*https://doi.org/10.31925/farmacia.2022.4.23* **ORIGINAL ARTICLE**

# A NOVEL LC-MS/MS ANALYTICAL METHOD FOR SIMULTANEOUS DETECTION OF ARTICAINE, ARTICAINE ACID, LIDOCAINE AND MONOETHYLGLYCINEXYLIDIDE (MEGX) IN HUMAN PLASMA

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**Abstract**

Articaine and lidocaine are the most used local anaesthetic agents in dentistry. There are different methods to identify local anaesthetics and their metabolites in human blood. The liquid-chromatography tandem mass spectrometry is one of them. The purpose of this study was to create an analytical method for the simultaneous detection of articaine, articaine acid, lidocaine and monoethylglycinexylidide (MEGX) in human plasma. The high performance liquid chromatography analysis was performed on a Thermo Dionex Ultimate 3000 LC system (Thermo Fisher Scientific, MA, USA) equipped with a quaternary pump, an autosampler and a thermostat for chromatographic columns. Chromatographic separation was performed under gradient conditions on a core shell Kinetex® 100 x 3.0 mm, 1.7 µm particles analytical column (Phenomenex, CA, USA). The procedure is fast and its appropriate for objective scientific results receiving.

**Rezumat**

Articaina și lidocaina sunt cele mai utilizate anestezice locale în stomatologie. Există diferite metode de identificare a anestezicelor locale și a metaboliților acestora în sângele uman, spectrometria de masă în tandem cu cromatografia de lichide fiind una dintre ele. Scopul acestui studiu a fost de a crea o metodă analitică pentru detectarea simultană a articainei, a acidului articainic, a lidocainei și a monoetilglicinxilididei (MEGX) în plasma umană. Analiza prin cromatografie lichidă de înaltă performanță a fost efectuată pe un sistem LC Thermo Dionex Ultimate 3000 (Thermo Fisher Scientific, MA, SUA) echipat cu o pompă cuaternară, un autosampler și un termostat pentru coloanele cromatografice. Separarea cromatografică a fost efectuată în condiții de gradient pe o coloană analitică Kinetex® 100 x 3,0 mm, cu particule de 1,7 µm (Phenomenex, CA, SUA). Procedura este rapidă și este adecvată pentru primirea de rezultate științifice obiective.

**Keywords**: local anaesthetics, liquid-chromatography, metabolites

## Introduction

Articaine hydrochloride is the most widely used local anaesthetic agent in dentistry containing ester and amide groups [6]. Due to the presence of ester moiety, articaine is rapidly metabolized by the blood pseudo-cholinesterases, unlike anaesthetics from amide group which are mainly metabolized by the liver. Consequently, plasma elimination half-life of articaine is approximately 20 minutes, whereas elimination half-life of other amide-type local anaesthetics is 100 minutes. According to fact that articaine is characterized by high percentage of protein binding (94%) and that, the main metabolite (articaine acid) is inactive, articaine has low central nervous system toxicity. The maximum plasma concentration of articaine is achieved 10 - 15 minutes after administration, while the time of maximum plasma concentration of articaine acid is achieved approximately 45 minutes after injection, independently of epinephrine co-administration [17]. In dental medicine, a 4% articaine with 1:200000 epinephrine is widely used for infiltration and nerve block anaesthesia [16]. Articaine is available in following concentrations: 2% with 1:200000 epinephrine; 4% without vasoconstrictors; 4% with 1:400000, 1:200000 and 1:100000 epinephrine [12]. The epinephrine addition is needed to produce vasoconstriction that leads to prolonged local anaesthesia and a short time of bleeding [15]. The maximum dose of articaine is 7 mg/kg body weight in adults. Patients with hypotensive conditions, congestive heart problems or decreased liver function (cirrhosis) are not able to perform the biotransformation of amide local anaesthetics. In this manner, slower biotransformation ability leads to increased anaesthetic blood levels and increased toxicity. The metabolites can be inert or toxic [8, 11]. Articaine and articaine acid are eliminated through the kidneys. Approximately 5 - 10% of articaine is excreted unchanged [10].

Lidocaine hydrochloride is an amide anaesthetic, which is metabolized by the liver to the monoethylglycinexylidide (main metabolite), 2,6-xylidine and glyceine-xylidide which are active [1, 9]. Approximately 10% of lidocaine is excreted unchanged through the kidneys. The maximum

plasma concentration of lidocaine is achieved 30 minutes after the administration; elimination half-life is between 90 and 120 minutes. The protein binding of lidocaine (65%) is less compared to articaine. Lidocaine hydrochloride has faster onset of anaesthesia, 3 to 5 minutes after injection. The duration of anaesthesia is approximately 60 minutes for pulp and between 180 and 300 minutes for soft tissues. For topical anaesthesia contain several forms spray (10%), gel (2 - 5%), patch (20%) *etc*. For anaesthesia (infiltration and nerve block anaesthesia) lidocaine is available as 2% plain solution without vasoconstrictors; 2% with epinephrine 1:50000, 1:80000 and 1:100000. The maximum dose of lidocaine is 7 mg/kg body weight in adults [12].

The literature reported different methods to identify local anaesthetics and their metabolites in human blood. Analysis of the anaesthetic metabolites (glucuronides or sulphates) is achieved only after acidic or enzymatic hydrolysis. Liquid-liquid extraction and solid-phase extraction are frequently used methods for local anaesthetics analysis. In gas chromatography, local anaesthetics are separated with capillary columns with polar or non-polar stationary phases. In liquid chromatography, reversed-phased columns C18 or C8, are the most commonly used for the separation of local anaesthetics. In gas-chromatography a flame ionization or mass detector are used, while in the liquid chromatography there may be used a triple quadrupole or ion trap mass detector. For the identification of local anaesthetics and their metabolites, LC-MS systems proved to have the highest limit of detection [4, 13, 14].

## Materials and Methods

*Chemicals and reagents*

Acetonitrile and methanol, used for LC-mobile phase and sample preparation are of LC-MS grade, and were purchased from Sigma-Aldrich (St. Louis, MI, USA). Deionized water was obtained in the laboratory by deionizer ELGA Veolia Purelab Chorus. The standards of lidocaine, articaine, lidocaine-d10, monoethylglycinexylidide (MEGX) were purchased from Sigma-Aldrich (St. Louis, MI, USA); standards of articaine-d7 and articainic acid were purchased from Toronto Research Chemicals (Toronto, ON, Canada); 98% formic acid and neostigmine bromide were purchased from Sigma-Aldrich (St. Louis, MI, USA). Stock solution of lidocaine (1 g/L), articaine (1 g/L), MEGX (1 g/L) and articainic acid (1 g/L) were prepared in methanol. Mixed stock solution consisted of lidocaine/articaine/MEGX/articainic acid (25:25:25:25, v/v/v/v). Internal standard solution (IS) which consisted of lidocaine-d10 and articaine-d7 (0.160 mg/L each) were prepared in methanol.

*Preparation of calibration curve and quality control samples*

Human plasma from healthy volunteers, who have signed informed consent to participate in the project, was used to prepare calibration curve and control samples. The Local Ethics Committee for Scientific Research of the Medical University - Plovdiv, Bulgaria approved this study and with the Helsinki Declaration of 1975, as revised in 2000. After blood sampling, plasma was obtained by centrifuge (4000 rpm, 4ºC). To 0.49 mL of the resulting plasma 0.01 mL of the corresponding working solution was added, mixed well and frozen at -20ºC until analysis. Calibration curve samples concentration was 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1.28, 1.92, 2.56 mg/L, and control samples concentration was 0.02, 0.05, 0.5 and 1.2 mg/L.

*Sample preparation procedure*

The procedure consists of several steps: 0.02 mL plasma were mixed with 0.02 mL IS and 0.360 mL MeOH for protein precipitation; shook well for 5 min and centrifuged at 0ºC and 15000 rpm for 10 min.; 0.1 mL from the upper organic layer were transferred to another tube, diluted twice with 0.1 mL of deionized water and 0.01 mL injected on to the chromatographic system.

*Liquid chromatographic and mass spectrometric conditions*

We used a Dionex Ultimate 3000 LC system (Thermo Fisher Scientific, MA, USA) equipped with a quaternary pump, an autosampler and a thermostat for chromatographic columns, and a triple quadrupole mass spectrometer TSQ Quantum Access Max (Thermo Fisher Scientific, MA, USA) with Heated electrospray ionization (HESI) source. Temperature of autosampler was set at 4ºC. Temperature of column thermostat was set at 28ºC. Chromatographic separation was performed under gradient conditions on a core shell Kinetex® 100 x 3.0 mm, 1.7 µm particles analytical column (Phenomenex, CA, USA). The mobile phases A and B, consisted of 0.1% formic acid in acetonitrile/water (90:10; v/v), and 0.1% formic acid in acetonitrile/water (10:90, v/v), respectively. The flow rate was 0.25 mL/min, and 18 min elution was performed as follows: linear gradient started at 7% A to 13% for 4 min; followed by linear gradient to 100% A for 1 min, and kept for 3 min. Finally, column was equilibrated at 7% A for 10 min. MS/MS analysis was performed with positive ionization mode, optimized as follows: spray voltage 3500 V; sheath gas, 30 arbitrary units; aux gas, 6 arbitrary units; vaporizer temperature 350ºC; capillary temperature 200ºC. Nitrogen was used as sheath and aux gas. Protonated molecules of analytes were used as precursor ions for selected reaction monitoring (SRM) with transitions of m/z 235.05 → 86.19 for lidocaine, 284.84 → 86.26 for articaine; for metabolites – 206.88 → 58.26 for MEGX and 271.20 → 86.19 for articainic acid; for internal standards 245.05 → 96.19 for lidocaine-d10 and 291.84 → 93.26 for articaine-

d7. Argon was used as collision gas; collision energy was 18 V, 15 V, 15 V, 14 V, 18 V and 15 V respectively.

*Method validation*

Selectivity was appraised with 6 individual human plasma matrices, using the technique of standard additions at two concentration levels with predefined normalized matrix effect within 85 - 115%. Low limit of quantification was evaluated with analyte signal at least five times the signal of a blank sample. Inaccuracy within and between-run should be in the range of 15% for quality control samples, and within ± 20% for the low limit of quantification sample. Imprecision within and between-run should also be in the same range. Method linearity in the defined calibration curve range should be with $R^2 > 0.996$. Freeze-thaw stability was ascertained for 4 cycles each lasting 24 h, post-preparative stability for 12 h and 24 h at 4 - 8ºC, short term stability of working solutions at room temperature for 24 h at daylight and for 24 h in the dark, stock solution stability and long-term stability in plasma for 30 days at -20ºC; all of the above within 15% of theoretical. Validation experiments were intended according to current EMA guidance for bioanalysis, and include 4 consecutive analytical runs in 4 contiguous days each with separate calibration curve, for assessment of precision and accuracy, with 5 replicates in the first day, and triplicate analysis of quality control and low limit of quantification samples in the following 4 days. For validation of method selectivity, matrix effect and stability experiments were performed. Carry-over effect from the system was checked by injecting blank plasma samples after injection of a spiked plasma samples.

## Results and Discussion

Local anaesthetics are usually transported in the blood, bound to the protein molecules. In order to determine the concentration of the analysed anaesthetics, it is necessary to release them from the transport molecules, which is achieved by protein precipitation. The sample preparation method we used involved a sample protein precipitation step. The LC-MS/MS chromatograms, obtained from patient's samples analysis, according to the described method are shown in Figure 1.

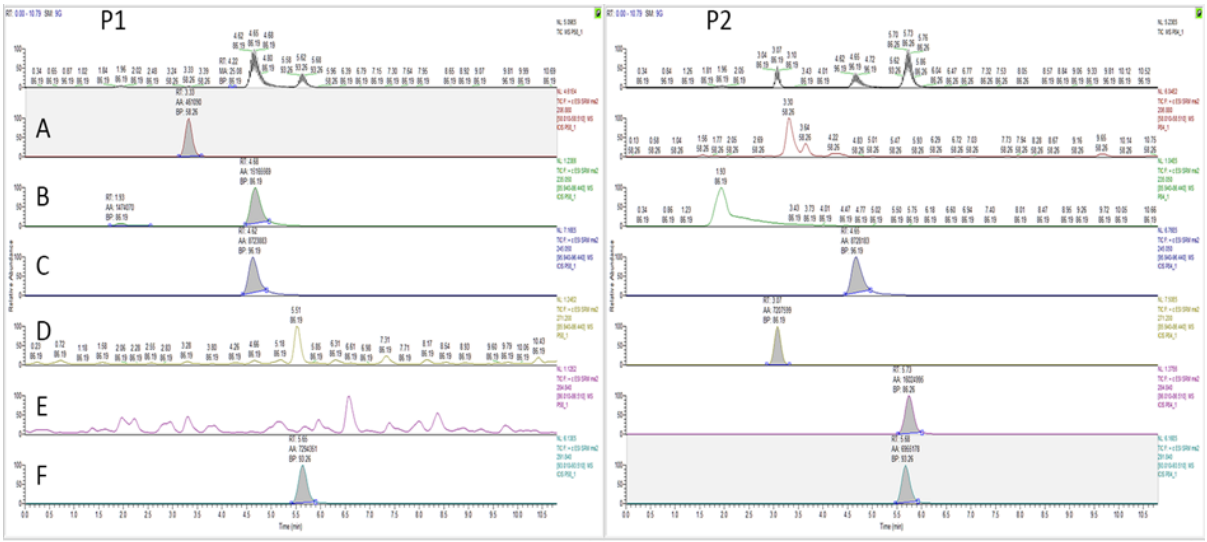


**Figure 1.**

Results from patient samples analysis. The signals of the respective analytes:
A – MEGX, B – lidocaine, C – lidocaine-d10, D – articainic acid, E – articaine and F – articaine-d7

Calibration was performed with nine calibration points at 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1.28, 1.92 and 2.56 mg/L of each measured analyte. Calibration curves were generated using the analyte to corresponding IS ratio by linear regression, and were linear with $R^2 = 0.997$ for articaine, 0.996 for lidocaine, 0.996 for articainic acid and 0.998 for MEGX. The lower limits of quantification were 0.02 mg/L for lidocaine, articaine, articainic acid and MEGX. Accuracy and precision calculated from the LLOQ and QC samples met the pre-defined acceptance criteria (Table I).

We presented the simultaneous detection of articaine, articaine acid, lidocaine and MEGX (monoethyl-glycinexylidide) in human plasma.

The mobile phases A and B in our study, consisted of 0.1% formic acid in acetonitrile/water (90:10; v/v), and 0.1% formic acid in acetonitrile/water (10:90, v/v), respectively. For mobile phase the most common components in other studies are acetonitrile and phosphate solution [2], acetonitrile with 0.1% formic acid (40:60, v/v) [7], acetonitrile-water 10 mM ammonium acetate 50:50 (v/v), pH 7, acetonitrile-buffer solution sodium acetate 10 mM and acetic acid 10 mM 50:50 (v/v), pH 4.7, respectively [14], phosphate buffer - acetonitrile (88:12, v/v) [19], dipotassium monohydrogen phosphate buffer and ortho phosphoric acid [5].

**Table I**

Accuracy of the assay

| QC-level | Accuracy (% from theoretical) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lidocaine | | | | Articaine | | | |
| | within-run (n = 5) | | between-run (n = 3) | | within-run (n = 5) | | between-run (n = 3) | |
| | min | max | min | max | min | max | min | max |
| **LLOQ** | 114.8% | 118.7% | 97.0% | 118.8% | 110.5% | 117.7% | 91.2% | 117.7% |
| **LOW** | 89.7% | 114.7% | 89.4% | 114.7% | 97.4% | 105.6% | 94.6% | 108.8% |
| **MED** | 88.1% | 90.5% | 86.4% | 97.7% | 89.8% | 91.6% | 89.8% | 101.4% |
| **HIGH** | 90.2% | 93.3% | 89.4% | 106.6% | 91.3% | 93.7% | 91.3% | 104.0% |

A method for the determination of articaine in human plasma, by liquid chromatography-mass spectrometry, in patients after a submucosal infiltration anaesthesia was developed in another study in positive-ion mode at 200°C with a linear calibration curve over the concentration range of 78.1 - 5000 ng/mL. The determination coefficients were > 0.996, total run-time < 3 min (fast method), accurate (bias < 16%), intra-assay and inter-assay precision < 14% (reproducible) with a quantitation limit of 78.1 ng/mL [7].

Another study described the simultaneous determination of articaine and its metabolite articainic acid in human serum by HPLC, using solid-phase extraction (SPE) for pre-concentration of both components. Ultraviolet (UV) absorption at 274 nm was used for measuring the analytes with a low limit of quantification of 10 ng/mL [19].

The liquid chromatography-tandem mass spectrometry in multiple reaction monitoring mode (transitions: articaine, 285 → 8658 m/z; mepivacaine, 247 → 9870 m/z; lidocaine (internal standard), 235 → 8658 m/z) allowed the simultaneous detection of articaine and mepivacaine in whole blood. The method proved to be highly sensitive with limits of quantifications for articaine and mepivacaine of 0.8 and 0.1 ng/mL, respectively [3].

**Table II**

Matrix effect of the assay, performed with 12 plasma samples, and 6 additional – 2 icteric, 2-haemolytic and 2 lipemic

| Sample | Matrix effect | | | | | |
|---|---|---|---|---|---|---|
| | Lidocaine | IS | Normalized | Articaine | IS | Normalised |
| **P1** | 113.4% | 107.1% | 105.8% | 104.1% | 105.0% | 99.2% |
| **P2** | 111.9% | 105.5% | 106.0% | 98.0% | 105.3% | 93.1% |
| **P3** | 105.5% | 110.0% | 95.9% | 97.5% | 105.4% | 92.6% |
| **P4** | 104.7% | 114.9% | 91.1% | 101.4% | 112.9% | 89.8% |
| **P5** | 109.0% | 115.3% | 94.6% | 101.5% | 111.5% | 91.0% |
| **P6** | 111.6% | 118.0% | 94.6% | 99.7% | 114.1% | 87.4% |
| **P7** | 108.1% | 106.2% | 101.8% | 99.4% | 103.2% | 96.3% |
| **P8** | 96.6% | 101.3% | 95.4% | 99.6% | 105.0% | 94.8% |
| **P9** | 109.1% | 108.5% | 100.5% | 102.0% | 106.3% | 96.0% |
| **P10** | 106.7% | 108.7% | 98.2% | 100.2% | 106.8% | 93.8% |
| **P11** | 99.6% | 99.0% | 100.7% | 88.7% | 98.2% | 90.3% |
| **P12** | 106.8% | 106.5% | 100.3% | 95.2% | 104.2% | 91.3% |
| | | | **min 91.1%** | | | **min 87.4%** |
| | | | **max 106.0%** | | | **max 99.2%** |
| **P_B1** | 110.0% | 88.3% | 124.5% | 100.6% | 86.9% | 115.7% |
| **P_B2** | 107.1% | 85.1% | 125.9% | 89.1% | 81.1% | 109.8% |
| **P_H1** | 96.4% | 90.0% | 107.1% | 88.7% | 86.8% | 102.2% |
| **P_H2** | 92.0% | 79.9% | 115.1% | 77.7% | 75.6% | 102.9% |
| **P_L1** | 146.0% | 91.8% | 159.0% | 133.3% | 87.7% | 152.1% |
| **P_L2** | 84.6% | 85.9% | 98.5% | 74.5% | 81.8% | 91.1% |

Regarding the extraction procedures of lidocaine, one study validated a method with linearity in the concentration range of 20 - 100 μg/mL and $R^2 = 0.999$ similar to our study. They found the limit of detection and the limit of quantification 1.54 μg/mL and 4.68 μg/mL, respectively [5].

In Canada it was reported method of liquid-liquid extraction of lidocaine and procainamide (internal standard) from human serum (0.25 mL). Linearity was in the range of 50 - 5000 ng/mL, $R^2 = 0.999$ [2].

In recent years capillary zone electrophoresis method was applied for the determination of lidocaine. The method showed good linearity with $R^2 = 0.999$, limit of detection 0.92 mg/ L, peak area with an intermediate precision > 3.2%, and recovery in the interval of 92 - 102% [20].

A spectrophotometric method for the determination of lidocaine hydrochloride was validated and developed in Iraq. The limits of detection and quantification were 0.024 mg/L, and 0.100 mg/L respectively. Intra-day accuracy and precision of the investigated method consisted of relative error (0.57%), and the relative standard deviation (0.25 - 1.23) [18].

In our study the normalized matrix effect was in the range of 87.4% - 106.0%, except for the plasma samples with haemolysis, lipemia and hyperbilirubinemia, where it reached 159% (Table II). No significant ion suppression was found for the individual plasma samples. Freeze-thaw stability estimated for three cycles of 24 hours each, was between -10.6% and 14.7% for lidocaine, between -8.7% and 8.8% for articaine, between -13.8% and 6.6% for MEGX and between -9% and 12.8% for articainic acid. Postpreparative stability evaluated at room temperature for 24 h was between -3.1 and 5.9% for lidocaine, 5.4 and 8.0% for articaine, 1.1 and 4.4% for MEGX, and 5.6 and 14.0% for articainic acid.

## Conclusions

This study presents a new method for the simultaneous determination of two local anaesthetics – articaine, lidocaine and their major metabolites (articainic acid, monoethylglycinexylidide) in human plasma using simple sample preparation procedure with protein precipitation step. The method was validated with reference to linearity, selectivity, matrix effect, stability, precision and accuracy of the assay. The lower limits of quantification for lidocaine, articaine, articainic acid and MEGX were determined. One of the most common application of the presented method is when compared mean plasma levels of buffered (alkalized) and non-buffered (non-alkalized) local anaesthetics to assess how rapid they are eliminated from the body.

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## Conflict of interest

The authors declare no conflict of interest.

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