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Efficacy of Articaine over Lidocaine – A Review

M.P. Santhosh Kumar M.D.S,
Reader, Saveetha Dental College and Hospital, chennai.

Abstract:

The currently available local anesthetic agents are capable of providing high quality nerve blockade in a wide variety of clinical circumstances. Our understanding of the mechanisms and consequences of toxicity is increasing rapidly. Knowledge of the chemistry of local anesthetics has enabled clinicians to exploit the increased safety. Local anesthesia is an important part of the daily routines for a dentist. There are many local anesthesia available of which the most commonly used is lidocaine. The purpose of this paper is to review the use of articaine in dentistry. Literature on use of articaine in comparison to lidocaine is reviewed. Literature review shows articaine is well tolerated and useful local anesthetic agent than lidocaine.

Key words: Local Anesthesia, lidocaine, articaine.

INTRODUCTION:

Pain control in clinical dentistry is mainly achieved using local anaesthetic (LA) drugs. A revolutionary advancement of the late 1800s was the discovery of local anesthetics that facilitated pain prevention without the loss of consciousness. Since that time, a broad spectrum of local anesthetics has been gradually developing. These developments in pain control have enabled the selection and use of local anesthetic drugs based on the individual requirements of patients and the type of procedures.

Articaine:

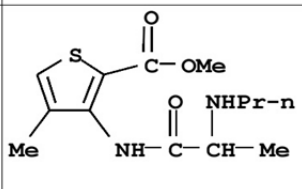
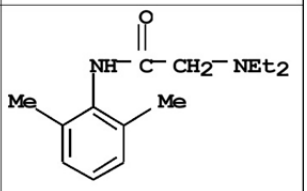
Articaine was originally synthesised as articaine in 1969 and entered clinical practice in Germany in 1976 (1). The name was changed in 1984, the year it was released in Canada (2). It then entered the United Kingdom in 1998, (1) the United States in 2000 (3) and Australia in 2005 (4). Currently, articaine is available as a 4% solution containing 1:100, 000 or 1:200, 000 adrenaline.

Lidocaine:

Upon its clinical availability in 1948, lidocaine hydrochloride became the first marketed amide local anesthetic (2). At that time, it replaced the ester-type local anesthetic procaine (Novocain) as the drug of choice for local anesthetics in dentistry. Lidocaine hydrochloride has maintained its status as the most widely used local anesthetic in dentistry since its introduction. Proven efficacy, low allergenicity, and minimal toxicity through clinical use and research have confirmed the value and safety of this drug. Thus, it became labeled the"gold standard" to which all new local anesthetics are compared (5).

Null Hypothesis: The null hypothesis was that no statistically significant difference exists between the anesthetic efficacy of initial administration of two percent lidocaine hydrochloride and four percent articaine hydrochloride, both with epinephrine 1:100,000 in dental applications.

Table (1) showing the properties of articaine and lidocaine:

Substance	Articaine	Lidocaine
Chemical formula	3-N-Propylamino-proprionyl-amino-2-carbomethoxy-4-methylthiophene hydrochloride	2- Diethylamino 2′, 6-acet-oxylidide 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)

GENERAL STUDIES:

1. CHEMICAL AND PHARMACOLOGICAL PROPERTIES:

The chemical and pharmacological properties of the two drugs can give valuable information about the clinical effects of both the drugs. Some of the most important properties of both articaine and lidocaine are listed below in Table (1).

2. ABSORPTION AND DISTRIBUTION:

Intravenously administered local anaesthetic is initially distributed to highly per- fused organs such as brain, kidneys and heart, followed by less well perfused tissues such as skin, skeletal muscle and fat. Local absorption into those organs will be affected by lipid solubility, pK_a, protein binding as well as binding to other blood born sites (*e.g.* ery- throcytes), tissue binding affinity and clearance, as well as patient factors such as cardiac output and metabolic status. The site of injected local anaesthetic has a significant effect on plasma levels with the highest peak levels from intercostal and caudal injections followed by lumbar epidural, brachial plexus, sciatic and femoral injections (6).

3. METABOLISM:

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 anesthetics.

Articaine:

The molecular structure of articaine is characterized by having both lipophilic and hydrophilic ends connected by a hydrocarbon chain. The "CO linkage" between the hydrocarbon chain and the lipophilic aromatic ring classifies articaine as being an ester local anesthetic, in which the link is metabolized in the serum by plasma cholinesterase. Articaine is quickly metabolized via hydrolysis into its inactive metabolite articainic acid, which is partly metabolized in the kidney into articainic acid glucuronide (7).

The pharmacokinetics and metabolism of articaine have been studied in ten patients undergoing intravenous regional anesthesia using 40 mL articaine 0.5% (200 mg) (8). During tourniquet application and regional analgesia, 55% of the administered dose was already hydrolyzed by plasma (20%) and tissue (35%) esterase activity. After releasing the tourniquet, articaine and its metabolite articainic acid appeared in the blood; articaine was rapidly eliminated with a half-life of approximately 60 minutes . Low systemic concentrations and rapid metabolism of articaine also have been observed in a study during and after tumescent local anesthesia (infusion) for liposuction using dosages up to 38.2 mg/kg body weight (9). Average maximum plasma concentrations (Cmax) for articaine ranged from 136 (hips) to 264 ng/mL (abdomen); the average extent of absorption (AUC) ranged from 827 to 2203 ng · h/mL. The corresponding Cmax and AUC values for articainic acid were substantially higher, ranging from 1719 to 7292 ng/mL and from 13,464 ng · h/mL (chin) to 74,962 ng · h/mL (abdomen), respectively. In liposuction, part of the applied drug is removed in the aspirate, and around 30% of the infused dose was recovered in the plasma.

Lidocaine:

The onset of action of lidocaine is about 45 to 90 sec and its duration is 10 to 20 min. It is about 95% metabolized (dealkylated) in the liver mainly by CYP3A4 to the pharmacologically active metabolites monoethylglycinexylidide (MEGX) and then subsequently to the inactive glycine xylidide. MEGX has a longer half-life than lidocaine, but also is a less potent sodium channel blocker (10). The volume of distribution is 1.1-2.1 l/kg, but congestive heart failure can decrease it. About 60-80% circulates bound to the protein $alpha_1$ acid glycoprotein. The oral bioavailability is 35% and the topical bioavailability is 3%.The elimination half-life of lidocaine is biphasic and around 90–120 min in most patients. This may be prolonged in patients with hepatic impairment (average 343 min) or congestive heart failure (average 136 min) (11). Lidocaine is excreted in the urine (90% as metabolites and 10% as unchanged drug) (12).

4. 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 (Malamed 1997).

Clinical studies:

Clinical comparison on efficacy of articaine over lignocaine:

Articaine has been widely used in dental surgery. Dentists started to use articaine around 1977 (13). In dentistry, articaine has been investigated extensively. Clinical trials comparing articaine mostly with lidocaine have varied in study design and site of action. The overwhelming majority of references in the literature describing the alleged neurotoxicity of articain concern paraesthesia and prolonged numbness after dental procedures. An excellent review of the dental literature was published last year (14). The authors concluded that articaine is a safe and effective local anesthetic drug to use in all aspects of clinical dentistry for patients of all ages, with properties comparable to other common local anesthetic agents. Although there may be controversy regarding its safety and advantages in comparison to other local anesthetics, there is no conclusive evidence demonstrating neurotoxicity or significantly superior anesthetic properties of articaine for dental procedures. The choice whether to use articaine or

another local anesthetic is based on the personal preference and experiences of individual clinicians (15). Currently, articaine is available as a 4% solution containing 1:100,000 or 1:200,000 epinephrine. Clinical trials comparing 4% with 2% solutions show no clinical advantage of 4% over a 2% solution (16,17).

Complications of articaine and lidocaine & Clinical comparison:

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, trismus, hematoma, oedema and facial nerve paralysis, and systemic complications such as overdoses and allergic reactions.

Another major complication found common in patients is known as 'Paresthesia'.

Clinical comparison:

Malamed & al. (2001) 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. The overall incidence of adverse events in the combined studies was 22 % in the articaine group and 20 % in the lidocaine group which are listed in Table (2).

Table (2) showing incidence of adverse effects of both articaine and lidocaine [Malamed & al. (2001)]:

Paresthesia controversy:

Paresthesia, a short to long-term numbness or altered sensation affecting a nerve, is a well-known complication of injectable local anesthetics and has been present even before articaine was available (18,19).

An article by Haas and Lennon published in 1993 (20) seems to be the original source for the controversy surrounding articaine.

This paper, analyzed 143 cases reported in to the Royal College of Dental Surgeons of Ontario (RCDSO) over a 21-year period. The results from their analysis seemed to indicate that 4% local anesthetics had a higher incidence of causing paresthesia, an undesirable temporary or permanent complication, after the injection. The authors concluded that "...the overall incidence of paresthesia following local anesthetic administration for non-surgical procedures in dentistry in Ontario is very low, with only 14 cases being reported out of an estimated 11,000,000 injections in 1993. However if paresthesia does occur, the results of this study are consistent with the suggestion that it is significantly more likely to do so if either articaine or prilocaine is used."

In another paper by the same authors (21), 19 reported paresthesia cases in Ontario for 1994 were reviewed, concluding that the incidence of paresthesia was 2.05 per million injections of 4% anesthetic drugs. Another follow up study by Miller and Haas published in 2000 (22), concluded that the incidence of paresthesia from either prilocaine or articaine (the only two 4% drugs in the dental market) was close to 1:500,000 injections. (An average dentists gives around 1,800 injections in a year (23).

Tablel 2

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)
Body as a whole		
Face edema	13 (1)	6 (1)
Headache	31 (4)	15 (3)
Infection	10 (1)	3 (<1)
Pain	114 (13)	54 (12)
Oral system		
Gingivitis	13 (1)	5 (1)
Nervous system		
Hypoesthesia	7 (<1)	5 (1)
Paresthesia	11 (1)	2 (<1)

Almost all recorded cases of long term numbness or altered sensation (paresthesia) seem to only be present when this anesthetic is used for dental use (no PubMed references for paresthesia with articaine for other medical specialties), and only affect, in the vast majority of the reports, the lingual nerve.

Nonetheless, direct damage to the nerve caused by 4% drugs has never been scientifically proven (24).

Some research points to needle trauma as the cause of the paresthesia events (25,26).

CONCLUSION:

Based on the results of this review, a clear difference between articaine and lidocaine was observed. An evidence-based approach to the current available literature suggests that articaine is an effective and well-tolerated anaesthetic for dental use when compared to lidocaine. However, practitioners should be aware of a possible, as yet unproven, link between 4% concentrations of local anaesthetic solution and nerve damage.

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