and lidocaine

The chemistry and pharmacology of a local anesthetic can give valuable information about which clinical effects you can expect when you use them. The most important ones for both articaine and lidocaine are listed in table 1.

Table 1, Physical/chemical properties		
Substance	Articaine	Lidocaine
Chemical formula	3-N-Propylamino-propionyl-amino-2-carbomethoxy-4-methylthiophene hydrochloride	2- Diethylamino 2', 6-acetoxylidide hydrochloride
Structure formula		
Classification	Amide	Amide
Molecular weight	284.38 (Jastak & al 1995)	234.34 (Jastak & al 1995)
Partition coefficient Log P (o/w)	2.07 (Hoechts Marion Roussel 1999)	2.44 (SRC PhysProp Database 2004)
Vd (ss)	7.7 +/- 5.1 L/kg (Oertel & al.1997)	91 (Jastak & al. 1995)
pKa	7.8 (Malamed 1997)	7.9 (Malamed 1997)
Lipid solubility	1.5 (malamed & al. 2000)	4.0(Malamed & al. 2000)
Plasma protein binding	76 % (pH 8.5) 54 % (pH 7.5) (Oertel & Richter 1998)	74 % (pH 8.5) 61 % (pH 7.5) (Oertel & Richter 1998)

Table 2, Content in one carpule pr. ml.		
Septocaine 1.7 ml	Septocaine forte 1.7 ml	Xylocaine/adrenaline 1.8 ml
Articain.hydrochlorid. 40mg, adrenaline 5 µg, natr. metabisulfis (E223) 0.5 mg, natr. edet. 0.25 mg, natr. chlorid 1.6 mg, natr. hydroxid., aqua ad inject. ad 1 ml.	Articain.hydrochlorid. 40 mg, adrenalin. 10 µg, natr. metabisulfis (E223) 0.5 mg, natr. edet 0.25 mg, natr. chlorid 1.6 mg, natr. hydroxid., aqua ad inject. ad 1 ml.	Lidocain.hydrochlorid. 20 mg, adrenalin. 12.5 µg, natr. chlorid. q.s., natr. metabisulfis (E223) 0.5 mg, aqua ad inject. ad 1 ml.

(Felleskatalogen 2003)

Factors affecting local anesthetic action

The dissociation constant (pKa) affects the onset of action. Lower pKa, means that more uncharged base molecules are present to diffuse through the nerve sheath; thus onset time is decreased.

Lipid solubility affects the anesthetic potency. Increased lipid solubility permits the anesthetic to penetrate the nerve membrane, which itself is 90 % lipid (Malamed 1997), more easily. Articaine differs from all other amide local anesthetics, in that it is derived from thiophene. As a result, the articaine molecule does not contain a benzene ring like the others but instead contains a thiophene ring. This renders the molecule more lipid soluble and therefore better able to cross lipid barriers, for example the nerve membrane (Isen 2000).

Protein binding affects the duration. Increased protein binding allows anesthetic cations to be more firmly attached to proteins located at receptor sites. Thus the duration of action is increased.

Vasodilator activity affects both the anesthetic potency and the duration. Greater vasodilator activity leads to increased blood flow to a region, which leads to a rapid removal of anesthetic molecules from the injection site. This will decrease both the anesthetic potency, and duration. Both articaine and lidocaine as plain solutions without a vasoconstrictor added would be ineffective and more toxic because of their vasodilator activity. In order to improve both the duration and safety, adrenaline is added which act as a vasoconstrictor. In Norway

there are different preparations available. Those that are available for time being are listed in table 3.

Table 3, Preparations			
Product	Content	Adrenaline	Manufacturer
Xylocain-adrenaline, 1.8 ml.	lidocaine 20 mg/ml + adrenaline 12.5 µg/ml	1:80 000	Dentsply
Septocaine forte, 1.7 ml.	articaine 40 mg/ml + adrenaline 10 µg/ml	1:100 000	Septodont
Septocaine, 1.7 ml	articaine 40 mg/ml + adrenaline 5 µg/ml	1:200 000	Septodont

(Felleskatalogen 2003)

Pharmacokinetics

Local anesthetics block the sensation of pain by interfering with the propagation of peripheral nerve impulses. Both the generation and the conduction of action potentials are inhibited. Electrophysiological data indicate that local anesthetics do not significantly alter the normal resting potential of the nerve membrane; instead, they impair certain dynamic responses to nerve stimulation (Strichartz & Ritchie 1987). Local anesthetics interfere with nerve conduction by blocking the influence of stimulation on Na⁺ permeability. A developing local anesthetic block is characterized by a progressive reduction in the rate and extent of depolarization and a slowing of conduction. Since the onset and rate of repolarization are not greatly affected by local anesthetics, the safety factor for transmission decreases. When depolarization is retarded such that repolarization processes develop before the threshold potential can be reached, nerve conduction fails (Jastak & al. 1995).

Uptake

When injected into soft tissues, local anesthetics exert a pharmacological action on the blood vessels in the area. All local anesthetics possess a degree of vasoactivity, although the degree may vary. Most local anesthetics produce dilation of the vascular bed into which they are deposited. To a slight degree these effects may be concentration dependent. A significant

effect of vasodilation is an increase in the rate of absorption of the local anesthetic into the blood, thus decreasing the duration of pain control while increasing the anesthetic blood level and the potential for overdose. These effects are also related to the vascularity of the injection site (Malamed 1997). To compensate for this effect, most local anesthetics are manufactured as solutions containing a vasoconstrictor, for example adrenaline or felypressin.

Distribution

Once absorbed into the blood, local anesthetics are distributed throughout the body to all tissues. The level of a local anesthetic drug in the blood from which it is distributed to certain target tissues/organs has a significant bearing on the potential toxicity of the drug. The blood level of the drug is influenced by the following factors:

- Rate at which the drug is absorbed into the cardiovascular system
- Rate of distribution of the drug from the vascular compartment to the tissues, which is more rapid in healthy patients.
- Elimination of the drug through metabolic and/or excretory pathways.

The latter two factors act to decrease the blood level of the local anesthetic. The rate at which a local anesthetic is removed from the blood is described as the elimination half-life of the drug, $t_{1/2\beta}$. Simply stated, the half life is the time required for a 50 % reduction in the blood level of the drug (Malamed 1997).

Metabolism (Biotransformation)

Metabolism of local anesthetics is important, because the overall toxicity of a drug depends on a balance between its rate of absorption into the bloodstream at the site of injection and its rate of removal from the blood the processes of tissue uptake and metabolism. The primary site of biotransformation of amide drugs is the liver. Liver function and hepatic perfusion therefore significantly influence the rate of biotransformation of an amide local anesthetic. Approximately 70 % of the dose of injected lidocaine undergoes biotransformation in patients with normal liver function. Patients with lower than usual hepatic blood flow (hypotension, congestive heart failure) or poor liver function (cirrhosis) are unable to biotransform amide local anesthetics at a normal rate. This slower than normal biotransformation rate leads to

increased anesthetic blood levels and potentially increased toxicity. Significant liver dysfunction (ASA IV-V) or heart failure (ASA IV-V) represents a relative contraindication to the administration of amide local anesthetics (Malamed 1997). Articaine differs from other amide local anesthetics, in that it has an extra ester linkage (COOCH₃). 90-95 % is metabolized in the blood, and only 5-10 % in the liver. This feature is clearly demonstrated when you compare the half-life (t_{1/2b}) between articaine and lidocaine. The elimination half-life for lidocaine is 90 min, versus that for articaine is 20 min (Isen 2000). This is the time it takes to reduce the plasma levels of the drug by 50 %. The major metabolic product of articaine is articainic acid. It is inactive as a local anesthetic, and systemic toxicity has not been observed (Oertel & al.1997). This finding is important because an active metabolite may affect toxicity and may exert undesirable side effects. In comparison, lidocaine has active metabolites. It is metabolised in the liver by the microsomal P450 enzyme system to monoethylglyceine and xylidide; xylidide is a local anesthetic and potentially toxic (Malamed 1997).

Excretion

The kidneys are the primary excretory organ for booth the local anaesthetic and its metabolites. A percentage of a given dose of local anesthetic drug will be excreted unchanged in the urine, and this varies according to the drug. Patients with significant renal impairment may be unable to eliminate the parent local anesthetic compound or its major metabolites from the blood, resulting in slightly elevated blood levels and an increased potential for toxicity. Thus significant renal disease (ASA IV-VI) represents a relative contraindication to the administration of local anesthetics. This includes patients undergoing renal dialysis and those with cronic glomerulonephritis and/or pyelonephritis (Malamed 1997). Articaine is largely excreted in the urine as the metabolite articaninic acid (64.2 +/- 14.4 %), followed by articainic glucuronide (13.4 +/- 5.0 %) and the parent drug (1.45 +/- 0.77 %) (Oertel & al. 1997). For lidocaine the excretion is also via the kidneys; less than 10 % unchanged, more than 80 % various metabolites (Malamed 1997).

Pharmacodynamics

The potency of articaine is 1.5 times that of lidocaine and 1.9 times that of procaine, and the toxicity is similar to that of lidocaine and procaine (Malamed 1997). The unintentional

intravascular injection of local anesthetic agents in dentistry can occur because of the high vascularisation of this area. The risk of such an intravascular injection is up to 20 % in conduction anesthesia of the inferior alveolar nerve (Oertel & al. 1997). The signs and symptoms are referable to the CNS and cardiovascular system. A comparison between articaine and lidocaine showed that the signs of CNS toxicity after intravenous administration of lidocaine were observed more frequently and at a higher degree of severity when compared with articaine. The cardiovascular parameters did not change (Oertel & al. 1997).

Clinical comparison of articaine versus lidocaine

Safety

Before a new local anesthetic drug can be introduced on the open market, it has to pass through several different levels of testing and developing. The first step is in vitro studies, and then we have animal testing and finally clinical testing. Lidocaine, which is a relatively old local anesthetic, has been studied thoroughly for many years, and has well known effects and side effects. The safety has also been under substantial investigation for many years. Articaine is not as old as lidocaine, although it was synthesized back in 1969. It has been used in several European countries for almost 30 years, and its safety has been well documented by several different studies.

The unintentional intravascular injection of local anesthetic agents in dentistry can occur because of high vascularisation in this area. The risk of such an intravascular injection is up to 20 % in conduction anesthesia of the mandibular nerve (Bartlett 1972). The signs and symptoms of local anesthetic agent toxicity are referable to the CNS and cardiovascular system. The initial subjective signs of CNS intoxication are general feeling of lightheadedness, dizziness, disorientation, drowsiness, anxiety, excitement and visual and auditory disturbances. Objective signs of early CNS toxicity consist of shivering, muscular twitching and tremors of the facial muscles. Oertel & al. showed that signs of CNS toxicity after intravascular injection of lidocaine were observed more frequently and at a higher degree of severity when compared with articaine (1977). The cardiovascular parameters did not change (Oertel & al. 1997). It was concluded that an unintentional intravascular injection of about 80 mg of articaine – the equivalent of 1 cartridge of the commercial 4 % solution – does not cause toxic effects in healthy patients. This is confirmed by the LD50, which for articaine

is 37 mg/kg, and for lidocaine 33.2 mg/kg (Borchard 1978). The LD50 number indicates the dose that is lethal for 50 % of a defined population.

The immunogenic potential of articaine is very low. Allergic-type reactions that have been reported with articaine include edema, urticaria, erythema and anaphylactic shock, and the frequency is comparable with that of lidocaine (Malamed & al. 2001). There are however several factors that may alter the predictability of allergic drug reactions. Age, genetics, frequency and duration of drug administration and route of administration are all factors that may contribute to the predictability (MacColl & Young 1989). Therefore patients allergic to articaine likely would be allergic to lidocaine and other amide local anesthetics. Articaine like lidocaine contains the vasoconstrictor preservative sodium metabisulphite and therefore may cause allergic reactions in patients with sulphite sensitivity, such as some people with allergic-type asthma (Malamed & al. 2001).

Some authors claim that articaine like prilocaine is capable of producing methemoglobinemia. But when used as directed for dental anesthesia, the occurrence of this side effect is highly unlikely, and no cases have been reported following the use of recommended dosages for dental local anesthesia (Isen 2000).

Earlier formulations of articaine and other local anesthetics contained a bacteriostatic, antifungal and antioxidant preservative for the local anesthetic itself, called methylparaben. It was proved allergenic, and was not removed from all formulations of articaine until the mid 1990's. This is one of the reasons that approval for the use of articaine was not sought in the United States until 1995.

Efficacy

An important property to look at when it comes to efficacy is the lipid solubility expressed by the partition coefficient. The lipid solubility determines to what degree the molecules penetrate nerve membranes. Several studies have been conducted to find out what the properties are for articaine, and the results of these studies vary. Borchard (1978) found that the partition coefficient for lidocaine was 2.9 (N-Heptan/buffer pH 7.4) and that for articaine was 32 (Octanol-1/buffer pH 7.35). Oertel & al. (1977) reported a partition coefficient for articaine of 52, similar to that of lidocaine (N-octanol /buffer, 37 °C). Casanovas & al found that the number for articaine was 123.0, while that for lidocaine was 10.0 (Casanovas & al. 1982). Another property which is important for the diffusion is the molecular configuration.

Articaine contains a thiophene ring instead of benzene like lidocaine. This gives the molecule better diffusion properties compared with lidocaine (Casanovas & al. 1982).

One of the reasons why articaine instantly became so popular in many countries was due to its excellent efficacy. Dentists claimed that they seldom missed with the inferior alveolar nerve block, and that buccal infiltration in the maxillary arch often was enough before an extraction of a molar, because of articaine's bone penetration properties. This seemingly excellent efficacy is reported from many dentists from around the world, based on their daily clinical practice.

The next step would therefore be to see if there is any literature to support these clinical findings. Malamed et al. (2001) compared the efficacy of 4 % articaine with adrenaline 1:100 000 with 2 % lidocaine with adrenaline 1:100 000. A total of 882 subjects received articaine, and 443 received lidocaine. The efficacy was determined by both subject and investigators using a visual analog scale, or VAS. The volumes and duration of anesthesia were as listed in table 4. They concluded that there were no significant differences between subjects receiving articaine and those receiving lidocaine, either for subjects or investigator ratings. This finding is similar to that obtained by Vehetalo & al. (1993).

Parameter	4 % articaine with adrenaline 1:100 000		2 % lidocaine with adrenaline 1:100 000	
	Simple	Complex	Simple	Complex
Number of subjects	675	207	338	104
Mean volume +/- SEM, ml.	2.5 +/-0.07	4.2 +/- 0.15	2.6 +/- 0.09	4.5 +/- 0.21
Mean dose +/- SEM (mg/kg)	1.48 +/- 0.042	2.36 +/- 0.094	0.80 +/- 0.031	1.26 +/- 0.065

Table 4b, Duration				
Parameter	4 % articaine with adrenaline 1:100 000		2 % lidocaine with adrenaline 1:100 000	
	Simple	Complex	Simple	Complex
Number of subjects	657	207	338	105
Mean duration +/- SEM, min.	36.4 +/-1.28	58.3 +/-3.07	37.7 +/-2.01	52.6 +/-3.99
Range, min.	0 – 217	1 – 215	0 – 220	1 - 171

Another study by Haas et al. (1990), compared articaine with adrenaline 1:200 000, and prilocaine with adrenaline 1:200 000. They wanted to test the claims that labial infiltration of articaine results in anesthesia of mandibular pulpal as well as maxillary and mandibular lingual soft tissue. Anesthesia was determined by measuring sensation to electrical stimulation at the tooth, labial and lingual soft tissue for canines and second molars. The result was that there were no significant differences.

This is in contrast to a study by Ruprecht & al. (1991) which compared equimolar concentrations of articaine and lidocaine. It showed that articaine had a significantly longer duration of pulpal anesthesia, regardless of the vasoconstrictor content.

Table 5, Comparison of equimolar concentrations of lidocaine and articaine with adrenaline.			
Solution	Onset, min.	Duration, min.	Frequency, %.
A 125 + E 27.3	4.7 +/- 1.58	54.4 +/- 22.58	100
L 125 + E 27.3	5.4 +/- 3.36	28.1 +/- 14.92	77.8
A 125 + E 54.5	5.0 +/- 2.83	66.8 +/- 22.70	100
L 125 + E 54.5	5.0 +/- 3.25	39.8 +/- 22.23	88.9
A 74 + E 54.5	4.2 +/- 1.58	91.2 +/- 41.60	100
L 74 + E 54.5	3.4 +/- 1.31	61.3 +/- 17.21	100

A 125 – 4.0 % L 125 – 3.4 % E 27.3 – 1:200000
A 74 – 2.4 % L 74 - 2.0 % E 54.5 – 1:200000

Winther & Nathalang showed that articaine was significantly superior to lidocaine with respect to frequency, extent and duration of analgesia (1972).

Another important issue is the concentration of adrenaline. The effectiveness of 4 % articaine associated with 1:100 000 or 1:200 000 adrenaline for inferior alveolar nerve blocks are the same (Tofoli & al. 2003). This is why 1:200 000 are the recommended concentration of adrenaline for dental procedures (Jacob 1989), except for those procedures (e.g. surgical interventions) that requires a larger degree of hemostasis. For these purposes the recommended concentration is 1:50 000 (Buckley & al. 1984) or 1:80 000 as used in Scandinavia.

An important issue when comparing two substances as articaine and lidocaine are the methods used. In order to get statistical significant data, one needs a large enough material containing a sufficient number of subjects. Many studies fail to show differences because of this problem. This may be one of the reasons why articaine in different studies tends to be somewhat more effective than lidocaine, although not significant.

Similar to other amide local anesthetics, articaine blocks sodium channels at a lower concentration than potassium channels, but lower concentrations of the thiophene derivate than of the benzene derivates are needed to block the ionic channels. Because of the higher partition coefficient of lidocaine, it seems that the action on these channels seems not to follow mere lipid solubility properties of the neutral drug. Differences in the interaction of local anesthetics with ionic channel proteins might in part be correlated to different binding properties to plasma proteins, as indicated by a higher affinity of articaine to plasma proteins as compared to lidocaine (Borchard & Drouin 1980).

Use in pediatric dentistry

In order for a local anesthetic to become popular, it is important that it is useful in a wide range of situations. Lidocaine has been used for both adults and children for more than five decades, and pediatric dentistry is for sure an important area.

Articaine should not be used in patients under 4 years of age, because safety and effectiveness in this group has not yet been seriously investigated (Felleskatalogen 2003), although 2 studies showed that articaine is likely safe for children under 4 years of age (Jacobs & al. 1995, Wright & al. 1989). When used in pediatric dentistry, it is important to remember that articaine is in a 4 % solution, and that maximum dose for children is the same as for adults; 7 mg/kg (0.175 mL/kg). For simple procedures the recommendation is 0.04

ml/kg, and for complicated procedures 0.07 ml/kg (Felleskatalogen 2003). It is important to have in mind that when you administer local anesthetic to children with small weight, the maximum dose can easily be reached. Table 6 shows the maximum recommended doses for articaine at different weights (Felleskatalogen 2003)

Table 6, Maximum recommended doses of articaine for different weights.	
Weight, kg	Maximum number of cartridges
10	1.03
15	1.54
20	2.06
25	2.57
30	3.09

Articaine 4 % with adrenaline 1:100 000 compared with lidocaine 2 % with adrenaline 1:100 000 shows that articaine is a safe and effective local anaesthetic for use in pediatric dentistry. Time to onset and duration of anesthesia are appropriate for clinical use and are comparable to lidocaine. No significant difference in pain relief was observed between articaine 4 % with adrenaline 1:100 000 and lidocaine 2 % with adrenaline 1:100 000 (Malamed & al. 2000). This is supported by other studies (Wright & al.1989).

In both the Norwegian “Felleskatalogen” and the manufactures recommendation for usage, articaine is not recommended for children under 4 years of age. The reason for this is as mentioned earlier, that the documentation of safety in this group is sparsely, and that controlled trials must be carried out. A retrospective report showed however that articaine had been successfully administered to children less than 4 years of age, and that articaine is likely safe for children under 4 years of age, and that the pharmacokinetic profile of articaine is very similar for children and adults. (Wright & al. 1989, Jacobs & al. 1995).

Another important issue when used in children under 4 years of age is the combination of local anesthetics and sedation. Treating children below 4 years of age for extensive dental caries is not easy; frequently it is desirable to use sedation agents to control behavior and accomplish the treatment as rapidly as possibly a minimum number of treatment sessions. There are many different forms of sedation, ranging from iatrosedation (behavior shaping),

conscious sedation (benzodiazepines) to general anesthesia (inhalation or intravenous) (Koch & Poulsen 2001). It is important to be careful when you administer local anesthetics to a sedated child, since there is a higher risk of adverse reactions to occur, and that there are a direct link between adverse reactions and local anesthesia volumes (Wright & al.1989, Weaver 1999). When restoring primary mandibular molars, the customary injection is a mandibular (inferior) dental nerve block. Block anesthesia has some disadvantages for children. Especially, the lengthy duration of the anesthesia allows for a greater possibility of postoperative trauma, such as lip or tongue biting. Also, parents must maintain close supervision while their children are under anesthesia.

Mandibular infiltrations have been a debated area. Some dentists claims that articaine has better bone penetration, and therefore could produce anesthesia to primary molars of children. The major obstacle in obtaining anesthesia from infiltrations in the mandible, is the density and thickness of the bone when compared to maxilla. Articaine possesses properties that make it suitable for infiltration techniques in the lower jaw, and that this should be the technique of choice, except for extractions where a nerve block is recommended. Infiltrations are also more suited for difficult and handicapped children, and it can be safely given to a reluctant child. Furthermore, the tongue is not affected, thus reducing the risk of postoperative bites (Dudkiewicz & al. 1997, Wright & al. 1991).

An important issue in obtaining good anesthesia in children is the influence of the children's behavior. There is a high relationship between children behaving cooperatively and comfort during procedures. Children who demonstrate comfort at the time of injection are likely to exhibit no pain during successive procedures (Wright & al. 1991).

Use in geriatric patients

Aging is associated with physiologic changes which could alter pharmacokinetics of drugs. Age-related changes in pharmacokinetics affect drug absorption, distribution metabolism, and elimination. Increase in body fat, decrease in lean body mass, and total body water, changes in hepatic metabolism, and renal elimination capacity in the elderly are of particular clinical significance. These changes should be taken into account when choosing drug therapy for older patients to minimize adverse effects and maximize potential benefits. Because the median age of the population is steadily increasing, more elderly patients are undergoing routine dental procedures for which local anesthesia could be required (Oertel & al. 1999).

Additionally, pharmacodynamic changes in the elderly can result in greater, or sometimes even lesser, drug sensitivity than that seen in a young individual. This means that, in theory, increased or decreased pharmacodynamic sensitivity in the elderly may coexist with or be independent of, pharmacokinetic changes (Oertel & al. 1999).

Concerning local anesthesia, most of our knowledge of pharmacokinetics is based almost entirely on investigations in young individuals (Nordenram & Danielsson 1990). The only local anesthetic agent that is tested extensively in elderly patients, is lidocaine (Oertel & al. 1999).

There are no statistical differences in C_{max} and T_{max} or t_{1/2} between young and older individuals (Oertel & al. 1999). This is a very important finding, indicating that there might be an age-independent plasma esterase function. This is in contrast to other amide local anesthetics, which is primarily metabolized in the liver, which has an capacity that decreases with age. There is a significant decrease in CL and V_{dss} of articaine in elderly, related to the decrease in lean body mass and increase in body fat (Oertel & al. 1999).

Taken into account that articaine shows an age-independent metabolism, there should be no reason to change the dosage in elderly patients. But, it is important to remember that articaine is a highly serum protein bounded drug, and changes in binding to serum are also a factor that could affect pharmacokinetics in the elderly.

Complications

A wide range of different complications can occur during or after the injection of local anesthesia. They can be divided into local complications, such as pain on injection, persistent anesthesia/paresthesia, trismus, hematoma, oedema and facial nerve paralysis, and systemic complications such as overdoses and allergic reactions.

Paresthesia can be defined as persistent anesthesia (anesthesia well beyond the expected duration), or altered sensation (tingling or itching) well beyond the expected duration of anesthesia (Malamed 1997). The definition of paresthesia also includes hyperesthesia and dysesthesia. Hyperesthesia is defined as increased sensitivity to noxious stimuli, and dysesthesia as painful sensation to nonnoxious stimuli (Dower 2003). The symptoms are most commonly associated with mechanical trauma during surgical procedures. During the administration of anesthesia for a mandibular nerve block, the lingual or inferior alveolar neurovascular bundle can be traumatized by the sharp needle-tip, the movement of

the needle, ekstraneural or intraneural hemorrhage from trauma to the blood vessels, or from neurotoxic effects of the local anesthetic.

A retrospective analysis of paresthesia after local anaesthetic administration for nonsurgical dental procedures over a 20-year period, from 1973-1993, was published by Haas and Lennon in 1995. Paresthesia was defined as numbness or tingling of the mouth or face. The analysis revealed a higher-than-expected frequency of paresthesia with articaine, based on the number of cartridges used (2.27 per 1 million injections vs. an expected frequency of 1.20 per 1 million injections). There were no significant differences found with respect to patient age, patient gender, or needle gauge (Haas & Lennon 1995).

The analysis was based on reports of paresthesia recorded by Ontario's Professional Liability Program (PLP) from 1973-1993, and restricted to non-surgical procedures. A total of 143 cases were registered in that period, and the location and symptoms were as listed in the table.

Table 7, Location and symptoms of paresthesia.

Location	Frequency	Additional symptoms					
		Drooling	Speech impediment	Taste loss	Tingling	Burning	Tongue biting
Lip	42	2	2	1	3	4	0
Tongue	92	3	9	23	10	11	6
Lip and tongue	9	1	0	2	1	2	2
Total	143	6	11	26	14	17	8

An interesting finding is the different frequency between paresthesia of the lingual nerve and the inferior alveolar nerve. The lingual nerve (tongue) is approximately twice as often involved as the inferior alveolar nerve (lip), 92 versus 42 cases. This finding is confirmed by Progrei and Thamby, which found the same distributes for the paresthesias (2000). The reason for this finding might be that in performing inferior alveolar nerve injections some practitioners change direction of the needle at the approximate depth of the lingual nerve. The sharp needle tip may lacerate the lingual nerve and/or artery on the initial or subsequent path. Another possible explanation might be that during a subsequent injection for the inferior alveolar nerve block, the needle might traumatize the more superficial lingual nerve but

without the “electric shock” sensation, because the nerve is usually anesthetized on the initial attempt (Dower 2003). The cause of the paresthesia may also be combination of neurotoxicity of the local anesthetic and trauma to the nerve (Kalichman & al. 1993). Another study by Malamed & al. (2001) did not confirm the previous studies and numbers that have been published. They conducted a study to compare the safety between articaine 4 % with adrenaline 1:100 000, and lidocaine 2 % with adrenaline 1:100 000. The authors wrote a report on three identical single-dose, double-blind, parallel-group, active-controlled multicenter studies. A total of 1325 subjects participated in these studies, 882 in the articaine group, and 443 in the lidocaine group. The table shows the adverse events reported by 1 percent or more of patients.

Table 8, Adverse events reported by 1 % or more of patients in either treatment group.		
Body system/adverse event	Treatment group	
	Articaine 4 % with adrenaline 1:100 000 (n = 882) % (n)	Lidocaine 2 % with adrenaline 1:100 000 (n = 443) % (n)
<i>Body as a whole</i>		
Face edema	13 (1)	6 (1)
Headache	31 (4)	15 (3)
Infection	10 (1)	3 (<1)
Pain	114 (13)	54 (12)
<i>Oral system</i>		
Gingivitis	13 (1)	5 (1)
<i>Nervous system</i>		
Hypoesthesia	7 (<1)	5 (1)
Paresthesia	11 (1)	2 (<1)

The overall incidence of adverse events in the combined studies was 22 % in the articaine group and 20 % in the lidocaine group. An attempt was made to obtain data regarding paresthesia after injection, during telephone follow-up 24 hours and seven days after the procedure with the same definition as Haas and Lennon (1995). The total number of subjects who reported these symptoms four to eight days after the procedure was 8 (1 %) in the

articaine group and 5 (1 %) in the lidocaine group. In 5 cases (4 with articaine and 1 with lidocaine) the symptoms did not begin on the day of study drug administration, suggesting that they were caused by the procedure rather than the anesthetic. Ultimately most cases of paresthesia resolve within eight weeks (Malamed 1997).

As can be seen from the text above there is somewhat contradicting numbers regarding paresthesia after injection of local anesthetics. Why the Haas & Lennon study found that the numbers of paresthesia for articaine was so high is somewhat uncertain, but some possible explanations might be considered. First of all the study was based on voluntary reporting from the dentist in Ontario, Canada. A high degree of subjectivity is involved, and this might influence on the numbers. Also in 1990 the PLP changed the insurance underwriters, and in anticipation of the change special notices and requests were sent to all dentists urging them to report any potential claims. This might have led to a greater number of reported cases. Second, articaine was introduced onto the Canadian market in 1985. After this, there where an marketed increase in the reported number of paresthesias. One reasonable explanation for this finding might be the increased attention that there always will be after the introduction of a new product onto the market. The dentists that changed to articaine most likely paid more attention to note any side effects than dentist that used the same local anesthetic that they had been used for many years.

Another explanation might be that in the Haas & Lennon study, cases where surgery was involved were excluded. This might hide the numbers of paresthesia actually related to the drug, and if for instance lidocaine is more used in surgery, this might lower the numbers of paresthesias related to lidocaine. Another issue is that the Canadian study does not provide information regarding the duration of paresthesia in the cases reported. It might be that some cases actually is a result of a somewhat longer duration of the anesthesia, that ultimately resolved after a relatively short period of time. Since most dentist feel that articaine has a somewhat better penetration than lidocaine, the technique that they uses have changed. In stead of inferior alveolar blocks, they infiltrate around the tooth, and hence the risk for traumatizing the lingual nerve increases.

Although there are no reports demonstrating that the needle used in dental syringes are large enough to produce a complete severance of the inferior or alveolar or lingual nerves, simple contact may be sufficient to induce a transient paresthesia (Malamed 1997). The 25-gauge needle is the largest needle commonly used in dentistry. With an external diameter of 0.45 mm, it is considerable smaller than the lingual nerve, which has been reported to have an average diameter of 1.86 mm (Kiesselbach & Chamberlain 1984).

Articaine is delivered as a 4 % solution in as opposed to lidocaine which is 2 %. It may be speculated that if there is a toxic local metabolite involved, it may manifest toxicity simply due to the higher concentration.

Another complication that might occur is paralysis of the oculomotor muscles, leading to diplopia and even temporary blindness. All such manifestations are transient and disappear on cessation of the anesthetic effects. In case of paralysis of the extrinsic musculature of the eye (especially the external rectus muscle), synchronic movement of the eyes becomes impossible, and diplopia appears. Such complications are possible when performing an posterior superior alveolar anesthesia. There are many different theories on the mechanisms behind these ophthalmologic complications, and it is likely that the local anesthetic solution diffuses directly from the pterigomaxillary fossa, through the sphenomaxillary cavity, to the orbit. This would affect the ciliary ganglion, located between the optic nerve and the external rectus muscle of the eye (Penarrocha-Diago & Sanchis-Bielsa 2000). The symptoms develop immediately after the injection of the anesthetic solution and can persist for between 1 minute and several hours, though they only rarely exceed the duration of the anesthetic effect. Most of the reported cases in the literature are produced by lidocaine and mepivacaine, but they may also happen after injections of articaine (Penarrocha-Diago & Sanchis-Bielsa 2000).

Why is articaine delivered as a 4 % solution?

Articaine is produced as a 4 % local anesthetic solution. This is in contrast to lidocaine which is a 2 % solution, and similar to prilocaine which also is a 4 % solution. Equal analgesic efficacy along with lower systemic toxicity (i.e., a wide therapeutic range) allows use of articaine in higher concentrations than other amide-type local anesthetics (Oertel & al. 1997). This is advantageous with respect to the required bone penetration, and hence it is possible to inject smaller volumes, thereby minimizing the injection induced pain.

One possible disadvantage with the higher concentration of the local anesthetic solution, is that it has been determined that local anesthetic- induced nerve injury is concentration dependent, with injuries increasing as concentration increases (Dower 2003).

Discussion

As can be seen from the text above, there are many aspects that has to be taken under consideration when comparing local anesthetic solutions. The quality and validity of data

from different studies varies tremendously, and it might be sometimes hard to really spot any differences. When comparing articaine to lidocaine, I started out with looking at the basic properties of the drugs. There are relatively few significant differences. One basic difference is that articaine contains a thiophene ring, compared to the benzene ring of lidocaine (Isen 2000). A number of authors claims that this makes the drug more lipophilic, but this is not reflected when comparing the n- octanol/Soerensen buffer, which shows varying numbers in different studies, some favoring articaine and others lidocaine.

Another basic property that differs among the two drugs is that articaine contains an extra ester linkage. This causes articaine to be hydrolyzed by plasma esterase as well as the microsomal P450 enzyme system in the liver. This again, causes the half life for articaine to be approximately 20 minutes, while that for lidocaine is 90 minutes (Isen 2000).

Articaine and lidocaine is marketed in different preparations. Articaine as an 4 % solution with adrenaline 1:100 000 (Septocaine forte) or 1:200 000 (Septocaine), and lidocaine as an 2 % solution with adrenaline 1:80 000. The fact that articaine is delivered as an 4 % solution, means that when one is calculating the maximum recommended number of carpules that might be used during one single procedure, it is approximately half as much as for lidocaine. Given the recommended maximum dose of 7 mg/kg body weight, the maximum number for articaine would be 7 carpules, while that for lidocaine will be 13.

The fact that articaine can be delivered with an adrenaline concentration of 1:200 000 is important in several situations. For pain control the recommended adrenaline concentration is 1:200 000, alternatively 1:100 000 where extended pain control is required (Jacob 1989). When it comes to post-operative pain, adrenaline is one of the major pain inducing factors, and limiting the concentration from 1:80 000 to 1:160 000 reduces the level of post-operative pain (Jorkjend 1998). For hemostasis the 1:50 000 dilution of adrenaline is more effective than less concentrated solutions (Buckley & al 1984), and adrenaline dilutions of 1:50000 and 1:100000 are considerably more effective in restricting surgical blood loss than local anesthetics without vasoconstrictor additives (Sveen 1979).

For some patients the use of adrenaline in local anesthesia might be dangerous, and potentially fatal. For instance patients with thyreotoxicosis, heart disease (ASA II-V), and patients taking drugs as MAO and TCA represents risk patients when using local anesthetics containing adrenaline (Malamed 1997). When it comes to treatment of these patient groups, the adrenaline concentration of the anesthetic solution becomes interesting. Articaine 4 % with adrenaline 1:200 000 might be a better choice in these situations compared to lidocaine 2 % with adrenaline 1:80 000.

Articaine is delivered as a 4 % solution and lidocaine as a 2 % solution. This again means that when the same recommendations for the maximum doses are applied, one can inject twice as many carpules of lidocaine when compared with articaine. This is important to be aware of during situations where more anesthetics have to be re-injected. But, there is another feature that has to be taken into account when one is re-injecting anesthetics and is concerned about the maximum doses, and that is the elimination half-life. As mentioned before, articaine contains an additional ester group that is quickly hydrolyzed by plasma esterases (Oertel & al. 1997). This gives articaine a elimination half-life of approximately 20 minutes, compared to that for lidocaine which is approximately 90 minutes. This makes re-injection of articaine safer, since the majority of that initial dose are metabolized after approximately half an hour, and the re-injected dose will not be added to the initial one (Isen 2000).

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