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Articaine Hydrochloride: Is it the Solution?

Abstract: In recent times there has been raised interest regarding the use of articaine hydrochloride as a dental local anaesthetic solution. The use of articaine hydrochloride as a dental local anaesthetic agent has been reported to be safe and effective. Paraesthesia is a rare but unwanted adverse effect attributed to the use of this local anaesthetic in dentistry, particularly following the administration of a nerve block injection. There is no evidence to support the opinion that the use of articaine carries a greater associated risk of paraesthesia than with the use of any other local anaesthetic.

Clinical Relevance: The aim of this article is to review the relative merits of articaine hydrochloride against its documented potential drawbacks. The article will also aim to update readers on the use of articaine hydrochloride for local analgesia in dentistry, including the pharmacology, efficacy and safety concerns (including the risks of nerve paraesthesia) commonly associated with the administration of this agent.

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The first local anaesthetic introduced to the dental profession was cocaine in 1886.[1,2] In 1905, procaine was developed by the German chemist, Alfred Einhorn. The popular use of procaine (Novocaine) continued into the mid 1940s. Both cocaine and procaine are ester-based compounds.[3] Lidocaine, also known as lignocaine, was the first amide-based category of local anaesthetic to be synthesized in 1943 and marketed in 1949.

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Lidocaine very soon became recognized as being the 'gold standard' of dental local anaesthetics, and has since been followed by other amide-containing local anaesthetics, such as mepivacaine, prilocaine, articaine, bupivacaine and etidocaine.[3]

In 1976, articaine was introduced to the European dental market following its development in 1969[4] in Germany. Until 1984, the drug was referred to as Carticaine. It is generally available in two commercial formulations, as articaine hydrochloride 4% with 1:100,000 adrenaline (A100), and 4% articaine hydrochloride with 1:200,000 adrenaline (A200). A popular brand of articaine in the UK is Septanest, marketed by Septodont. Other popular brand names include, Ubistesin and Ubistesin Forte (3M ESPE), Articadent (Dentsply), Zorcaine (Carestream Health/Kodak) and Astracaine (Dentsply, originally by AstraZeneca).

Although evidence to support the anecdotal claim that articaine is a superior agent in comparison to other popular local anaesthetics is largely lacking, the use of this drug has proved to be very popular among general dental practitioners and endodontists over the course of the past decade.[3] The aim of this paper is to review the pharmacology, efficacy and safety concerns commonly cited with the administration of this drug in dentistry.

Pharmacology of articaine

All local anaesthetics have three molecular components, an aromatic benzene ring, an intermediate amide or ester chain and a terminal amine.[5]

Articaine is a unique local anaesthetic as it contains both an amide group and an ester linkage. It has a thiophene ring instead of a benzene ring and has the chemical formula of 3-N-propylamino-proprionylamino-2-carbomethoxy-4- methylthiophene - $C_{13}H_{20}N_2O_3S$.

The terminal amine of articaine is of the tertiary amine variety, which renders the molecule lipid soluble. The presence of a thiophene ring will also further enhance the lipid solubility of this agent. Owing to the relatively greater lipophilic nature of the articaine, a solution containing articaine has

a relatively greater potential to penetrate through the neuronal sheath and membrane, respectively, when compared to other local anaesthetic agents.[4,5]

Of additional importance to the above phenomenon is the dissociation constant (pKa) of articaine, which affects the onset of action of the agent; articaine has a pKa of 7.8 (whilst lidocaine has a pKa of 7.9).[6] The lower the relative pKa value, the greater the proportion of the uncharged base molecules that will be available to diffuse through the nerve sheath, which may prove significant when a local anaesthetic is administered to anaesthetize abscessed or inflamed tissues, where there is a concomitant decrease in physiological pH of the affected tissues.

A 2.2mL cartridge (Figure 1) consisting of 4% articaine hydrochloride with adrenaline 1 in 100,000 (A100) usually contains 88 mg (40mg/mL) of articaine and 10µg/mL adrenaline.[7]

The maximum recommended dose for 4% articaine is 3.2 mg/lb or 7 mg/kg body weight for adult patients; a total dosage application of 500 mg is considered to be the absolute maximum. The use of this drug is not recommended for patients under the age of four years. However, the administration of 2% articaine for paediatric dentistry has been reported to be clinically acceptable, due to the lower serum levels of the maximum concentration of articaine coupled with the relatively shorter half-life of 4% articaine.[8] To avoid excessive dosage in obese children, the dose should be calculated on the basis of ideal weight for height.[9]

Articaine hydrochloride has a half-life of approximately 20 minutes, in comparison to lidocaine, which has a half life of 90 minutes, thereby rendering the former less systemically toxic than other local anesthetics.[5] Articaine's metabolites are excreted from kidneys mainly as articainic acid as the primary metabolite (which is inactive). About 5–10% of articaine is eliminated unchanged.[10] The ester group present in articaine is hydrolyzed by plasma esterases, hence articaine is relatively rapidly metabolized immediately upon administration, whilst its amide group is bio-transformed in the liver by hepatic microsomal enzymes (cytochrome p450), which is a relatively slow process.

Efficacy

Whilst it is believed that 4% articaine has a relatively quicker time of clinical onset and a more profound duration of clinical activity, respectively, when compared with other local anaesthetic agents, there is debate over the potency of this drug when compared to other local anaesthetic agents.

Whilst Malamed *et al* have reported there to be no significant difference in the relative pain relief offered between 2% lidocaine with 1:100,000 adrenaline and 4% articaine with 1:100,000 adrenaline, respectively,[4] a relatively recent systematic review has elucidated conflicting results.[11] The latter showed that the probability of attaining successful anaesthesia with 4% articaine solution containing 1:100,000 adrenaline was almost four times greater than with a similar volume of 2% lidocaine containing 1:100,000 adrenaline, when considering infiltration anaesthesia. The latter technique is a common procedure to anaesthetize maxillary teeth and mandibular anterior teeth. Further studies have shown that, whilst 4% articaine offers superior levels of anaesthesia in the anterior maxillary region (maxillary lateral incisor tooth) when compared to 2% lidocaine, the level of superiority achieved appears to be less evident in the maxillary molar areas (maxillary first molar).[12] Similar variations have been reported for mandibular teeth, possibly accounted for by differences in the thickness of its cortical plate going from the anterior region to the posterior.[13]

Evidence for the superiority offered by articaine hydrochloride when applied via the inferior alveolar nerve block (IANB) technique was also reported by Brandt *et al*.[11] However, the relative level of potency of the agent when administered via the IANB technique was noted to be considerably lower than the relative potency when applied by the infiltration technique, using a similar volume of lidocaine at the stated aforementioned dose, with an odds ratio of 1.57.[11] However, it would appear that neither one agent demonstrated superiority over the other when administered to symptomatic teeth. It is also important to stress the limitation of comparing a 4% solution (of articaine hydrochloride) with a 2% solution (of lidocaine).[11]

Meta-analyses undertaken by Paxton and Thome[14] and Katyal,[15] respectively, have also described a higher level of superiority of a solution containing 4% articaine hydrochloride with 1:100,000 adrenaline with that of a solution of 2% lidocaine containing 1:100,000 adrenaline, when applied to anaesthetize first permanent molar teeth, regardless of the mode of anaesthetic administration.

Whilst there is some evidence to support the notion that, in the presence of inflamed pulpal tissues, articaine has been shown to be more effective in attaining effective pulpal anaesthesia in the maxillary posterior region (when compared to lidocaine),[16] there is, however, insufficient evidence to support a similar level of superiority for mandibular teeth, where the

Figure 1. Articaine cartridge (Septodont) after use showing how little solution is required for the administration of two supra-crestal infiltrations for the case shown in Figure 2.

solution has been delivered by means of an IANB technique.[17] The use of the Gow-Gates block technique to deliver articaine to anaesthetize inflamed pulpal tissues has been suggested to provide a more effective method in possibly attaining a desired level of anaesthesia.[18]

The administration of articaine in the posterior mandible has been shown to be significantly more effective than lidocaine (2% containing 1:100,000 adrenaline) in achieving pulpal anaesthesia where both agents were delivered by buccal infiltration alone.[19] It was also demonstrated that articaine was faster than the lidocaine with respect to the time of clinical onset of pulpal anaesthesia.[19]

It has also been reported that, where 4% articaine with 1:100,000 adrenaline was administered to the subjects (between two different appointments with an interval of more than one week), buccal infiltration had a significantly faster onset of pulpal anaesthesia and, indeed, more successful anaesthesia (54%) than IANB (43%). The latter concluded that clinicians may consider the use of articaine administered by a buccal infiltration as a viable alternative to the IANB in the mandible to anaesthetize the mandibular first molar due with a possible faster onset of pulpal anaesthesia.[20] Another study has reported the use of articaine delivered by buccal infiltration alone to be more effective than lidocaine applied by the inferior alveolar technique for anaesthetizing mandibular first molar teeth.[21]

The additive administration of lidocaine (delivered by the IANB technique) and articaine (buccal infiltration) could, however, potentially increase the level of pulpal anaesthesia attained in the mandibular premolar and molar region.[22]

The concentration of the vasoconstrictor present in the anaesthetic solution appears only to have limited impact on the efficacy of a given agent.[23,24] However, the inclusion of adrenaline in 4% articaine is considered to be essential for the consistent achievement of profound anaesthesia.[24]

Adverse effects (excluding paraesthesia)

Commonly cited adverse effects of 4% articaine hydrochloride on the CNS include restlessness, anxiety, tinnitus, light-headedness, excitement, convulsions, dizziness, tremors, depression and drowsiness.[25] Ophthalmologic complications have additionally been reported to occur with the use of articaine. Such ocular complications may be due to diffusion of the anaesthetic solution through the bone and soft tissues, or perhaps be accounted for by articaine's ability to interrupt motor and sensor pathways.[26] Kocer *et al* reported the occurrence of ophthalmic complications (diplopia on lateral gaze) for up to one day following the administration of two carpules of articaine with 1:100,000 adrenaline via the IANB.[27]

Headaches, facial oedema and gingivitis have also been described as common adverse effects.[25] Skin necrosis of the chin after IANB with 4% articaine containing 1:200,000 adrenaline has also been reported.[28]

The effect of 4% articaine hydrochloride on the cardiovascular system include:

- Reduced myocardial contractility;
- Peripheral vasodilation;
- Depressed cardiac conduction and excitability;
- Ventricular arrhythmia;
- Cardiac arrest; and, rarely,
- Death.[29]

As the drug is metabolized in the liver, caution needs to be applied when its use is planned for patients with severe hepatic impairment.

However, articaine is one of the local anaesthetics that has a relatively higher level of safety due to its rapid breakdown to an inactive metabolite (articainic acid) and results in a very low systemic toxicity.[30,31]

Allergic reactions to local anaesthetic are extremely rare but allergic reactions, such as skin rashes and itching following the administration of articaine, have been reported in the contemporary literature.[32] Hypersensitivity may also occur due to the presence of sodium metabisulphite, which is commonly added to local anaesthetic solutions as a preservative agent.

Paraesthesia

Paraesthesia is one of the unwanted adverse events which has been associated with the use of local analgesia, particularly when administered via the IANB technique.[33] Paraesthesia has been defined as 'an unusual abnormal, but not painful, spontaneous or evoked sensations (tingling or pricking), and burning sensation'.[33]

Dentists often comment about the possibly increased risk of paraesthesia associated with articaine. Much of this may stem from post-marketing observational research undertaken in Denmark, which showed that the incidence of reports of nerve injury when articaine was administered via the IANB technique was 20-fold greater than with other local anaesthetics.[34]This is indeed surprising, given that the articaine hydrochloride molecule is reported as being less neurotoxic than other anaesthetics.[35,36]

The aetiology of paraesthesia is not exactly known, but may be related to a possible plethora of factors such as:

- Needle injury of the lingual and inferior alveolar nerve being accidentally inflicted during the undertaking of the IANB technique;
- Intra-neural haematoma;
- Extra-neural haematoma;
- Oedema (extra- and intra-neural);
- Chemical neurotoxicity of articaine.[37]

Another possibility that would explain the alleged risk of paraesthesia is the phenomenon of the 'Weber effect',[38] where a new product when introduced to the marketplace is subject to a closer level of scrutiny by users than more traditional, well-known products. The latter often results in the tendency towards the reporting of adverse effects associated with the newer product. The profile of the number of adverse events reported for articaine, as presented in a recent publication, is in perfect accordance with the Weber effect.[37] This effect may possibly explain why, shortly after the introduction of articaine 4% containing1:100,000 adrenaline in 2000 in the USA, there was a peak in the incidence of the reporting of paraesthesia during the following two years, which then concomitantly reduced despite the number of cartridges being used increasing.

It would appear that the lingual nerve is more frequently affected than the inferior-alveolar nerve.[39] It has also been shown approximately that 70% of permanent nerve damage is sustained by the lingual nerve, as opposed to a 30% occurrence with the inferior alveolar nerve.[39] According to present data, 85%–94% of the non-surgical paraesthesia induced by

local anaesthetics (including 4% articaine) generally recovers spontaneously within eight weeks from the point of administration. For the remainder of patients who do not display resolution, it has been reported that approximately one-third of them will eventually recover, whilst two-thirds will unfortunately never attain a complete level of recovery.[39]

The suggested reason for the lingual nerve being twice as frequently affected by paraesthesia as the inferior alveolar nerve may relate to the fascicular pattern of the injection site. In one-third of the cases, the lingual nerve has only one fascicle above the lingula of the mandible, whilst the inferior alveolar nerve typically has a multifascicular pattern.

When the patient's mouth is open, the lingual nerve is anatomically relatively more anteriorly placed and stretched; therefore, the lingual nerve may not then have the desired level of flexibility to deflect the needle. The largest needle, which is usually used in dental injections, is a 25-gauge needle. A 25-gauge needle has an 0.45 mm external diameter. The average diameter of lingual nerve is 1.86 mm; therefore the 25-gauge needle has considerably less thickness than the lingual nerve.[37]

During any type of nerve block technique in which the needle needs to touch bone, it can bend the bevel inwards or outwards. The barbed needle may damage the nerve (inferior alveolar or lingual) during withdrawing the needle. This trauma may explain the cause of paraesthesia and trismus.[40]

An *in vivo* study published in 2012 measured the toxic effect of articaine 4% with adrenaline, lidocaine 2% with adrenaline and adrenaline alone on rat mental nerves. The authors showed that adrenaline alone was significant in leading to a higher level of inflammation than the two other test groups. They also concluded that articaine 4% was not toxic to the nerve tissue.[41] These results are in agreement with two *in vitro* studies on neuroblastoma cells,[35,36] which both ranked molecules regarding their neurotoxicity.

An alternative injection site to the traditional buccal sulcus infiltration is the supra-crestal injection, which has been used by the authors for many years (Figure 2). A recent evaluation in general practice indicated a high success rate and minimal patient discomfort.[42] This technique is a much less invasive alternative to the intra-osseous injection, which is unpopular and requires more expensive and complex equipment, including handpieces, drills and syringes.[43]

Conclusion

Articaine appears to be a safe and effective drug for use with routine clinical dental procedures. Its adverse effects are very rare. Articaine-induced paraesthesia after inferior alveolar nerve block is no longer a controversial issue and is no greater than for other local anaesthetics in use in the dental clinic. Articaine has rapid onset and profound duration of action and displays superior efficacy when compared to other popular anaesthetics, such as lidocaine, when delivered by infiltration. It may be possible to replace the inferior alveolar nerve block technique by a buccal infiltration of articaine to minimize the risk of paraesthesia further.

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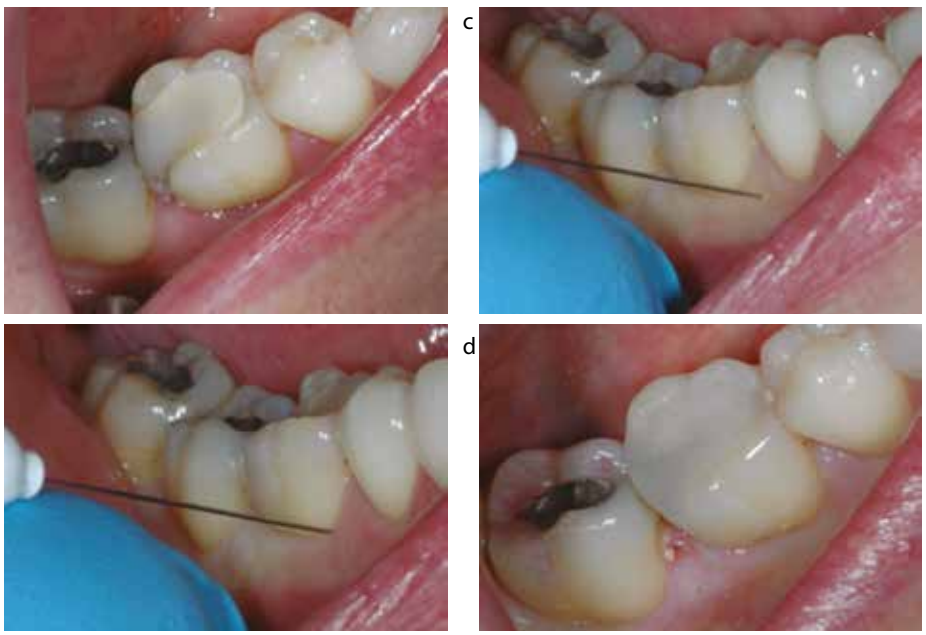

Figure 2. **(a)** A failed composite resin is to be replaced in LR6. **(b)** The site of an intra-ligamentary injection is illustrated for comparison. **(c)** The site for the supra-crestal injection is shown 5 mm below the tip of the papilla and 3 mm away from the gingival margin. **(d)** The restoration has been replaced and the gingival blanching is still visible, providing useful haemostasis following trauma from the matrix band and wedge placement.

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