Review Article

Articaine: An Alternative to Lignocaine

Seema Malhotra[1], Vinay Kumar Gupta[2], Swastika Suvirya[3], Nitin Singh[1], Rachana Bahuguna[1] and Suleman Abbas Khan[1]

ABSTRACT

Aim: A review on articaine sheds light on a new anaesthetic with better pharmacokinetics and pharmacodynamics than lidocaine and lesser toxicity.

Summary: Indispensible aspect of patient care is local pain management by anesthesia. Lignocaine has been the gold standard for pain control in dentistry. Articaine is the newest local anesthetic which was approved by the Food and Drug Administration (FDA) in April 2000. For achieving adequate anesthesia a lesser volume but a higher concentration of articaine is used. Articaine is safe for procedures requiring short duration of action with fast onset and faster offset of sensory and motor effects. Articaine related analgesic potency is intermediate. It may be an alternative to lidocaine in future as shows better properties.

Keywords: Articaine, local anaesthetic, pharmacodynamics, pharmacokinetic

INTRODUCTION

Rapid advancement in pharmacotherapeutics necessitates clinicians to constantly apprise themselves of new drugs, drug interactions and useful therapeutic trends. Indispensible aspect of patient care is local pain management by anesthesia[1]. Local anesthetics block peripheral nerves and are used to prevent pain, to provide motor blockade during surgical or dental procedures, and in the management of chronic pain.[2] Prevention of pain can cultivate the bond and trust of health care professionals and patient thereby alleviating apprehension. Articaine is available in 4% strength with 1:100,000 or 1:200,000 epinephrine. It is classified as an amide local anesthetic because of the linkage between its lipid-soluble ring and terminal amine and differs from the other amide local anesthetics because it contains a thiophene ring (in place of benzene ring). Thus, it is only amide anaeshetic that also contains an ester group. This thiophene ring allows greater lipid solubility facilitating diffusion across the lipid-rich nerve membrane to access target receptors.[3]

Dr Seema Malhotra completed her graduation (BDS) from Vinayaka Mission Dental College Sitapur in year 2003 and postgraduation (MDS) in Pedodontics & Preventive Dentitsry from Faculty of Dental Sciences, King George's Medical Univeristy, Lucknow (UP), India in 2008. Currently, she is working as Reader in Saraswati Dental College & Hospital, Lucknow (UP), India.

[1]Departments of Pedodontics & Preventive Dentistry, Saraswati Dental College & Hospital, [2]Public Health Dentistry, Faculty of Dental Sciences, [3]Dermatology, Venereal & Leprosy King George's Medical University, Lucknow (UP), India.

Address for Correspondence:
Dr Seema Malhotra, Department of Pedodontics & Preventive Dentistry, Saraswati Dental College & Hospital, 233 Tiwari Ganj, Faizabad Road, Chinhat, Lucknow (UP), India.
Contact: +91 9794262027, E-mail: seema0677@gmail.com
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Method of data collection and interpretation: Literature search was conducted in MEDLINE (PubMed) and the Cochrane Central Register of Controlled Trials (CENTERAL). Additionally, reference lists of selected papers were hand searched for further relevant peer review articles. The search was limited to articles and books in English. Different combinations of relevant keywords were used to identify articles.

PHARMACODYNAMIC PROPERTIES

Mechanism of action: The blocking action of articaine on the sodium channel is state dependent: it has the highest affinity for the open state, an intermediate affinity for the inactivated state, and the lowest affinity for the resting state.[4] The onset of anesthesia following administration of articaine with 1:100000 epinephrine has been shown to be within 1 to 9 minutes of injection. The onset of action of 4% articaine with 1:200000 epinephrine is 1.5-1.8 minutes for maxillary infiltration and 1.4-3.6 minutes for inferior alveolar nerve block.[5,6] Complete anesthesia lasts approximately 1 hour for infiltrations and for nerve block approximately 2 hours. Both concentrations impart a rapid onset of analgesia and a similar degree of pulpal (approximately 1 hour) and soft tissue analgesia (3-5 hours).[7]

The potency in the 4% articaine with 6 microgram/mL epinephrine was 2.8 times that of the lignocaine.[8]

PHARMACOKINETIC PROPERTIES

Absorption and distribution: Articaine with an additional ability to form an intramolecular hydrogen bond modulates lipophilicity of articaine leading to enhancement of its diffusion through membranes and connective tissue.[9] Due to high lipid solubility it was observed that after extraction the concentration of articaine in the alveolus of a tooth in the upper jaw was about 100 times higher than that in systemic circulation.[10]

Distribution of drug depends upon the degree of tissue and plasma protein binding.[11] Articaine containing 1:200,000 epinephrine reaches peak blood concentration in about 25 minutes following a single-dose dental injection. Peak plasma levels of articaine achieved after 68mg (1.7 ml) is 385 ng/mL.[12]

Metabolism and elimination: Due to the presence of ester it is metabolised both in plasma and tissue, its metabolism is fast as there is large difference between the serum concentration of articaine and articainic acid. Almost 95% of the drug is broken down by plasma cholinesterases.[3] The human liver microsome P450 isoenzyme system metabolizes approximately 5% to 10% of available articaine with nearly quantitative conversion to articainic acid.[12]A study demonstrated articaine undergoing pH-dependent Michaelis-Menten kinetics signifying local saturation of the serum esterases at higher substrate concentrations, causing higher articaine/articainic acid metabolic ratio which results in persistence of the efficacy of local anesthetic and low systemic toxicity.[13]

Articaine is excreted primarily through urine with 53-57% of the administered dose eliminated in the first 24 hours following sub-mucosal administration. The half-lives of elimination (t½ alpha and t½ beta) of articaine are 0.6 and 2.5 hours, whereas the apparent half-life of the metabolite articainic acid is 2.5 hours. Intrinsic half-lives of articainic acid are: t½ alpha 12 minutes, and t½ beta 64 minutes.[12] Articainic acid is the primary metabolite in urine. A minor metabolite, articainic acid glucuronide only excreted in urine as it is glucuronidated by the tubular cells.

CONSIDERATIONS

Articaine is metabolized in the serum by plasma cholinesterase hence patients with liver diseases show decrease in synthesis of cholinesterase. In patients with severe renal failure accumulation of articainic acid and glucuronidated articainic acid can occur, which can theoretically cause local anesthetic systemic toxicity (LAST). Caution to be applied in heart blocks patients and in patients to receive potent general anesthetic agents as cardiac arrhythmias may occur. Systematic allergic reactions caused by articaine have been reported.[14]Articaine use in pregnancy should be limited to cases in which if the predicted benefit validates the risk to the fetus and in nursing women caution should be exercised as no confirmed report have been published citing its non excretion in human milk.

Children: Special caution should be observed when using the amide local anesthetics because a lower intrinsic clearance or a decreased serum protein binding can easily lead to an increased risk of toxic reactions in younger patients.[15] Due to a greater local blood flow and cardiac output than in adults the absorption of local anesthetics from mucous membrane after topical anesthesia is increased in children. In a study investigating 27 children 3–12 years of age, the authors advised the use of 2% articaine in pediatric dentistry because of the lower Cmax and the shorter half-life,[16] but Articaine 4% with epinephrine 1:100,000 is also shown to be effective and safe for use in pediatric dentistry.[17] Recommendations regarding maximum doses of local anesthetics is 5–7 mg/kg.[18] When used in combination with sedatives there could be masking of the clinical signs, hence the lower limit for children aged 4-12 years should be <5mg/kg.[19]

Safety and Toxicity: Sulfur molecule an integral part of the thiophene ring of articaine HCl is not available to act as an allergen, hence can be given safely to patients with known sulfur allergy. Articaine does not liberate a metabolite resembling PABA and does not introduce concern regarding immunogenicity.[20] Due to fast hydrolysis lesser quantity of a thiophene derivative in a product may be needed to block the ionic channels in the endoneurium[21] and most of articaine reaches systemic circulation as inactive metabolite, thus reducing the risk of systemic intoxication[20, 22] and articaine is safe and efficient with no adverse effect.[23] An in vitro study using a of 4% articaine into rat sciatic and cat sciatic nerves observed that the average axonal cross-section areas were unaffected when matched to the non-injected opposite side,[24] hence paraesthesia may not solely be due to articaine derivatives. Malamed reported 2% incidence of accidental lip injury.[25] According to a study paraesthesia with soft tissue injury at 5 hrs was evident in local anesthesia site particularly in relation to children younger than 7 years.[26] Clinical profiles of neurotoxicity of articaine have been based on the reported incidence of paresthesia in dentistry.[27-29] In 2005, the US Food and Drug Administration required a new paresthesia warning in the package insert.[30] Articaine has myotoxic effects (sustained contraction of the masticatory muscles) as it competitively inhibits Ca-ATPase enzyme activity in concentrations lower than those used in dentistry[31] and inhibits phosphorylation of the enzyme by inorganic phosphate.[32] Other reported adverse reactions to articaine are hypersensitivity,[33] ophthalmologic complications,[34-37] ischaemic skin necrosis[38] and fever, chills and arthralgia.[39] Articaine produces moderate fluctuations in action potential morphology even in the circumstances of overdose as its

suppressive effects on the inward and outward currents are comparatively stable.[40] The wide safety index permits for earlier re-injection during a dental appointment, with fewer worries of attainment of toxic levels.[41]

Comparison of Articaine with Lignocaine: For achieving adequate anesthesia a lesser volume but a higher concentration of articaine is used as it is 1.5 times as potent as lidocaine.[19]

Molecular dynamics simulations in a lipid bilayer: Variances in the behaviour of lidocaine and articaine can be drawn to the presence of the second ester group in articaine which provides high affinity to polar atoms of the lipid headgroup and water. Consequently, charged articaine molecule adopt orientation parallel to the bilayer surface, resulting in stronger deterioration of the hydrogen bond structure comparing to charged lidocaine molecules.[42]

Spinal anaesthesia: The frequency of nerve damage with intrathecal articaine seems to be low.[43,44] Articaine when used at 2%–3% demonstrated to be very suitable for spinal anesthesia in day-care patients undergoing lower limb surgery[45] as early ambulation is possible due to quick recovery of both motor as well as sensory block.[44] Greater incidence of neurotoxicity with lignocaine is seen therefore articaine could be a substitute for short acting (ambulatory) spinal anesthesia.

Opthalomology: There was less intensity of pain during infilteration administration of Articaine than lignocaine,[46] rapid onset of anaesthesia,[46-49] significant higher effectiveness of block,[46,50-51] rapid onset of ocular akinesia,[49,51,52] faster offset of anesthesia[47]and ocular akinesia.[52] Articaine requires less volume and less number of supplemental injections to achieve optimal anesthesia,[52] hence articaine can be a suitable alternative to lignocaine for opthalmic surgeries.

Otorhinolayngology: Higher effectiveness of block, significantly lower pain sensation postoperatively and less analgesic intake was observed in the articaine group as compared to lignocaine group.[53]

Dermatology: In a study beneficial effect of Articaine hydrochloride 4% with 1:100.000 epinephrine was validated for infiltrative anesthesia in cutaneous surgery.[54]

Tumescent Local Anesthesia: In a study, Articaine HCl was established to be a safe anesthetic for tumescent liposuction as no cardiac side effects or symptoms of central nervous intoxication and sufficient analgesia was observed,[55] Lidocaine metabolite 2,6-dimethylalanine is considered to have a carcinogenic potential which is not seen articaine, therefore, it was concluded that an inadvertent intravascular injection of articaine 80 mg does not cause toxic effects in healthy individuals. Hence articaine use in varcose vein surgery is growing.[56]

IV Regional Analgesia: Earlier onset of sensory block[57,58] and shorter elimination time[58] of articaine over lidocaine favors the use of articaine for iv regional analgesia in day care settings.

Brachial Plexus Blockade: The result of a study reflects that preference to articaine can be given for achieving brachial plexus block as compared to lignocaine as the onset of sensory block and motor block was comparable.[59]

Dentistry: The interest in articaine has increased tremendously over the last few years and especially in dentistry. The results of many studies on comparing articaine with lidocaine concluded that pulpal anesthesia,[60-62] anesthetic success,[63-66] onset of anesthesia,[61,67-69] and duration of anesthesia[68,70-71] with respect to lidocaine was found to be superior. Many studies[60-75] have compared articaine with lidocaine, the results of various studies have been tabulated and shown in table 1.

CONCLUSION

An earlier onset of action, lower peak plasma concentration, lesser elimination time, faster offset of sensory and motor effects, negligible effect on cardiovascular parameters and no serious adverse events with the use of articaine making it a better alternative to lignocaine.

Table 1: Comparison of Articaine with Lidocaine

Location and Method	Study	No of Subjects	Evaluation Scale Used	Outcome
Maxillary buccal infiltration in irreversible pulpitis	Srinivasan *et al.*[60]	40	Endo ice, VAS	Articaine more effective than lidocaine in anaesthesing pulp in first molar
Bucal infilteration in mandibular posterior teeth in volunteers	Robertson[61]	68	EPT,VAS	Articaine better in achieving pulpal anesthesia with faster onset of anesthesia.
Post mandibular buccal infilteraion in voluneers	Abdulawahab[62]	18	EPT, VAS	Articaine : Complete pulpal anesthesia better with with higher soft tissue numbness Similar adverse events

Maxillary Lateral incisor and maxillary molar infiltration n volunteers	Evans[63]	80	EPT,VAS	Articaine more effective than lidocaine in anaesthesing lateral incisor Wearing of subjective numbness (day 1-3) was parallel
Buccal infilteration in mandibular first molar for pulpal anaesthesia	Kanaa[64]	31	EPT,VAS	Anesthetic success is higher for articaine with similar onset of lip numbness and injection discomfort
IAN B with supplemental buccal and lingual infiltrations in volunteer	Aggarwal[65]	87	Ice stick, EPT,VAS	Articaine provided greater anesthetic success with similar post injection pain
Supplemental buccal infilteration of mandibular first molar after IANB in volunteers	Haase[66]	73	EPT,VAS	Significantly better anesthetic success for articaine Similar intensity of pain during administration and post injection
Incisive/mental nerve block in volunteers	Batista da Silva[67]	40	EPT,VAS	Superior onset of anesthesia for canine upon administering Articaine: Duration of soft tissue and pulpal anesthesia:significantly higher for 1 and 2 premolar No difference in injection pain and post operative pain
IANB with and without articaine as buccal infilteration in vital teeth	Kanaa[68]	36	EPT,VAS	Discomfort only when lidocaine used without articaine
Primary intraligamentary injection in volunteers	Berlin[69]	51	EPT	Onset of pulpal anesthesia with articaine was significantly higher with similar anesthetic success and duration of anaesthesia
Maxillary infilterations and mandibular block for operative procedures	Ram[70]	62	The modified behavioural pain scale, Taddio Wong–Baker faces pain rating scale (FPS)	Efficacy parallel Longer soft tissue numbness with articaine Similar adverse effects
Gow gates and Maxillary infilteration for posterior teeth in irreversible pulpitis	Sherman[71]	42	Endo Ice, VAS	Duration of pulpal anesthesia lower with articaine No difference in pain post treatment
IANB in volunteers	Mikesell[72]	57	EPT,VAS	Similar intensity of pain during administration and post injection No difference in anesthetic success
IANB for mandibular posterior teeth in irreversible pulpitis	Claffey[73]	72	Endo Ice,VAS	Anaesthetic success similar
Supplemental anesthesia in maxillary and mandibular teeth in irreversible pulpitis	Rosenberg[74]	47	VAS, Endo ice	Similar mean VAS score, Mean percentage change VAS between initial and supplements and VAS for maxillary and mandibular teeth
IANB irreversible pulpitis	Tortamano[75]	40	Endo frost, EPT, Verbal analogue scale	Similar pulpal anesthesia and pain
Mandibular block anesthesia in vital teeth	Hillerup[18]	52	Suderland's neurosensory function	Sensory impairment higher with articaine

(EPT : Electric Pulp Tester; VAS : Visual Analogue Scale; IANB : Inferior Alveolar Nerve Block)

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