PROSPECTS
IN PHARMACEUTICAL SCIENCES

Prospects in Pharmaceutical Sciences, 24(1), 31-38
https://prospects.wum.edu.pl/

*Review Article*

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

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*Received: 16.06.2025 / Accepted: 28.07.2025 / Published online: 13.08.2025 / Published in final version:*

**ABSTRACT**

The importance of local anaesthetics in dentistry cannot be overestimated. Being the most commonly used drugs in 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 the amino-amide class. The paper focuses on articaine — a peculiar amino-amide local anaesthetic, which exhibits exceptional features distinguishing it from 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 the future. Despite the wide safety margin of the agent, articaine, like any other local anaesthetic, may induce unwanted side-effects, which were also described here, and their management was briefly presented.

**KEYWORDS:** articaine, local anaesthetics, dentistry.



## 1. Introduction

One cannot imagine today's dental practice without effective local anaesthesia. Intra-operative pain control with the means of local anaesthesia forms a pivotal and indispensable element of dentistry, allowing for painless interventions in all its fields and specialties. Local anaesthetics currently used in the dental office are the most commonly employed drugs by dentists, at the same time being the safest and most effective agents preventing and relieving pain known to medicine [1]. These medicines show high affinity for voltage-dependent sodium channels (Nav); they block them and prevent the influx of sodium cations through the membranes of the neuron, in this way hindering 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, was almost completely replaced with the second, and, except for 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 the overwhelming majority belong to the amino-amide group. These agents exhibit desirable properties, such as lower incidence of allergy and short latency period, which results in relatively fast onset of action, all distinguishing them from the less favourable characteristics of their 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 entire amino-amide class in terms 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 proportions) is present [4]. As the water solubility of the free base of the local anaesthetic is insufficient, in formulations for injection, articaine appears

in the form of a 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 in Fig. 1

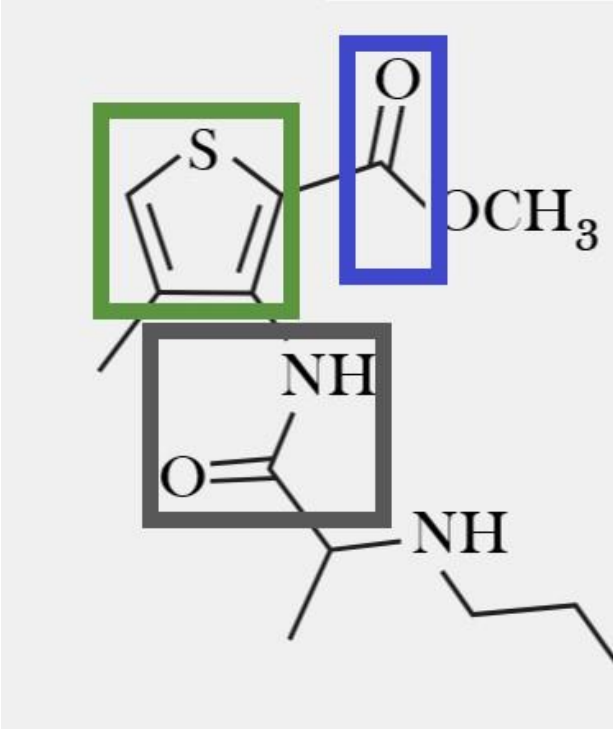


**Fig. 1.** The chemical structure of articaine and its distinguishing features.

The first remarkable difference is the presence of the thiophene ring (in the green square in Fig. 1), instead of the popular benzene ring found in other drugs from the group. 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]. The amide linkage (in the grey square in the figure), binding the lipophilic aromatic ring with the hydrophilic amine end, justifies the fact that the drug is counted as an amino-amide agent; however, articaine's molecule possesses an additional side-chain linked with an ester bond (in the blue rectangle in Fig. 1). That distinctive property is significant in practical terms, as the ester bond 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 the dose administered is thus already metabolised in plasma, while the 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 for example alcohol-dependent persons [6]. Rapid breakdown of articaine molecules by plasma carboxylesterases contributes to the short plasma half-life of the drug, which for a plain solution is usually assessed as not exceeding 20 minutes [7].

### 3. The mechanisms of articaine-induced nerve block — the drug's use in 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 (Nav) 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 conduction block in fibres with a larger diameter, like those responsible for touch, pressure sensation, and motor functions, requires higher concentrations of the 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 at room temperature [9,10]. A maximum dose recommended by manufacturers is 7 mg/kg of patient's body weight [9,10]. The lowest age of patients in whom the drug can be safely administered, according to the manufacturers' guidelines, is four, although recent studies support the drug's use in even younger populations [11,12]. According to some authors, the maximum dose in children should not exceed 5 mg/kg of patient's body weight, while others, considering the rapid metabolism of the drug, recommend the same dose as in adults (7 mg/kg of patient's body weight) [13,14]. The rapid metabolism, peculiar for the drug, depends on the levels of esterase enzymes. In clinical situations in which the enzymes' plasma concentrations are lower, like in insufficient renal function, cachexia, large skin burns, and some malignant neoplasms, the time needed for breaking down the molecules of articaine, although still short, is likely to be longer than usual. Particular attention should be paid to female patients in the third trimester of pregnancy or those using oral hormone contraceptives, as both situations are related to a decrease in cholinesterase class enzyme levels in plasma [8]. The tendency toward lowering plasma levels of the enzymes mentioned was observed also in 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 everyday dental practice in this special group [4].

Articaine was first synthesized in West 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 overcome when the drug is administered in a higher, 4% concentration [16,17]. Repeated attempts at the use of 2% articaine, which can still be found in the 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, an 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]. Recent years brought formulations with even lower content of epinephrine, e.g. a dilution of 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 was Japan, where they became available in January 2025 [20].

An added, yet surprising, value of articaine is its high degree of antimicrobial action. Although nearly all cation forms of amino-amide class local anaesthetics (except for ropivacaine) are endowed with some antimicrobial properties, in the case of articaine the features are more pronounced and show the most favourable profile, and, what is important, are directed against microbial species present in the oral cavity [21,22,23]. The proposed mechanism of action consists of the drug's 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 satisfactory 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, a number of subsequent papers justifies the drug's position in all fields and specialties of dental practice. Short onset of action and excellent tissue permeation endears the agent to dentists all over the world [9]. The last quality of articaine results in higher intraneural concentration, more extensive longitudinal spreading, and ensues better conduction block obtained after its administration in comparison to lidocaine — the model drug of the group [24]. It was suggested, that the thiophene ring, in addition to increasing the drug's ability to diffuse with ease in tissues, enables obtaining ion-channel block at lower concentrations than in the case of benzene derivatives [25].

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

A quite significant body of literature is dedicated to the use of articaine in a supplementary buccal injection after an inferior alveolar nerve block (IANB). Reports conclude that such a strategy enhances the anaesthetic effectiveness of IANB, even when other agents were used in the first block [26]. Additional articaine buccal infiltration after IANB is employed in dental practice with 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 so encouraging that supplementary buccal infiltration with articaine may even be considered a rescue method of local anaesthesia in cases in which the effects after IANB are not satisfactory [28].

The excellent properties of articaine widely used in infiltrative methods of local anaesthesia do not rule out the drug's use in truncal blocks, including IANB — the most commonly used nerve block employed in dental practice [29]. A recent systematic review justifies the use of articaine in this method as a means of intra-procedural pain control in such demanding and challenging procedures as lower third molar surgical extractions. 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 surprising, especially, given the drug's rapid metabolism, but tissue and nerve fibre permeation, together with epinephrine-induced vasoconstriction, are the most probable reasons for that outcome [1]. As the drug is available in solution form, except for infiltrative and truncal anaesthesia, 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 for the full unfolding of the anaesthetic effect, together with an increase in both the degree of anaesthesia and the patient's comfort during administration, may be obtained by 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 contain epinephrine, due to the preservatives stabilising this sensitive catecholamine, the character of the solution is acidic, therefore some patients may experience a 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 the formulation injected addresses the cause of the burning sensation [31]. Out of the two commercial local anaesthetic alkalinization systems that can be used in dentistry, currently available in the US, only one (Onset, manufacturer: Onpharma) can be employed for articaine formulations, and 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 at temperatures exceeding 25°C (77°F) the agent is easily broken down, which practically rules out this method in the case of the overwhelming majority of the drug's dental formulations available [32].

Given the 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 dental practice, is the application of gauze packs soaked with anaesthetic solution intended for the submucosal injection [35]. In procedures performed in head and neck tissues, such a strategy was tested in a 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, which can be employed in the dental office, is as a pulp-dressing. Although when compared with eugenol, articaine provided less reduction in pain in emergency pulpotomy, it is still a valid alternative, notably considering that it is also easily available as one of the most often used local anaesthetics. In such indication, the cotton pellet soaked with solution is applied into the chamber of the affected tooth, and 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 a commercially available solution was combined with dexamethasone and administered in the surgical site in a submucosal injection after lower third molar extraction [37].

Despite satisfying properties of the drug's formulations available, recent years brought an interesting body of research on experimental nano-lipid and nano-encapsulated articaine solutions — preparations with enhanced ability for tissues penetration, usually characterised by longer time of the effect obtained, when compared to unmodified solutions [38,39]. Both experimental types of formulations were tested in animal models, and of the note, in the 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 as effective as 4% drug solution in intraoperative pain control in a number of studies [18].

**6. Side effects and their management**

As with every drug available, articaine may induce unwanted side-effects, and their management does not differ from the strategies employed in the 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 the 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 were 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 the 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 infection, which may occur due to negligence in procedure, rather than properties of the formulation, for example when the needle is inserted through a submucosal abscess, bringing the bacteria deeper, the entity reported may be related to epinephrine content [1]. Considering the high amount of epinephrine (dilution 1:100,000 — so-called "forte" formulations), an effect not unlikely to occur in this case is oral-mucosa hyperaemia in the area of solution administration — a result of 'rebound' dilation of local blood vessels after marked vasoconstriction previously induced [1]. Perhaps local hyperaemia of the gum in the alveolar ridge was mistaken for gingivitis by some patients.

Like any other medicine, articaine is burdened with the risk of administration in excessive doses. Usually it appears as a consequence of inadvertent intravascular administration, especially in children (low body weight), particularly when effects obtained are not satisfying and the agent is repeatedly administered during one appointment. The general symptoms of articaine overdose do not differ from those in cases of other amino-amides, and are described with the acronym LAST (local anaesthetic systemic toxicity). The ubiquitous nature and wide distribution of voltage-gated sodium (Nav) channels — the main target of local anaesthetics commonly used in dentistry, including articaine — plays a vital role in mechanisms of this pathology. The Nav channels are found in all electrically excitable tissues, including peripheral and central neurons and the pacemaker and conducting tissues of the heart, which explains the division of the LAST symptoms into two main groups: neurological and cardiac [10]. Of note, animal studies conducted clearly indicate articaine's low potential for depressive action on 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 a hospital setting. Given the low potential of articaine for cardiotoxicity, though, such extreme situations do not happen often. One has to remember the other active ingredients of articaine dental formulations, especially epinephrine. The catecholamine may also be overdosed, therefore its maximum 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 the oral cavity and the eye socket results in ocular complications of dental local anaesthesia, and this statement is true for articaine as well. Among documented cases, the most common side-effect of local anaesthesia related to ocular tissues, regardless of 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 accommodation

disturbance, enophthalmos, miosis, and ophthalmoplegia are incidental [41]. Ocular symptoms may occur after administration in the alveolar ridge in the region of the posterior teeth in the maxilla. In patients with relatively small maxilla, like slight women and children, there is a risk that apart from a nerve block obtained in the sensory nerves of the upper alveolar plexus, the fibres of the 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 popular opinion, a recent systematic review of ocular complications could not prove a direct association between the excellent tissue penetration properties of articaine and 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 commonly affecting the lingual nerve after IANB. Although the chief cause of postprocedural paraesthesia in dentistry is 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 likely to be affected [46]. The effects may be transient or permanent, and the latter tend to occur less often. Some researchers are of the opinion that the risk of unwanted effects of this kind is more prominent when high- concentration formulations are used, notably 4% articaine and 4% prilocaine, while other authors point out 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 includes 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]. Independently of the majority of the side-effects already discussed, the management of allergic reactions to articaine use does not differ from the measures taken in the case of similar symptoms related to other drugs of the group, and depends on the severity of signs [48]. The mild, late allergic reactions (urticaria, itching) occurring within hours after administration require nothing more than symptomatic treatment. Usually, in such cases, pharmacotherapy can be limited to oral antihistaminic drugs [49]. The matter is different with anaphylaxis. This life-threatening emergency requires prompt epinephrine administration via i.m. injection. The timely administration of adrenaline is pivotal to a favourable outcome. Additional measures such 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 the severity of symptoms encountered, the fact of their occurrence must be written down in the patient's 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 the case of skin tests, only plain formulations of local anaesthetics can be used, as a vasoconstrictor falsifies the outcome of the test by restricting skin flushing in case of an 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, and apart from the aforementioned 'rebound' hyperaemia, these may include transient blanching of the mucosa or even, rarely, ischemic necrosis [52,53]. The locations where the risk of such an adverse outcome is most pronounced are the hard palate — due to its anatomy — and the mandible after radiotherapy. In fact, in the latter case, 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, as a stabilising agent in the formulation. Some patients may be allergic to these agents. Of note, this rare allergy affects a higher percent of asthmatic patients in comparison with the 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, when 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, and 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 the maxilla and mandible, enabling effective anaesthesia even in such challenging clinical situations as procedures in the first lower molars, which, when other drugs are used, usually require IANB. That particular feature justifies naming the drug 'the queen of infiltrative anaesthesia'. Despite its wide use in infiltration, articaine administration is not limited to this type of nerve block, and the drug may

also be administered with success in nerve blocks. Despite popular opinion, the risk of paraesthesia or transient ocular complications, according to the literature, cannot be directly related to articaine's high tissue penetration, nor is it characteristic for that particular agent, at least not to a degree that would exclude the drug from use in nerve blocks, especially IANB. The properties of the drug justify its topical administration, though, surprisingly, such formulations are not yet available, and research in this field still is needed, especially since 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, which 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 are mild and transient in their nature. That, however, should never dispense us from the need for vigilance, so vital in medical practice, even regarding such a helpful and safe agent as articaine.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The author declares no conflict of interest.

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