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Review Article

ARTICAINE – THE QUEEN OF AN INFILTRATIVE ANAESTHESIA? A PECULIAR AMINO-AMIDE LOCAL ANAESTHETIC AND ITS USE IN THE DENTAL PRACTICE FROM A PHARMACOLOGICAL PERSPECTIVE

Marcin Pasternak[1]*

[1] *DDS, Department of Pharmacology, Faculty of Medicine, Jagiellonian University Medical College, 16 Grzegórzecka Str., 31-531 Kraków, Poland*

* Correspondence, e-mail: marcin.pasternak@uj.edu.pl

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ABSTRACT

The importance of local anaesthetics in dentistry cannot be overestimated. Being the most often used drugs in the dental practice, these medicines are simply indispensable, as they allow for intra-operative and partly post-operative pain control in procedures performed. The injectable agents, currently employed in dentistry, belong, almost exclusively, to amino-amide class. The paper focuses on articaine – a peculiar amino-amide local anaesthetic, that exhibits exceptional features distinguishing it from the other drugs in the group and endearing it to dental practitioners all over the world, at the same time. The structure of the drug is presented and characteristics arising from its unique attributes are discussed. The article covers the practical aspects of articaine use in various fields of dentistry and oral surgery and arising prospects for future. Despite the wide safety margin of the agent, articaine, like any other local anaesthetic may induce unwanted side-effects, they were described also and their management was briefly presented.

KEYWORDS: articaine, local anaesthetics, dentistry

1. Introduction

One can not imagine today's dental practice without an effective local anaesthesia. Intra-operative pain control with the means local anaesthesia forms pivotal and indispensable element of dentistry, allowing for painless interventions in the case of all its fields and specialties. Local anaesthetics, currently used in the dental office, are the most often employed drugs by dentists, being the safest and most effective agents preventing and relieving pain known to medicine, at the same time [1]. These medicines show high affinity for the voltage-dependent sodium channels (Na_v), they block them and prevent the influx of sodium cations through the membranes of the neuron, hindering in this way the conduction of impulses in sensory nerves. The potency of local anaesthetic drugs depends primarily on the concentration of the solutions used, while possible side effects are dose-dependent [1].

Amino-ester and amino-amide drugs form the two main groups of local anaesthetics. The first, older class, in injectable dental local anaesthesia almost completely was replaced with the second, and, except topical formulations of benzocaine and tetracaine popular in some countries, amino-ester local anaesthetics are hardly seen in the contemporary dental office [1].

Local anaesthetic drugs used in intraoral procedures in overwhelming majority belong to the amino-amide group. These agents exhibit desirable properties, as lower incidence of allergy, short latency period that results in relatively fast onset of action, all distinguishing them from less favourable characteristics of amino-ester counterparts. Generally, amino-amide local anaesthetics are metabolised in the liver, however there is one significant exception – articaine [1]. The drug stands out in the all amino-amide class in context of chemical structure and resulting properties, that endear it to dental practitioners all over the world [2].

2. Articaine – its structure and characteristics

Articaine bears the chemical name of methyl ester of 4-methyl-3[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid [3]. In all formulations available, the racemic mixture of the drug, ((±)articaine, i.e. (+)articaine and (-)articaine in equal proportion) is present [4]. As the water solubility of the free base of the local anaesthetic is insufficient, in formulations for injection, articaine appears in a form of water-soluble hydrochloride salt [1]. The agent belongs to the amino-amide local anaesthetics class, but is distinguished by peculiarities of the chemical structure shown on the figure 1.

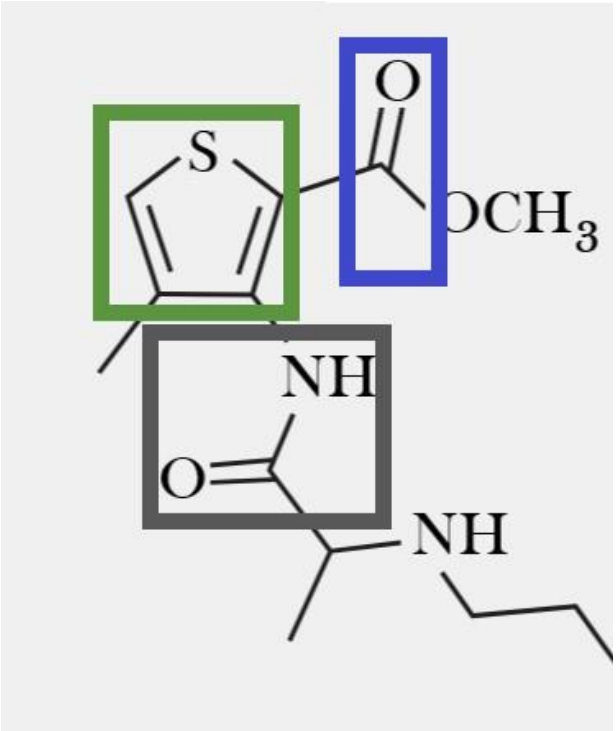

Fig 1. Chemical structure of articaine and its distinguishing features.

Description within the text.

The first remarkable difference is the presence of the thiophene ring (in green square on the fig. 1), instead of, popular in other drugs from the group, a benzene ring. This feature is responsible for excellent lipophilicity, facilitating more efficient diffusion of the drug into surrounding tissues and through the nerve cell lipid membrane [1;3;5]. Amide linkage (in grey square in the figure), binding the lipophilic aromatic ring with hydrophilic amine ending, justifies the fact, that the drug is counted into amino-amide class, however, articaine's molecule possesses an additional side-chain linked with an ester binding (in blue rectangle in figure 1). That distinctive property is big in practical consequences, as the ester binding is rapidly broken by esterase class enzymes ubiquitous in plasma and in tissues. The resulting product of the reaction mentioned is biologically inactive articainic acid [4]. About 90 – 95% of a dose administered is thus already metabolised in plasma, when remaining 5-10% undergoes hepatic metabolism [1]. That exceptional attribute in the class makes articaine the drug of choice in patients with insufficient liver function, including e.g. alcohol-dependent persons [6]. Rapid break down of articaine molecules by plasma carboxylesterases contributes to the short plasma-life of a drug, which for plain solution is usually assessed as not exceeding 20 minutes [7].

3. The mechanisms of articaine-induced nerve block, the drug's use in a various populations of patients

Like other local anaesthetics used in dentistry, articaine blocks nerve conduction by reversibly binding to the α-subunit of the voltage-gated sodium channels (Na_v) within the inner cavity of the nerve, thus reducing sodium influx, so the threshold potential is not reached and impulse conduction stops. 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. The degree of neuronal block is affected by the diameter of the nerve. The block of the conduction in fibres with larger diameter, like those responsible for touch, pressure sensation and motor functions, requires higher concentrations of local anaesthetic, compared with small myelinated fibres (pain afferents) and even smaller vascular sympathetic nerve fibres. The easily achieved block of the latter is responsible for the local vasodilation after the administration of pure articaine solution [8]. Articaine is lipid soluble, highly protein-bound (94%), and has a dissociation constant (pKa) of 7.8 in room temperature [9;10]. A maximal dose recommended by manufacturers is 7 mg/kg patient's body weight [9;10]. The lowest age of patients, in whom the drug can be safely administered, according the manufacturers' guidelines, is four, although, the recent studies are supporting the drug use in even younger populations [11;12]. According some authors, the maximal dose in children should not exceed 5 mg/kg patient's body weight, while others, considering rapid metabolism of the drug, recommend the same dose as in adults (7 mg/kg patient's body weight) [13;14]. The rapid metabolism, peculiar for the drug, depends on the levels of esterase enzymes. In clinical situations, when the enzymes plasma concentrations are lower, like insufficient renal function, cachexia, larger skin burns and some malignant neoplasms, the time needed for breaking the molecules of articaine, although still short is likely to be longer than usual. Particular attention should be paid for female patients in the third trimester of pregnancy or using oral hormone contraceptives as both situations are related to the decrease of cholinesterase class enzymes levels in plasma [8]. The tendency to lowering plasma levels of the enzymes mentioned was observed also in the senior populations. Although the significance of the decrease is still discussed, the articaine use in the lowest effective doses is a prudent and recommended strategy in the everyday dental practice in this special group [4].

Articaine was first synthesized in Western Germany in 1969 under the label, HOE 40-045, and then released for clinical use under the name 'Carticaine hydrochloride' seven years later [3;13]. The first clinical trials of the drug were conducted by Winther and Nathalang in 1971 [15]. Researchers found that 2% articaine with 1:200,000 adrenaline was superior to 2% lidocaine with 1:200,000 adrenaline in anaesthetic duration and extent, and that profound anaesthesia was obtained for all teeth except mandibular molars. That inconvenience can be overcame, when the drug is administered in a higher, 4% concentration [16;17]. Repeated attempts of the use of 2% articaine, that can still be found in literature, clearly show, that in lower concentration the drug is simply less effective, and justify the fact, that for dental use articaine is commercially available as 4% solution formulations [18].

In 1984, the name was changed from carticaine to articaine, and its use was authorised in Canada [13]. In 2000, articaine formulation was approved by the US FDA as a 4% solution with 1:100,000 adrenaline under the name Septocaine (manufacturer Septodont), six years

later the FDA approved 4% articaine with 1:200,000 adrenaline [3]. Last years brought formulations with even lower content of epinephrine, e.g. in dilution 1:400,000, particularly useful in paediatric dentistry [14]. Formulations of plain articaine (4% solution without vasoconstrictor, e.g. Ultracain D, Sanofi-Aventis, France) are also obtainable in some countries, including the drug's homeland - Germany [19]. The last, among developed countries, that authorised articaine dental formulations is Japan, where they became available from the January 2025 [20].

An added, yet surprising value of articaine is its high degree antimicrobial action. Although nearly all cation forms of amino-amide class local anaesthetics (except of ropivacaine) are endowered with some antimicrobial properties, in case of articaine the features are more pronounced and show the most favourable profile, what is important, directed against microbial species present in oral cavity [21;22; 23]. The proposed mechanism of action consists the drug interactions with prokaryotic lipid layers with subsequent formation of pores in membranes and eventual lysis of the bacterial cell [21]. In fact, the bactericidal properties of articaine prompted researchers to add the drug's base as an alkaline component in materials for root canal filling used in endodontics, with satisfying effects obtained [21].

4. Articaine – its place in the dental armamentarium

In their article written twenty years ago, Vree and Gielen observed that '*in dentistry, articaine is the drug of choice in the vast majority of the literature*' [4]. And indeed, number of subsequent papers justifies the drug position in all fields and specialties of the dental practice. Short onset of action, excellent tissue permeation endears the agent to the dentists all over the world [9]. The last quality of articaine results in higher intraneural concentration, more extensive longitudinal spreading, and ensues better conduction blockade obtained after the administration in comparison to lidocaine - a model drug of the group [24]. It was suggested, that thiophene ring, except of increasing the drug's ability to diffuse with ease in tissues, enables obtaining ion channels block at lower concentration than in the case of benzene derivatives [25].

The pronounced lipophilic properties of articaine increases the number of teeth, that can be successfully anaesthetised with infiltration [10]. In many cases it allows dental practitioners to choose infiltration instead of truncular local anaesthesia like inferior alveolar nerve block (IANB), especially in paediatric dentistry, where the porous structure of cortical bone in a young mandible is acting hand in hand with high permeability of the drug [1;14].

Quite significant body of literature is dedicated to the use of articaine in a supplementary buccal injection after the IANB. Reports conclude that such strategy enhances the anaesthetic effectiveness of IANB, even when the other agents were used in the first block [26]. Additional articaine buccal infiltration after IANB is employed in the dental practice with a considerable success even in challenging clinical situations, like the presence of inflammation in the region affected [27]. Reports on clinical efficacy of this strategy are encouraging so far, that supplementary buccal infiltration with articaine may even be considered as a rescue method of local anaesthesia in cases when the effects after IANB are not satisfying [28].

The excellent properties of articaine widely used in infiltrative methods of local anaesthesia does not rule out the drug use in truncular blocks, including IANB - the most often nerve block employed in dental practice [29]. The recent systematic review justifies the use of articaine in this method as a mean of intra-procedural pain control in so demanding and challenging procedure as lower third molar surgical extraction. Articaine was proven to be superior to lidocaine for use in lower third molar surgeries due to its higher success rate, shorter onset of action, greater control of intraoperative pain, and a longer duration of the anaesthetic effect [30]. The last property may seem to be surprising, especially, given the drug's rapid metabolism, but tissue and nerve fibres permeation together with epinephrine-induced vasoconstriction are the most probable reasons for that outcome [1]. As the drug is available in the form of solutions for injection, except of infiltrative and truncular anaesthesia, with success it can be administered in intraligamentary and intraosseous methods as well [1;10].

5. Articaine – prospects for the future, proposed formulation modifications and new applications in dental practice

A shortening of the time needed to for the full unfolding of the anaesthetic effect, together with an increase both of the degree of anaesthesia and patient's comfort during administration, may be obtained by the solution alkalinization, like in the case of other drugs from the group [1;16]. This method is especially effective in the case of IANB. As an overwhelming majority of the drug formulations available are containing epinephrine, due to the preservatives stabilising this sensitive catecholamine, the character of solution is acidic, therefore some patients may experience the burning sensation, during solution administration, regardless of the earlier use of topical anaesthetic in the region of injection. The solution alkalinization, often termed – not quite correctly, from the chemical point of view - "buffering", is a valuable option in this case, as the increase of pH value of formulation injected addresses the cause of the burning sensation [31]. Out of the two currently available in the US commercial local anaesthetic alkalinization systems, that can be used in dentistry, only one (Onset, manufacturer: Onpharma) can be employed for articaine formulations, the chair-side methods described in literature may also be used for this purpose [31].

The matter is different in the case of another way of increasing the comfort during the local anaesthetic administration and shortening the onset time as well, which is to warm the solution to values close to body temperature – here the limiting factor is the epinephrine content in dental articaine preparations. Adrenaline in solutions is thermosensitive and already in temperatures exceeding 25°C (77°F) the agent is easily broken, what practically is ruling out this method in case of the overwhelming majority of the drug's dental formulations available [32].

Given a high lipophilicity of the drug, the fact, that topical formulations of articaine are commercially unavailable, is at least surprising. All the more encouraging are the observations and reports on attempts at local use of the drug in laryngological surgery, a field of medicine quite close to dentistry and oral surgery [33;34]. The simplest method of topical administration, that can be used in the dental practice, is application of

the gauze packs soaked with anaesthetic solution intended for the submucosal injection [35]. In procedures performed in head and neck tissues such strategy was tested in rhinological setting. The nose packs prepared in that way decreased the postoperative pain and, due to the epinephrine content, restricted bleeding after septoplasty [33]. Similarly, immediate topical application of the drug to the tonsillar bed right after the surgery, enhanced postoperative pain management efficacy [34].

A distinct way of the drug's topical use, that can be employed in the dental office, is a pulp-dressing. Although when compared with eugenol, articaine provided lesser reduction in pain in emergency pulpotomy, it is still a valid alternative, notably considering that it is also easily available as one of most often used local anaesthetics. In such indication, the cotton pellet soaked with solution is applied into the chamber of the affected tooth, the resulting effect is obtained rapidly [36].

Intriguingly, despite a moderate time of action, articaine was proven to be a valuable option in postoperative pain management. An encouraging effect in postprocedural pain control was obtained when commercially available solution was combined with dexamethasone and administered in the surgical site in submucosal injection after lower third molar extraction [37].

Despite satisfying properties of the drug's formulations available, recent years brought attempts of an interesting body of research on experimental nano-lipid and nano-encapsulated articaine solutions – preparations with enhanced ability of tissues penetration, usually characterised with longer time of the effect obtained, when compared to unmodified solutions [38;39]. Both experimental types of formulations were tested in animal models, of the note, in case of the latter, articaine-loaded poly-ε-caprolactone nano-capsules allowed for the effective use of 2% drug concentration in postoperative pain management [38;39]. This latter finding is all the more interesting because, as mentioned earlier, the lower, 2% concentration of articaine, used in the unmodified solution was not effective as 4% drug solution in intraoperative pain control in a number of studies [18].

6. Side effects and their management

As every drug available, articaine may induce unwanted side-effects, their management does not differ from the strategies employed in case of similar outcomes related to other agents from the class. Malamed et al. assessed the safety of articaine (4% solution enriched with epinephrine in dilution 1:100,000) in comparison to lidocaine (in 2% concentration, with the same catecholamine in the identical amount added), the first and model drug of the group, for years considered as a golden standard of local anaesthesia in dental practice [40]. The complete incidence of all adverse events was similar in both groups – 22% and 20%, for articaine and lidocaine formulations, respectively. The majority of events reported was mild, and on average self-limiting. The researchers observed no marked difference in the incidence and kind of events. Headache (4%), facial oedema (1%), gingivitis (1%) and paraesthesia and hypaesthesia (1%) were found to be chief complaints. The incidence of headache, and the latter two symptoms described by patients was slightly higher for articaine, although the difference had no statistical significance [40]. Gingivitis among the events disclosed is a particularly puzzling one, especially regarding the antimicrobial properties of the drug [21;22;23]. Contrary to the infection, which may occur due to the negligence in procedure, rather then properties of the formulation, for example when the needle is inserted through submucosal abscess, bringing the bacteria deeper, the entity reported may be related to epinephrine content [1]. Considering high amount of epinephrine (dilution 1:100,000 – so called "forte" formulations), an effect less unlikely to occur in this case is the oral mucosa hyperaemia in the area of solution administration – a result of 're-bound' dilation of local blood vessels after marked vasoconstriction previously induced [1]. Perhaps local hyperaemia of the gum in alveolar ridge was mistaken with gingivitis by some of patients.

Like any other medicine, articaine is burdened with the risk of the administration in excessive doses. Usually it appears in consequence of inadvertent intravascular administration, especially in children (low body weight), particularly when effects obtained are not satisfying and the agent is repeatedly administrated during one appointment. The general symptoms of articaine overdose do not differ from the cases of other amino-amides, and are described with an acronym LAST (local anaesthetic systemic toxicity). The ubiquitous nature and wide distribution of voltage-gated sodium (Na_v) channels – the main target of commonly used in dentistry local anaesthetics, including articaine – plays a vital role in mechanisms of this pathology. The Na_v channels are to be found in all electrically excitable tissues, including peripheral and central neurons and the pacemaker and conducting tissues of the heart, what explains the division of the LAST symptoms in the two main groups: neurological and cardiac [10]. Of the note, animal studies conducted clearly indicate articaine's low potential for depressive action in the heart, especially when compared to bupivacaine [4;10]. The management depends on the kind of symptoms prevailing and their severity, and may include symptomatic treatment in the dental office (oxygen administration, benzodiazepines in case of seizures, e.g.) or resuscitation and, chiefly in the case of arrythmias and other severe cardiac symptoms, further treatment in hospital setting. Given the low potential of articaine cardiotoxicity, though, such extreme situations do not happen often. One has to remember about other active ingredients of articaine dental formulations, especially epinephrine. The catecholamine may also be overdosed, therefore its maximal dose– on average 200 µg for adults and 100 µg for children - is an important fact in the assessment of the number of ampoules, that could be safely administered during one appointment [1;14]

The close vicinity of oral cavity and eye socket results in ocular complications of dental local anaesthesia, and this statement is true for articaine as well. Among documented cases, the most often side-effect of local anaesthesia related to ocular tissues, regardless the agent used, is diplopia (39.8%), followed by ptosis (16.7%), mydriasis (14.8%), and amaurosis (13.0%) [41]. Reports on other symptoms, like an accommodation disturbance, enophthalmos, miosis, and ophthalmoplegia are incidental [41]. Ocular symptoms may occur after administration in alveolar ridge in the region of the posterior teeth in maxilla. In patients with relatively small maxilla, like slight women and children, there is a risk that except of a nerve block obtained in the sensory nerves of the upper alveolar plexus the fibres of oculomotor nerves also may be affected. In the majority of cases the effects are transient [42]. Anatomy may be a

factor far more important, than the properties of the drug, as one can encounter reports on similar outcomes, occurring in female patients after the administration of agents different than articaine (e.g. mepivacaine with epinephrine formulation) in the literature [43]. Contrary to the popular opinion, recent systematic review of ocular complications, could not prove direct association between excellent tissue penetration properties of articaine with the adverse ocular effects [44]. Due to the prevailing transient nature of symptoms, their management, if needed, remains purely symptomatic.

Another issue is the risk of neurological pathologies, especially paraesthesia, most common affecting the lingual nerve after IANB. Although the chief cause of the post-procedural paraesthesia in dentistry is the procedure-related injury, a local anaesthetic may also be a culprit [45]. The anatomy and low number of fibres are among the most probable reasons making the lingual nerve most feasibly to be affected [46]. The effects may be transient or permanent, and the latter tend to occur less often. Some researches are of the opinion, that the risk of unwanted effect of this kind is more prominent when the high drug concentration formulations are used, notably 4% articaine and 4% prilocaine, while other authors point that the data available does not justify such conclusions [1].The reports on paraesthesia and other local neurological complications related to the use of articaine, prompted even a number of practitioners to restrict the use of the drug only to infiltrative methods of local anaesthesia, avoiding its administration in IANB. Given the information from the reports, however, such precaution seems to be excessive [3]. The standard management of paraesthesia include general oral administration of group B vitamin formulations, preferably with alpha-lipoic acid, while the use of Sollux lamp irradiation is among the most often employed non-pharmacological measures [1].

Allergic reactions to articaine, although extremely rare, are by no means non-existent, and as such should not be overlooked by dental practitioners [47]. Indifferently to the majority of the side-effects already discussed, the management of allergic reactions to the articaine use does not differ from the measures taken in case of similar symptoms related to the other drugs of the group, and depends on the signs severity [48]. The mild, late allergic reactions (urticaria, itching) occurring within hours after administration require nothing more than symptomatic treatment. Usually, in such cases, pharmacotherapy could be limited to the oral antihistaminic drugs [49]. The matter is different with anaphylaxis. This life-threatening emergency requires prompt epinephrine administration in i.m. injection. The timely administration of adrenaline is pivotal to a favourable outcome. Additional measures as glucocorticoids and antihistaminic medications, together with oxygen administration play a supportive role and can never replace prompt, if needed repeated, epinephrine i.m. injection in recommended doses (0.5 mg for adults) [50]. Irrespectively of severity of symptoms encountered, the fact of their occurrence must be written down in patient medical records, and it is prudent to use other local anaesthetics in further dental care [10]. Regarding allergy diagnosis, one has to bear in mind, that in case of the skin tests, only plain formulations of local anaesthetics can be used, as vasoconstrictor falsifies the outcome of the test, by restricting skin flushing in case of existing reaction [51]. As in many countries, including Poland, articaine is available only in formulations with epinephrine, the plain formulations required for allergic skin tests should be imported from abroad, for example from the drug's homeland - Germany [1;19;51].

Also unwanted effects after articaine formulation administration may be a result of other ingredients than the drug itself. It is especially true in the case of epinephrine. While the most common adverse effect associated with adrenaline is vasovagal syncope, other symptoms resulting from the induced vasoconstriction may also occur, apart from the aforementioned 're-bound' hyperaemia, these may include transient blanching of the mucosa or even, rarely, ischemic necrosis [52;53]. The locations where the risk of such adverse outcome is most pronounced is hard palate – due to its anatomy – and mandible, after radiotherapy. In fact, in the latter case, the plain local anaesthetic formulations are the most prudent choice [1;14]. Similarly, drug interactions are more likely to occur between the patient's medications and epinephrine instead of articaine, therefore as always dental practitioners, should not forget about them [1]. The lability of catecholamines in water solutions, forces the use of preservatives, commonly metabisulfites, stabilising agent in formulation. Some patients, may be allergic to these agents. Of the note, this rare allergy affects a higher percent of asthmatic patients in comparison with general population (even 5% versus 1.4%), and, despite its low occurrence, the problem is a vital one, from the practical point of view, as i.m. epinephrine is a drug of choice in anaphylaxis, and its subcutaneous injection forms an important alternative in asthmatic attack management, while standard bronchodilators are not at hand [1;8]. A suggested and valuable strategy in cases of known metabisulfite allergy is desensitisation [54].

7. Summary

A peculiar chemical structure of articaine marks the drug out from other agents of the amino-amide local anaesthetic class. Its excellent properties, notably short onset time, lipophilicity resulting in high tissue permeation, unique metabolism that is not burdensome for the liver, encourage dentists all over the world to employ this drug formulations in everyday practice. The use of articaine in the methods of infiltration anaesthesia is prompted by its high ability to reach sufficient concentrations in maxilla and mandible, enabling effective anaesthesia even in such challenging clinical situations as procedures in the first lower molars, that, when other drugs are used, usually require IANB. That particular feature justifies naming the drug as 'the queen of infiltrative anaesthesia'. Despite wide use in infiltration, articaine administration is not limited to this type of nerve block, the drug may also be administrated with success in nerve blocks. Despite the common opinion, the risk of paraesthesia or transient ocular complications, according to the literature cannot be directly related to the articaine's high availability of tissue penetration, nor is characteristic for that particular agent, at least not in a degree, that would exclude the drug use in nerve blocks, especially IANB. The properties of the drug justify its topical administration, though, surprisingly, such formulations are yet not available, and research in this field still is

needed, especially that outcomes from ENT trials are encouraging. The results from research on novel nanolipid and nano-encapsulated articaine formulations are interesting and show another promising prospect for this special agent. Like other amino-amide local anaesthetics used in dentistry, articaine is a relatively safe drug, although, like every other medication its use is not free of the risk of unwanted effects. Furthermore, dental practitioners and oral surgeons, should not forget about the other active components of the drug's formulations, notably epinephrine, that alone may also be a factor contributing to unwanted effects occurrence. Adverse outcomes related to articaine formulations administration are rare, and in the overwhelming majority mild and transient in their nature. That, however, should never dispense us from the need for vigilance, so vital in medical practice, even regarding so helpful and safe agent, as articaine.

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