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Pharmacokinetics of Local Anesthetics in Dentistry: The Example of Articaine-Containing and Mepivacaine-Containing Anesthetics

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Abstract:

Aim. To analyze current data on the pharmacokinetics of drugs used for local anesthesia in dental practice, with particular emphasis on articaine-containing and mepivacaine-containing anesthetics.

Materials and Methods. The study of up-to-date information from the Cyberleninka, Elibrary, Google Scholar and PubMed electronic databases was carried out during a systematic review of the literature. Selected and included articles, the content of which concerns the pharmacokinetics of local anesthetics articaine and mepivacaine.

Results. 55 publications were reviewed. After analyzing the literature for inclusion criteria, the total number of publications has become 42.

Conclusions. According to the analyzed data, the choice of local anaesthetic solution should be made individually for each patient and be based on the pharmacokinetics of the drug.

Keywords: local anesthetics, articaine, mepivacaine, pharmacokinetics.

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Фармакокинетика местных анестетиков в стоматологии: пример артикаинсодержащих и мепивакаинсодержащих анестетиков

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Резюме:

Цель. Анализ современных данных о фармакокинетике препаратов, используемых для местной анестезии в стоматологической практике, уделив особое внимание артикаинсодержащим и мепивакаинсодержащим анестетикам.

Материалы и методы. Изучение современной информации из электронных баз данных Cyberleninka, Elibrary, Google Scholar и PubMed проводилось в ходе систематического обзора литературы. Отобраны и включены статьи, содержание которых касается фармакокинетики местных анестетиков артикаина и мепивакаина.

Результаты.: Было проанализировано 55 публикаций. После анализа литературы на предмет критериев включения общее количество публикаций составило 42.

Выводы. Согласно проанализированным данным, выбор раствора местного анестетика должен осуществляться индивидуально для каждого пациента и основываться на фармакокинетике препарата.

Ключевые слова: местные анестетики, артикаин, мепивакаин, фармакокинетика.

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INTRODUCTION

Local anesthetic (LA) medications have become an integral part of dental practice in the modern world. Local anaesthetics are widely used for pain relief during invasive manipulations in the patient's oral cavity.

The term local anesthesia refers to the reversible inhibition of the generation and conduction of excitation through the impact on the endings of sensory nerves and nerve fibers. [1, 2]

LA's pharmacokinetics is an significant area in dentistry that studies the absorption, distribution, biotransformation and elimination of drugs in the body. Understanding the pharmacokinetics of LA allows dentists to choose the most effective and safe anesthesia individually for each patient.

The pioneer of local anesthetic effect, as exemplified by local injection of cocaine subcutaneously, was a physician, professor of medicine – Vasily Konstantinovich von Anrep. The results of his experiments were published in 1879 in the German journal Archiv fur Physiologie. Almost a century later, in 1957, mepivacaine was synthesised and between 1969 and 1974 articaine was discovered, local anesthetic drugs successfully used by dentists to date. [8]

There are two groups of anesthetics on the modern dental market: esters and amides. This literature review will focus on local anesthetics from the amide group, in particular articaine- and mepivacaine-containing anesthetics.

AIM

To analyse current data on the pharmacokinetics of mepivacaine and articaine-containing drugs for local anaesthesia.

MATERIALS AND METHODS

This review article was written by searching the electronic databases Google Scholar, PubMed, Elibrary, Cyberleninka, and prearticle reference lists.

Search terms included. For Russian sources: «pharmacokinetics of local anaesthetics «the use of articaine», «mepivocaine», «articaine». For foreign sources: «the use of articaine», «the use of mepivocaine», «pharmacokinetics of local anesthetics» (Table 1).

Publications were included based on the following inclusion criteria:

1. Articles dated 1995 and later.
2. Examination of the relevance of data on the pharmacokinetics of local anesthetic drugs.
3. Consideration of drug processes in the human body

The consideration and analysis of the articles were conducted in several stages.

The first criterion for selection was choosing publications whose titles included at least 1 search term. Next, works dated later than 1995 were excluded. The last stage involved studying the content of the full-text versions of the selected articles.

Cochrane Collaboration data were used to assess the risk of systematic error. [27, 28] And tests were performed at each of the selection stages according to Higgins et al [27]. The levels of systematic error, are as follows:

- low – all criteria fulfilled;
- moderate – one criterion is missing;
- high – two or more criteria are missing;
- unclear – little detail to make a risk decision.

RESULTS

55 articles were reviewed, of which 35 were from PubMed, 7 from Google Scholar, 5 from Elibrary and 7 from Cyberleninka. After applying exclusion criteria, the final number of studies included was 42. Current data on the pharmacokinetics of site anesthetic drugs were analysed in the selected articles.

DISCUSSION

Pain occurring at a dental appointment imposes both emotional and physical stress on the patient. Modern medications for local anesthesia not only eliminate unpleasant sensations during invasive manipulations, but also regulate the most crucial physiological processes in the body. [4, 9, 12, 31]

Modern local anesthetic solutions, in addition to the main active ingredient – the local anesthetic itself, also include adjuvants: vasoconstrictor (to enhance and prolong the effects of local anesthetics); vasoconstrictor stabilizer (sodium bisulfite, preventing the oxidation of adrenaline); preservatives, which allow maintaining the sterility of the solution (usually parabens). [4, 13]

Chemical structure of amide anesthetics

The structure of LA consists of three parts.

1. lipophilic part is represented by an aromatic compound. Due to the presence of this component, the molecule LA has the ability to pass through membranes represented by the bilipid layer of phospholipid molecules. [2, 10, 17]
2. The hydrophilic part is represented by a tertiary amine and a proton acceptor. The structure of this part contains a nitrogen atom interacting with the protein receptor located on the membrane of the nerve fibre. [2, 10, 17]
3. The intermediate part is the binding component of the lipophilic and hydrophilic parts. It can be represented by ester or amide bonds. [2, 10, 17]

Articaine-containing LA

Articaine is a methyl ester of 4-methyl-3-[2-propylaminopropionamido]-2-thiophenecarboxylic acid and is a thiophene derivative. The presence of a thiophene ring in the chemical structure of articaine distinguishes this anesthetic from other LA. [38]

Mepivacaine-containing LA

Mepivacaine retains the 2,6 – xylidine group in the aromatic ring, the intermediate chain is shortened, and the terminal tertiary amine is replaced by a less basic methylpiperidine ring. [20]

Absorption of local anesthetics

Local anesthetic drugs based on mepivacaine and articaine are widely utillized for various types of anesthesia: infiltration, nerve block and periodontal anesthesia. [4, 22, 25]

Anesthetic administration in dental practice is carried out parenterally by injection into the submucosa of the oral cavity. Anesthetic depot is formed in the subcutaneous adipose tissue with its subsequent diffusion into the surrounding tissues. [4] The concentration of MA in blood plasma is influenced by various factors: injection site, time of day, composition of the anesthetic solution, its physicochemical properties. [24]

Well vascularised tissues enable active penetration of the anesthetic into the bloodstream, thereby reducing the

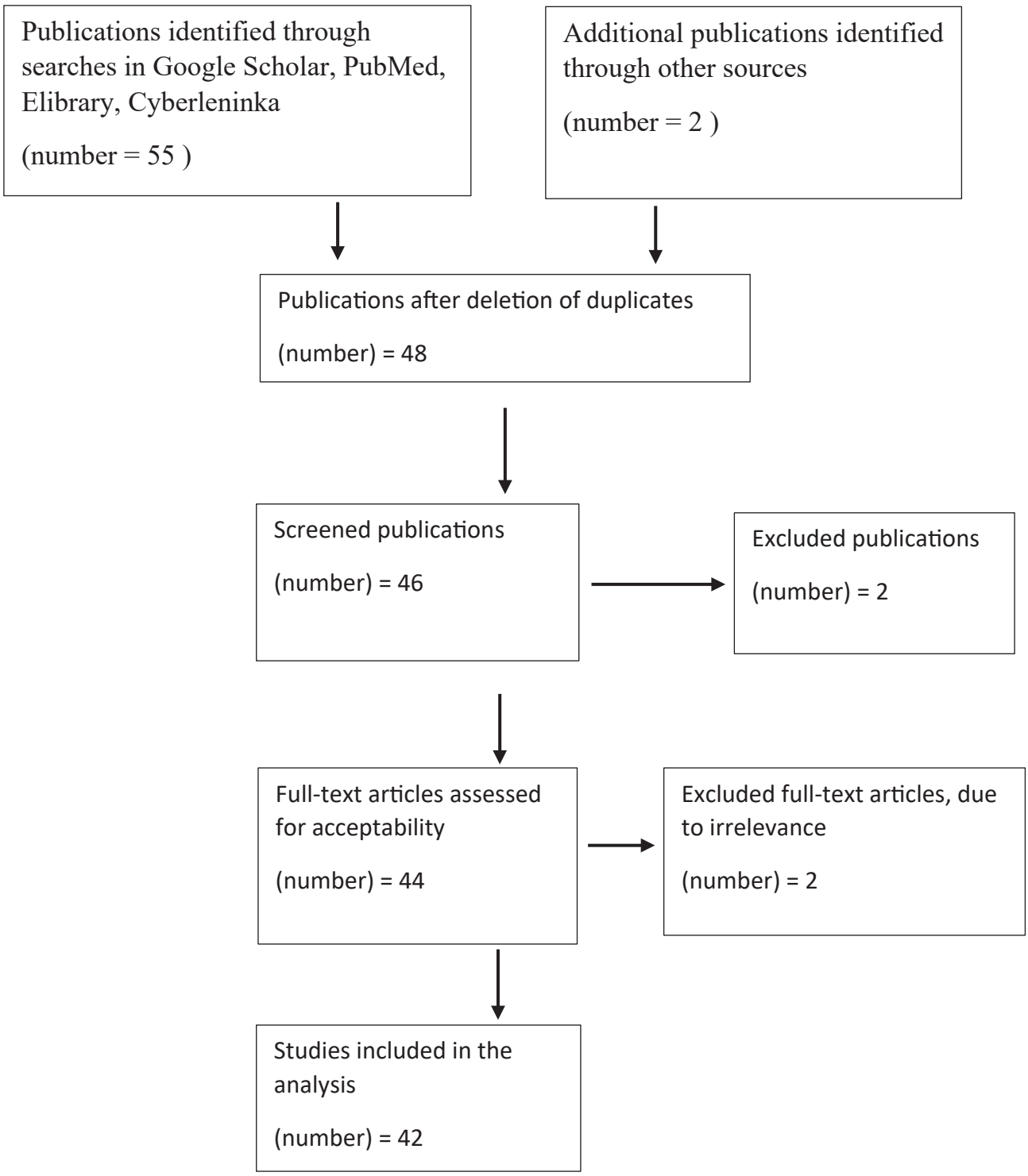
duration of the analgesic effect of the drug. [15, 18] The lipophilicity of LA is directly related to the speed of drug onset, with higher solubility in lipids allowing for faster penetration of the nerve sheath and axonal membranes. [21, 31]

Vasoconstrictors in local anesthetic solutions

Local anesthetic solutions may contain vasoconstrictors, substances that cause local vasoconstriction at the injection site. The most common such substance is adrenaline (epinephrine) at concentrations of 1:100 000 and 1:200 000 (5mcg/ml). The authors note that the presence of vasoconstrictor in LA, prolongs the absorption time of the anesthetic, resulting in prolonged analgesic effects, increased effectiveness of pain relief, and reduced systemic toxicity of the drug. [4, 15, 16, 20, 41]

Articaine-containing anesthetics are the preferred choice of dentists in most clinical cases. In terms of anaesthetic activity, 40 mg/mL 4 % articaine hydrochloride and 0.006 mg/mL adrenaline hydrochloride shows a similar effect to the use of 2% 20 mg/mL lidocaine hydrochloride and 0.0125 mg/mL adrenaline. [26] Articaine-based LA can be used in concentrations of articaine 2% (most used in paediatric dentistry) and articaine 4%, have a negligible vasodilating effect and can be used with or without a vasoconstrictor, if

Table 1. **Article selection process [32].**
Таблица 1. **Процесс отбора статей [32].**



there are contraindications to its use. [29, 34] Using articaine 4% 60-80 mg with epinephrine 1:200 000, achievement of complete anesthesia is noted in 90% of cases. This amount of anesthetic (up to 80 mg) does not cause a systemic toxic reaction in the healthy patients. [34]

The duration of anesthesia can reach 45-60 minutes when adding epinephrine at a concentration of 1:200000, and when using a vasoconstrictor at a concentration of 1:100000 – up to 180 minutes. In an acidic environment, the analgesic effect of local anesthetics reduce, which should be taken into account in the presence of inflammation in the area where anesthesia is planned. Articaine penetrates through the hematoplacental barrier to a minimal extent and is hardly excreted in breast milk. [6, 7, 24]

The pKa of articaine-containing anesthetics is 7.8 (shows weakly basic properties), which is close enough to the physiological pH value of extracellular fluid. This index indicates that the concentration of non-ionised form of LA preparation with articaine will be higher, and as a consequence, anesthesia will occur in a shorter time and will be more effective. The presence of thiophene ring in the chemical structure of articaine causes its high lipophilicity. [1, 2, 3, 16]

Research has shown that mepivacaine-containing anesthetics are drugs with a moderate duration of anesthetic effect (60-90 minutes). Mepivacaine is applied at concentrations up to 3% without the addition of a vasoconstrictor due to the absence of vasodilatory properties in this particular drug; instead, it has a slight vasoconstrictive effect. [20, 35]

The pka of mepivacaine-containing anesthetics is 7.7. It was observed that when working in infected tissues, mepivacaine-based LA would lose 64.7 % of efficacy, which is an advantage relative to lidocaine (72.8 %). Preparations with a pH above 4.9 demonstrate better patient tolerance due to reduced soreness during solution injection [5, 37].

Amide LA diffuse better into surrounding tissues, so that the anesthetic effect occurs faster. [13] For mepivacaine, the authors note the onset of action in 15-30 minutes [31], while articaine exhibits a faster anesthetic effect, with numbness noted as early as 5-7 minutes from the time of injection. [16, 26]

Distribution and biotransformation of local anaesthetics

After administration, local anesthetics solutions enter the systemic bloodstream and bind to blood proteins such as albumin and glycoproteins. This binding allows local anesthetics to interact with receptors responsible for sodium channels opening.

For articaine, the authors report a percentage of binding to blood proteins above 90%, while for mepivacaine this figure is 80% or higher.

The level of affinity a drug has for proteins indicates its effectiveness, with higher binding levels suggesting greater efficacy. [4, 14, 30]

The process of articaine metabolism begins immediately after the administration of the drug. Under the influence of esterases contained in the body, the carboxyl group of the articaine molecule is hydrolysed. Articaine is an amide anesthetic possessing a ester group and it differs from other similar anesthetics in its ability to undergo hydrolysis by non-specific blood esterases. This process leads to the biotransformation of 75% to 90% of articaine into its inactive metabolite, articaine acid. This is confirmed by the significantly higher concentration of articaine in alveolar blood (117 mg/L) compared to systemic blood (14.4 mg/L), as reported by the authors of the study. Due to this process, the systemic toxicity of the drug is significantly reduced, and the drug exhibits a short-term exceeding of threshold values, making it possible to administer repeat injections and use higher concentrations of the drug. [31, 41]

According to the study data, the maximum plasma concentration (Cmax) at 60mg of 4% articaine without vasoconstrictor was 1.805 ± 243 ng/ml, when the dose was increased up to 120mg Cmax was 3.438 ± 553 ng/ml. The above data indicate that the maximum concentration of the drug in plasma increases in direct proportion to the increase of LA dose. The tmax value for articaine was 5-15 minutes, for articaine acid 45 minutes. [15, 33, 37]

Metabolism of mepivacaine occurs in the liver and is associated with active participation of microsomal enzymes, especially the p450 enzyme. This produces an N-dimethylated and aromatically hydroxylated metabolite. [23]

In the study conducted for mepivacaine-containing anesthetics patient was administered 108 mg mepivacaine with 54 μg adrenaline the maximum blood concentration of the drug (Cmax), was reached by 20 minutes and was 2.33 ± 0.35 μg/ml. At the end of the second hour, the plasma concentration decreased to 1.05 ± 0.18 μg/ml.

When the dose of mepivacaine was increased to 216 mg with the addition of 108 mg epinephrine, the Cmax was 4.01 ± 0.69 μg/ml, decreasing after 2 hours to 4.01 ± 0.69 μg/ml.

Therefore, we can see a direct proportionality between the dose of mepivacaine and its plasma concentration. [15, 36]

Elimination of anesthetics

The predominant mechanism of elimination of articaine and its inactive metabolites is through the renal excretion with urine. Articaine acid is metabolized by renal tubule cells by glucuronidation. The percentage of excretion of articaine in unchanged form is approximately 1.45 ± 0.77%, 64.2 ± 14.4% for articaine acid, and 13.4 ± 5% for glucuronidated articaine acid. Publications also contain renal clearance values, which are: articaine – 1.35 ± 27 l/h, articaine acid – 7.18 ± 1.81 l/h.

60 mg of 4% articaine without vasoconstrictor was administered, the clearance was 3.836 ml/min; when the dosage was increased to 120 mg, the clearance is 3.735 ml/min.

The elimination half-life (t1/2) of articaine is 20-30 minutes, and 90 minutes for articaine acid and its metabolites, indicating a high metabolic rate and efficient elimination of articaine from the body. [4, 33, 40]

Mepivacaine-containing anesthetics are eliminated as inactive metabolites, only 5-10% of mepivacaine is excreted unchanged. The half-life (t1/2) of mepivacaine is 114 minutes, which is significantly longer than the t1/2 of articaine, indicating a longer duration of action of mepivacaine as a local anesthetic. [15, 36]

Understanding the pharmacokinetic parameters Cmax (maximum plasma concentration of the drug) and t1/2 (drug elimination half-life) is important for assessing the systemic toxicity of the drug, as well as determining the maximum dosage and the frequency of administration.

In a study conducted by Dinakaran Venkatachalam et al., the pharmacokinetics of articaine were investigated in a group of 6 goats. The goats were administered subcutaneous injections of 0.5 ml of 1.5% articaine hydrochloride (resulting in a total dose of 30 mg) and intravenous injections of 4% articaine hydrochloride (at a dose of 8 mg per kg of body weight). The following data were obtained:

Subcutaneous injection: Cmax (maximum plasma concentration) was 587 ± 175 ng/ml, Tmax (time to reach Cmax) was 0.22 ± 0.09 minutes, and half-life (T1/2) was 1.26

± 0.34hours. Intravenous injection: T1/2 was 0.66 ± 0.14 hours. [39]

The study noted the manifestation of articaine toxicity after its administration. Initially, sedation was observed, followed by ataxia disorder and clinical manifestations of seizures associated with the toxicity of the drug. The mean seizure concentration of articaine in plasma, when infused intravenously at 4 mg per 1 kg per minute (mean total dose at which seizure onset was noted was 16.24 ± 1.79 mg kg-1), was 9905 ± 2383 ng/ml-1, while the mean seizure concentration of articaine acid was 1517 ± 914 ng/ml-1. These findings demonstrate a significant exceedance of the seizure concentration over Cmax after intravenous administration of articaine. Based on this, we can conclude the high level of safety of articaine-containing local anesthetics. [39]

CONCLUSIONS

Local anesthetics are an integral part of dental practice, allowing for more comfortable and painless treatment of patients. LA block the transmission of nerve impulses and temporarily eliminate the pain sensation. For maximum safety and efficacy of local anesthesia, the type and dose of anesthetics should be individually selected based on their pharmacokinetic parameters.

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