


## UNCLARITIES ABOUT ARTICAIN: CONTRAINDICATIONS

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## ABSTRACT

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**Background** Articaine is one of the most widely used local anesthetics in dentistry. It is formulated with epinephrine in a 1:100,000 or 1:200,000 concentration as a vasoconstrictor. The addition of epinephrine gives the drug an extensive list of formal contraindications.

**Objective** To review the literature on the chemistry and safety of articaine with epinephrine, and to review the validity of each of the contraindications.

**Data sources** The base knowledge was the result of reading a handbook on local anesthesia. Afterward, a literature search was made for publications between 1990 and 2019 concerning contraindications to articaine and dental epinephrine. Some articles about the pharmacological properties of articaine were also used. Finally, what was used was the list of contraindications in the package leaflet of articaine in Belgium as stated on 11/11/2019.

**Study selection** Articles of good quality and with clear information discussing and explaining these contraindications were included.

**Data extraction** Information about which contraindications, which drug interactions, and what physiological reasoning is behind them was extracted.

**Data synthesis** This information was synthesized in an extensive overview. First, the profile, safety and pharmacological properties of articaine with epinephrine were reviewed. Afterwards, an overview of the contraindications and drug interactions was given as stated in the package leaflet and each of them was explained.

## KEYWORDS

Articaine; Epinephrine; Pharmacology; Contraindications; Pregnancy.

## 1. INTRODUCTION

Articaine is a dental local anesthetic of the amide group. It is the only anesthetic specifically developed for use in dentistry. It was first synthesized in 1969 when it was still referred to as carticaine. Its name changed to articaine in 1976 when it reached the markets in Germany [1]. In the following years, articaine got approval for clinical use around the world and has steadily become increasingly popular.

It is the second most used dental local anesthetic in the United States with a market share of 39,3% in 2018 (the most popular still being lidocaine, the golden standard in local anesthetics) [1]. In Germany, it is even more popular, accounting for 97% of local anesthetic use by dentists in 2018 [2].

The package insert of articaine in Belgium (Septanest by Septodont) contains a lot of contraindications to articaine itself as well as to the added vasoconstrictor,

epinephrine. While most contraindications theoretically make sense, the majority of them do not elicit a clinically significant hazard.

This paper is aimed to review the clinical characteristics of articaine and to analyze the validity of the contraindications to this drug as mentioned in the package insert.

## 2. MATERIALS AND METHODS

For the preparation of this review and introduction to this subject in general, Malamed's Handbook of Local Anesthesia (seventh edition) was read. After that PubMed, Trip database and Limo were searched for the different aspects of articaine discussed in this paper. For articaine, a search was conducted on different keywords for safety, clinical characteristics, interactions, and contraindications. The same was done for epinephrine in dental use and pregnancy, cardio-

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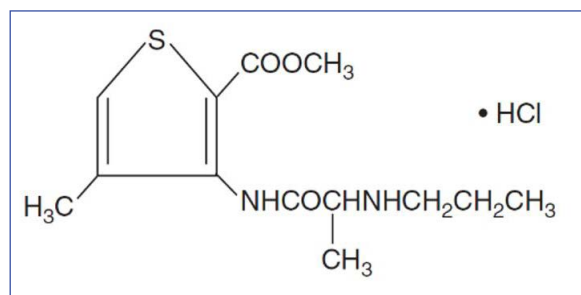
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**Figure 1.** The chemical structure of articaine.  
 Malamed SF. *Handbook of Local Anesthesia*. 7<sup>th</sup> ed. St Louis: Mosby; 2019, Fig. p72

vascular effects, safety in cardiovascular compromised patients, contraindications and interactions. The most relevant articles were selected to create a narrative review, portraying an overall picture of the current ambiguities about articaine.

### 3. CLINICAL CHARACTERISTICS

In Belgium, Articaine cartridges are currently available in two formulations: Articaine hydrochloride 4% with epinephrine 1:200.000 (Septanest Normal<sup>®</sup>) and 1:100.000 (Septanest Special<sup>®</sup>).

#### 3.1. Articaine Hydrochloride 4%

##### 3.1.1. Structure

Articaine (or 4-methyl-3-[2-(propylamino) propion-amido-2-thiophenecarboxylic acid methyl ester] is classified as an amide local anesthetic, although it is a unique entity within the amide local anesthetics (see Fig. 1). It is the only one containing an aromatic ring rather than a benzene ring [2]. This thiophene ring ensures greater lipid solubility which makes it great for penetrating tissue and would ensure better bone penetration, thereby increasing potency [1]. Furthermore, the structure contains an ester-linkage which makes it susceptible to hydrolyzation by plasma esterases. Articaine also has a higher degree of protein binding (95%) than the other amide anesthetics [2]. It exerts its pharmacodynamic action by reversibly binding and inhibiting the alpha-unit of the voltage-gated sodium channels, which prevents the propagation of action potentials in neurons [3].

##### 3.1.2. Pharmacokinetics

The ester-linkage embedded in the amide structure makes articaine a hybrid molecule. This gives it a unique pattern of metabolization. As soon as the drug reaches the plasma, the carboxylic acid ester groups are hydrolyzed by plasma esterases producing a primary inactive metabolite: articainic acid [2]. About 90% of the drug undergoes this rapid process and this would contribute to the lower systemic toxicity of the drug. Further metabolization of the amide linkage happens by microsomal enzymes in the liver just like the other amide anesthetics. This turns articainic acid into articainic acid glucuronide, which is in turn excreted through the kidneys. Approximately 5-10% is excreted unchanged [3].

##### 3.1.3. Duration of action and elimination half-life

Articaine is an intermediate-acting local anesthetic providing pulpal anesthesia for approximately 60 minutes and soft tissue anesthesia for 3 to 5 hours [2]. Because of the rapid plasma hydrolysis, articaine has a significantly shorter elimination half-life (27 minutes) than the other amide anesthetics like lidocaine (90 minutes) [1]. This half-life is not related to the duration of clinical action but is a measure for how long it takes for the drug to be eliminated from the circulation. This fast elimination means it is clinically advantageous when treating pregnant, lactating or pediatric patients because there is less exposure time to the drug [2].

##### 3.1.4. Maximum dosage

Articaine has a maximum recommended dose (MRD) of 7.0 mg/kg to prevent the occurrence of an overdose reaction [1]. Although local anesthetics are safe drugs, an overdose is possible as with any drug, so there are a few things to keep in mind. Hepatic and renal dysfunction will lead to increased anesthetic blood levels [1]. Liver dysfunction is not an absolute contraindication to local anesthetics, but they should be used thoughtfully as their half-life will increase and blood levels will be higher. In this case, articaine could be the anesthetic of choice because of its partial metabolization in blood plasma. Moreover, some patients have atypical serum pseudocholinesterase, which occurs in approximately 1 in 2820 individuals [1]. To prevent overdose reactions, there are injection techniques that should be respected. Before injecting the drug, the practitioner should always carefully aspirate the syringe to avoid intravascular injections. Furthermore, the injection rate appears to be one of the most important factors for overdose: a rapid intravenous injection (<15 seconds) of a cartridge lidocaine 2% gives highly elevated blood levels, which can cause an overdose reaction [1]. Therefore, it is recommended to administer the cartridge slowly (>60 seconds) so the blood levels will not be as high and the risk of overdose reactions will be significantly reduced [1].

Finally, the maximum dosage of 7.0 mg/kg is of utmost importance. A 1.8 ml cartridge of 4% articaine contains 72 mg of articaine, meaning a healthy adult weighing 72 kg can receive a maximum of 7 cartridges (504 mg). However, it is unlikely these maximum numbers would be achieved during routine dental care since there is rarely a need for more than three to four cartridges in one appointment [1].

Obtaining anesthesia of the complete adult mouth is possible with only six cartridges using regional block anesthesia, and only two cartridges in the primary dentition.

Nonetheless, the use of excessive volumes is the most frequent cause of overdose reactions [1]. As a dentist or oral surgeon, you should always calculate the maximum recommended dose for your patient, especially in risk populations (pregnant women, children, cardiac patients).

### 3.2. Epinephrine

Epinephrine, a vasoconstrictor, is added to the local anesthetic solution for several reasons. Its vasoconstrictor effect delays the absorption of the local anesthetic, reducing systemic toxicity. It increases the depth and duration of anesthesia, the dose of anesthetic can be reduced, and it provides good hemostasis [1].

#### 3.2.1. Implications

Epinephrine has a direct effect on the myocardium and on the vascular tone that can result in hypertension or even ventricular fibrillation. Especially in cardiac patients, who do not have as much reserve as healthy patients, this could potentially be a problem. That is why the addition of epinephrine to a local anesthetic cartridge comes with a lot of clinical implications. A lot of the contraindications listed in the package leaflet of articaine formulations (like Septanest) are actually contraindications to the administration of epinephrine, which will be discussed later.

#### 3.2.2. Cardiovascular effect

There are a few considerations to be made on the dental epinephrine use in cardiovascular patients. Pain and fear induce endogenous catecholamine release which emphasizes the importance of adequate pain control, especially in cardiac patients [1]. Effective pain control is less likely to be achieved when a vasoconstrictor is excluded from the local anesthetic solution. Even when using precautions (careful aspiration, slow injection), using the vasoconstrictor can cause an elevation of epinephrine blood levels and can result in a moderate increase in the cardiac output and stroke volume. Blood pressure and heart rate are minimally affected at these low dosages [1]. It should be noted that the dosages in the cartridges are minimal (a 1.8 mL cartridge of epinephrine 1:200 000 contains only 0.009 mg of epinephrine). By comparison, when other clinicians use epinephrine, it is usually intramuscular/intravascular in an emergency setting (anaphylaxis, cardiac arrest) and the dose is considerably higher (0.3 to 1 mg). In the small quantities used in dentistry, the cardiovascular effects of the systemically absorbed epinephrine are modest [1]. There are of course several situations where vasoconstrictors in local anesthetics should be avoided because the risk is too great. However, most of these circumstances (like uncontrollable hypertension, uncontrollable arrhythmias, ...) are actually contraindications to elective dental care altogether [1].

#### 3.2.3. Maximum Dosage

In this context the New York Heart Association recommended a maximal dose of 0.2 mg for cardiac patients back in 1955 [1]. Later, Bennett recommended a maximum dose of epinephrine in cardiac risk patients (ASA 2 or 3) of 0.04 mg or roughly 4 cartridges of a 1:200 000 epinephrine solution [4]. Malamed also states that a smaller dose of 0.04 mg appears to be tolerated in cardiac patients [1]. This 40 µg can be administered safely to cardiovascular compromised patients [5].

A recent systematic review confirmed the safe use of  $\leq 4$  cartridges of the higher concentrated lidocaine with 1:100,000 epinephrine in cardiac patients [6]. Although this is a useful guideline, it should not create a false sense of security. The practitioner should always proceed with caution and be aware of possible side effects. In any case, for cardiac patients the lowest concentrated articaine formulation (1:200 000) seems to be the anesthetic of choice given the lower epinephrine load.

## 4. CONTRAINDICATIONS AND PRECAUTIONARY CIRCUMSTANCES

As with all medications, there is a package insert with contraindications (either absolute or relative), conditions that require extra caution, possible drug interactions (see Fig. 2) [7]. As mentioned above, a lot of these contraindications are included because of the presence of epinephrine. Several of these contraindications or precautions are historic in nature and more of a formality. There are numerous comments to be made on the package leaflet that are contrary to everyday clinical practice. This makes it a debatable subject in the context of possible litigation. A general rule can be applied in most of the following instances, as explained by Malamed: if the patient is deemed healthy enough to undergo elective dental treatment, the use of proper anesthesia is indicated [1]. When using a vasoconstrictor in your local anesthesia, the maximum recommended dose should be calculated and in some cases, it could be necessary to restrict the dose. Always use as minimal vasoconstrictor as possible.

### 4.1. Contraindications

#### 4.1.1. Allergy

Historically, with the use of ester anesthetics, although still rare, an allergic reaction occasionally happened. With the rise of the amide anesthetics however, this changed for the better. Articaine has low immunogenicity and it does not have the allergen p-aminobenzoic acid as a metabolite (contrary to ester local anesthetics) [2]. The sulfur contained in the thiophene ring will also not provoke allergic reactions as it is embedded in the ring and cannot be seen by our immune system [2]. Although the incidence of 'alleged' allergy is rather high, true documented allergy to an amide local anesthetic is extremely low but it has been reported [8]. However, the cartridge solution contains 0,15 to 2.0 mg/ml sodium metabisulfite, an antioxidant added to prevent the oxidation of epinephrine thus increasing preservability, but also a known allergen [2,9]. Adverse reactions to the ingestion of alimentary sulfites can cause a severe and prolonged asthmatic crisis or even anaphylactic shock [9]. However, the dose in a typical meal after which such reactions occur appears to be a lot higher (25 to 200 mg of sulfites) than those used in dentistry [9]. If a true allergy to the amide local anesthetics or

<p><b>SEPTANEST NORMAL (Articaine 4% with epinephrine 1:200,000)</b></p> <p><b>When shouldn't you use this drug</b></p> <ul style="list-style-type: none"> <li>- Allergy to this or a similar drug or one of the compounds</li> <li>- Severe arrhythmias and you don't have a device</li> <li>- Refractory epilepsy</li> <li>- Porphyria</li> <li>- Child &lt; 4 years old</li> <li>- Disease by overproduction of thyroid hormones</li> <li>- Diabetes mellitus</li> </ul> <p><b>When should you be extra careful with this product</b></p> <ul style="list-style-type: none"> <li>- Cardiovascular disorders (arrhythmias, hypotension, coronary insufficiency, arterial hypertension)</li> <li>- Neurological disorders</li> <li>- Asthma</li> <li>- Treatment with antidepressants and suffers from muscle fatigue</li> <li>- Severe hepatic disorder</li> <li>- Do not use it in infected or inflamed areas because the efficacy will decrease</li> </ul> <p><b>Drug-drug interactions</b></p> <ul style="list-style-type: none"> <li>- Guanethidine and analogues</li> <li>- Halogenated inhalation anesthesia</li> <li>- TCA and SNRI</li> <li>- MAO-I</li> </ul>
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**Figure 2.** Contraindications and precautionary circumstances in the package insert of Septanest normal in Belgium (articaine 4% with 1:200,000 articaine), consulted on 10/10/2019 (translated in English).

sulfites exists, it is an absolute contraindication for its use. The actual incidence of an allergy to either articaine or to metabisulfite is unknown, but a clinically relevant reaction remains extremely rare.

#### 4.1.2. Severe arrhythmias without a device

Severe arrhythmias like ventricular tachycardia or ventricular fibrillation are life-threatening types of arrhythmias with the risk of sudden death [10]. Logically, patients with severe arrhythmias that are not under control by medication or do not have a device (like an implantable cardioverter-defibrillator (ICD) or a pacemaker) should not receive a local anesthetic with a vasoconstrictor [10]. On the other hand, such a condition is considered a contraindication to elective dental care whatsoever [1].

#### 4.1.3. Refractory epilepsy

Overdose reactions caused by the toxicity of local anesthetics include possible seizures, which is why local anesthetics should not be used if a patient's epilepsy is not under control with medication [1].

#### 4.1.4. Porphyria

There were historical reports of local anesthetics causing methemoglobinemia, a cyanosis-like state with decreased oxygen-carrying capacity of the blood [1]. These reports concerned prilocaine (not articaine) and being only a relative contraindication for prilocaine, methemoglobinemia should not develop in a healthy ambulatory dental patient [1]. In the database of drugs for use in porphyria from Sweden and the UK, articaine is listed as "safe" and "probably not porphyrinogenic" [11,12].

#### 4.1.5. Children younger than 4 years of age

The greatest concern in this population is the risk of overdose: a rapid (<15 seconds) intravenous injection of a full cartridge would likely induce a rapid onset of severe seizure activity [1,2]. Proper techniques like aspiration and slow injection are of utmost importance in the pediatric population [1,2].

As most of the local anesthetic overdoses develop as a result of an overadministration, articaine (with its short elimination half-life) is the least likely to induce an overdose [1]. However, two concerns should always be considered. First, because of the smaller weight, children are more susceptible to an overdose reaction [1]. Second, prolonged anesthesia can possibly lead to self-inflicted injury by biting the lip or tongue after the procedure [1].

The MRD should always be calculated according to their weight. It should be noted that the entire primary dentition can be anesthetized using approximately only two cartridges. This means that for dental treatment, usually less than one cartridge is needed [1]. The package insert states that articaine should not be used on children under four years of age given the lack of data about the safety in this population [7]. However, a survey of 373 American dentists showed that 21% had used articaine in the age group of 2-3 year-olds [13]. A retrospective study that dates back to 1989 found data on 211 children under the age of four years of age receiving 240 doses of articaine [14]. There were no adverse reactions known to the clinicians or noted in the medical file [13].

Limited data suggest the use of articaine in children under four years of age appears to be safe as long as the clinician keeps to the maximum dose restrictions, but more research is needed to fully establish the safety in this population. A study about safety in children under four years of age is now in progress [15].

#### 4.1.6. Disease by overproduction of thyroid hormones

The thyroid hormone has a direct effect on the myocardium, which is why we see a lot of hypertension, atrial tachydysrhythmias and cardiac insufficiency in patients with hyperthyroidism [9].

A life-threatening complication concerning the thyroid is thyrotoxic crisis [9]. Because of the resemblance of the cardiac effects of thyroid hormone to those of catecholamines, it has been suggested that a synergistic effect might occur between the two [9]. The possible potentiation of the vascular effect of thyroid hormone by a vasoconstrictor would plead for a formal contraindication for the use of vasoconstrictors in such patients [9]. However, studies testing this possible hypersensitivity to catecholamines show inconsistent results [9].

In the case of thyrotoxicosis, elective dental care altogether is absolutely contraindicated [9].

If a patient's hyperthyroidism is under control, proper local anesthetic use with vasoconstrictor is indicated [1]. In patients with clinically overt hyperthyroidism (also bearing in mind the often-associated subclinical cardiac disease), there would be a higher risk to

hyperrespond on these epinephrine doses (tachycardia, elevated blood pressure) [9]. In these cases, vital signs should be monitored when using vasoconstrictors [1].

#### 4.1.7. Diabetes mellitus

This contraindication has been based on a warning concerning the use of large quantities of epinephrine (like for the treatment of allergic reactions or regional anesthesia) [9]. Epinephrine opposes the action of insulin, making it a hyperglycemic hormone [9]. Chances of complications vary within the population: For example, insulin-dependent diabetics or uncontrolled diabetics are at greater risk for complications such as acid ketosis and hyperglycemic coma, although this is very unlikely to happen at the low dosages used in dentistry [9]. Another possible problem with (insulin-dependent) diabetics is that they usually defer eating for a few hours after a dentist appointment because of the residual anesthetic effect [1]. This can alter their normal diet with a risk of hypoglycemia, which is why a diabetic should modify their insulin doses in advance if needed [1].

Vasoconstrictors can be used safely for the majority of diabetic patients as long as their condition and diet are under control [9]. As with all risk populations, to minimize the risk the lowest possible dose should be used [9]. However, we must detect patients with uncontrolled diabetes as they could pose an increased risk for complications [9].

#### 4.2. When should you be extra careful with this drug?

##### 4.2.1. Cardiovascular disorders (arrhythmias, hypotension, coronary insufficiency, arterial hypertension)

Some other cardiovascular disorders also present a contraindication to elective dental care: unstable angina, 6 months after coronary artery bypass surgery or myocardial infarction or hypertension in excess of 200 mmHg systolic or 115 mmHg diastolic [1].

Each of these cases is a medical emergency and requires treatment to stabilize the situation. Obviously, these should be taken care of before going to the dentist. If the patient is deemed healthy enough to receive dental care, correct local anesthesia is indicated [1].

The safe use of vasoconstrictors in cardiac patients is the subject of a huge debate. The dose restriction, recommended by Malamed and Bennett, of 0.04 mg of epinephrine appears to be safe and beneficial in cardiac patients who have stable disease [1,4].

##### 4.2.2. Asthma

A few papers in the 1980s warned dentists to avoid local anesthetics with vasoconstrictors in asthmatic patients because allegedly a substantial proportion of asthmatics are potentially sensitive to sulfite [9]. Pérusse addressed this matter already in 1989 and explained that this recommendation should at least be restricted to steroid-dependent asthma patients [9]. Given this concern, there was a study reporting an alleged sulfite sensitivity threshold of 0.6 to 0.9 mg [9]. However, a later investigation documented that only

a minority of sulfite-sensitive patients would react to a challenge test smaller than 10 mg/ml (a multitude of the dose normally used in local anesthetics) [9].

It should be noted that most of these papers date from before 1990 and are not up to date. For the last 20 years, there are only limited data like case reports or reviews on reactions to local anesthetics in asthmatic patients.

Given the high prevalence of asthmatic disease and the absence of reported cases in the literature, this contraindication could be disputed.

##### 4.2.3. Severe hepatic disorder

Severe hepatic disease would logically suggest a relative contraindication as amide anesthetics are metabolized in the liver [1].

Hepatic disease would decrease the elimination of the drug, increasing possible toxicity [1]. However, given the ability of articaine to be rapidly hydrolyzed for 90% by plasma esterases into an inactive compound, articaine is the preferred option in patients with hepatic dysfunction [1].

##### 4.2.4. Do not use it in infected or inflamed areas because the efficacy will decrease

The increased acidity in an inflamed or infected area results in less effective and profound anesthesia as this disturbs the mechanism of action [1]. However, stating that in this case this drug should not be used is a bit curious as you will obviously need the best anesthesia possible when providing dental care in an already inflamed or infected area.

##### 4.2.5. Pseudocholinesterase deficiency

Another ambiguous point is the clinical significance of a pseudocholinesterase deficiency. As it turns out 1 in 2820 individuals have an atypical serum pseudocholinesterase, a genetic trait resulting in a relative pseudocholinesterase deficiency [1].

This results in a decreased metabolism of ester anesthetics and it presents a relative contraindication to their use. Haas states that little clinical effect would be expected unless the dose would be very high [16]. Malamed states that amide local anesthetics do not present an increased risk of high blood levels in these patients given their hepatic metabolism [1].

For articaine, however, as a hybrid molecule classified as an amide local anesthetic, the clinical significance is unclear as it is still metabolized by the liver.

Given this dual metabolism, the clinical impact of this trait in a patient would be small. However, the practitioner should still be cautious for possible overdose reactions as articaine blood levels could be somewhat increased.

#### 4.3. Drug-drug interactions

##### 4.3.1. Guanethidine and analogues

Guanethidine is an adrenergic neuronal blocker inhibiting the release of norepinephrine from sympathetic nerve terminals [17]. Long-term use could result in postsynaptic receptor upregulation increasing the responsiveness to adrenergic

vasoconstrictors [17]. Another possible mechanism of potentiation is the competitive inhibition of the adrenergic reuptake transporter [17]. This interaction received a 4 rating (just like thyroid hormone) as a reaction is "possible" [17]. The same recommendation as for TCAs apply [17].

#### 4.3.2. Halogenated inhalation anesthesia

The use of halogenated inhalation anesthetics like halothane could potentiate the arrhythmogenic effect of epinephrine and result in a cardiac dysrhythmia [17]. The treating anesthesiologist should be aware of this possible interaction.

#### 4.3.3. TCA and SNRI

Tricyclic antidepressants (TCAs) are mainly used in the treatment of depression. TCAs act the same as SNRIs by inhibiting serotonin (SERT) and norepinephrine (NERT) transporters thus blocking the reuptake of neurotransmitters in the synaptic cleft [18]. This way, they could enhance the cardiovascular actions of exogenously administered vasopressors. This enhancement appears to be fivefold to tenfold for levonordefrin and norepinephrine, two rarely used vasoconstrictors [18]. For epinephrine, this potentiation is approximately twofold [18].

Whether or not this potentiation results in a clinically significant adverse reaction with the dosages used in dentistry is debatable [18]. Reports of this interaction resulting in a series of hypertensive crises in patients, of which one patient died, contributed to the fear of using vasoconstrictors in patients taking TCAs [19]. These cases are referred to a lot in the literature. However, this needs some rectification as Boakes et al were misquoted: the patient who died was not taking a TCA [20]. The other patients with adverse reactions appeared to experience these reactions because of the use of norepinephrine as a vasoconstrictor (instead of epinephrine) [20]. Patients taking TCAs may also have different electrocardiographic changes. While antiarrhythmogenic in low doses they are arrhythmogenic in overdose, making it a hazard for serious arrhythmias in combination with a local anesthetic [18]. Yagiela et al recommend limiting the dose of epinephrine to one-third of the normal maximum dose for patients taking TCAs [17]. This should preserve the patient for any problem arising because of interactions [17].

#### 4.3.4. MAO-I

Mono-amine-oxidase inhibitors (MAO-I) could theoretically potentiate the actions of vasopressors by inhibiting their biodegradation by monoamine oxidase in the presynaptic neuron [1].

This could result in a hypertensive crisis, which can be seen with phenylephrine, a vasoconstrictor currently no longer used [1]. However, research on this subject is unified on the fact that there is no clinically significant interaction taking place with epinephrine [17,18]. This is partially due to the fact that this exogenously administered epinephrine is preferably metabolized by catechol O-methyltransferase [17].

Yagiela states that "the continued listing of this interaction in the package insert for local anesthetics with vasoconstrictors is simply a testament to the bureaucracy of the U.S. FDA" [17].

#### 4.4. Pregnancy and lactation

All local anesthetics can cross the placenta and enter the system of a developing fetus [1]. In general, dental treatment should optimally be avoided in the first 10 weeks because this is when the teratogenic risk is the greatest [21]. Elective dental treatment is usually planned in the second trimester [21]. Although articaine is classified as a class C drug, Malamed prefers the use of articaine because of the shorter exposure time as the elimination half-life is only 27 minutes compared to the 90 minutes of lidocaine [2]. A formulation with a vasoconstrictor is indicated as they reduce systemic toxicity and will not affect uterine blood flow in the low dosages used in dentistry [22]. A prospective study following 210 women that underwent local anesthetic exposure during pregnancy found no significant difference in gestational age or median birth weight [23]. Within the study limitations (small sample size, heterogeneous nature of birth anomalies) that permit detection of a 2.65-fold increase, no associated increased risk was found for major anomalies [23]. Amide local anesthetics are considered safe to use during pregnancy if administered with the proper aspiration technique. Lidocaine is the drug with the most experience and data in pregnant women and is categorized as a class B drug. Because of the lack of data, articaine is categorized as a class C drug. For breastfeeding, lidocaine is the only "S" local anesthetic. Articaine is considered "S?" (safety in nursing infants unknown) [2]. The current recommendation is to use the "pump & discard" method: following exposure of the drug to a nursing woman, she should pump and discard for a 4-hour period (covering six elimination half-lives) to minimize infant gestation [2].

## 5. DISCUSSION

There are some comments to be made about the package insert of articaine. There should be no unfounded statements about the possible contraindications or interactions concerning articaine with epinephrine. A restricted dose of 40 µg epinephrine (4 cartridges of 1:200,000) is tolerated in cardiac patients whose disease is under control. Some other contraindications are too generalized (diabetics, asthmatic patients, ...). Interaction of epinephrine with TCAs and general anesthetics is well-documented and should be prevented by using a dose restriction [17]. The interaction with thyroid hormones and guanethidines is much less compelling, meaning a vasoconstrictor can be used safely within the normal dosages [17]. For MAO-I's there is absolutely no scientific evidence of a significant interaction [17]. Something to keep in mind concerning the drug-drug interac-

tions is the tendency for receptor down-regulation after repeated exposure to a certain compound [17,18]. This phenomenon, which would apply to a patient taking TCA's for a longer time or a patient with hyperthyroidism, would reduce the possible risk of a damaging effect as a result of an interaction [20]. There exist a lot of other interactions and contraindications, but with a dose restriction in some cases if necessary, articaine can be administered safely without or with minimally increased risk. The relevance of these contraindications could be argued in case of litigation. To summarize the debate on the contraindications, Malamed states that if a patient is deemed healthy enough to undergo elective dental treatment, local anesthetics are indicated [1].

## 6. CONCLUSION

Because of its unique properties (plasma hydrolyzation) and its lower epinephrine concentration compared to the lidocaine formulation, articaine is the better choice in certain clinical situations (like hepatic dysfunction, patients with cardiovascular morbidity or cases where the clinician wants to be prudent for possible interactions). In the package insert of articaine, there are a lot of contraindication (either abso-

lute or relative) that are open to debate.

Theoretically, a lot of interactions with either diseases or other drugs are possible. In the current literature, however, there are not many cases that demonstrate these interactions. In clinical practice the relevance of most of the possible interactions is modest. Most of the adverse reactions are caused by the overadministration of the drug. Adverse reactions can be prevented by being aware of the maximum recommended dose and by using proper injection techniques (aspiration and slow injection). The contraindications in the package leaflet are mainly too broad and should be better defined for use in everyday clinical practice.

## CONFLICT OF INTEREST

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## CV

Nicolas De Ridder (DOB: 28th of May, 1996) obtained his bachelor's degree in Medicine at the Catholic University of Leuven, Belgium (magna cum laude). He is currently in his final year of master in Medicine, expected to graduate in July 2020. He has acquired experience in internships in the department of Stomatology, Oral and Maxillofacial surgery under the supervision of Professor Constantinus Politis at UZ Leuven.

## Questions

### 1. What is the current maximum recommended dose of epinephrine in dental cartridges for patients with cardiovascular disease per dental appointment?

- a. 9 µg;
- b. 40 µg;
- c. 200 µg;
- d. There is no dose restriction.

### 2. In which case is articaine absolutely contraindicated?

- a. Allergy to amide anesthetics;
- b. Patients taking MAO-I;
- c. Patients with (controlled) hyperthyroidism;
- d. Patient with diabetes.

### 3. What would ensure a greater bone penetration capacity of articaine compared to other local anesthetics?

- a. Thiophene ring;
- b. Ester-linkage;
- c. High protein binding;
- d. Primary metabolite (articainic acid).

### 4. Which positive effect is not attributed to the addition of epinephrine to articaine?

- a. Less blood loss and better vision;
- b. Longer and more profound anesthesia;
- c. Less systemic absorption;
- d. Faster time of onset.