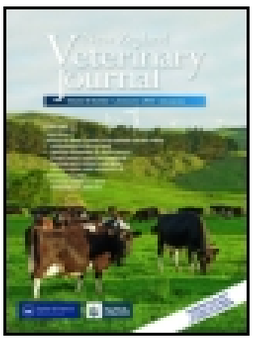

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Scientific Article

Pharmacokinetics of articaine hydrochloride and its metabolite articainic acid after subcutaneous administration in red deer (*Cervus elaphus*)

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Abstract

AIM: To develop and validate a simple and sensitive method using liquid chromatography-mass spectrometry (LC-MS) for quantification of articaine, and its major metabolite articainic acid, in plasma of red deer (*Cervus elaphus*), and to investigate the pharmacokinetics of articaine hydrochloride and articainic acid in red deer following S/C administration of articaine hydrochloride as a complete ring block around the antler pedicle.

METHODS: The LC-MS method was validated by determining linearity, sensitivity, recovery, carry-over and repeatability. Articaine hydrochloride (40 mg/mL) was administered S/C to six healthy male red deer, at a dose of 1 mL/cm of pedicle circumference, as a complete ring block around the base of each antler. Blood samples were collected at various times over the following 12 hours. Concentrations in plasma of articaine and articainic acid were quantified using the validated LC-MS method. Pharmacokinetic parameters of articaine and articainic acid were estimated using non-compartmental analysis.

RESULTS: Calibration curves were linear for both articaine and articainic acid. The limits of quantifications for articaine and articainic acid were 5 and 10 ng/mL, respectively. Extraction recoveries were >72% for articaine and >68% for articainic acid. After S/C administration as a ring block around the base of each antler, mean maximum concentrations in plasma (C_{max}) of articaine were 1,013.9 (SD 510.1) ng/mL, detected at 0.17 (SD 0.00) hours, and the C_{max} for articainic acid was 762.6 (SD 95.4) ng/mL at 0.50 (SD 0.00) hours. The elimination half-lives of articaine hydrochloride and articainic acid were 1.12 (SD 0.17) and 0.90 (SD 0.07) hours, respectively.

CONCLUSIONS AND CLINICAL RELEVANCE: The LC-MS method used for the quantification of articaine and its metabolite articainic acid in the plasma of red deer was simple, accurate and sensitive. Articaine hydrochloride was rapidly absorbed, hydrolysed to its inactive metabolite articainic acid, and eliminated following S/C administration as a ring block in red deer. These favourable pharmacokinetic properties suggest that articaine hydrochloride should be tested for efficacy as a local anaesthetic in red deer for removal of velvet antlers. Further studies to evaluate the safety and residues of articaine hydrochloride and articainic acid are required before articaine can be recommended for use as a local anaesthetic for this purpose.

KEY WORDS: *Articaine hydrochloride, local anaesthetic, liquid chromatography-mass spectrometry, pharmacokinetics, red deer*

C_{max}	Maximum concentration in plasma
DMA	2,6-dimethylaniline
LC-MS	Liquid chromatography-mass spectrometry
T_{max}	Time to reach maximum concentration in plasma

Introduction

Antlers are unique structures found in cervids which may be cast and regrown annually (Price and Allen 2004). Velvet antlers are highly innervated and vascularised cartilaginous structures that are harvested for commercial purpose in New Zealand, China, Canada and North America. In New Zealand the removal of velvet antlers (velvetting) can only be carried out after desensitisation of the antlers (Anonymous 1992). A complete ring block around the antler pedicle, using the local anaesthetic lidocaine hydrochloride, is the most widely used and reliable technique to desensitise antlers before velvetting (Johnson *et al.* 2005; Woodbury *et al.* 2002). However there are concerns regarding residues of lidocaine in the harvested velvet antlers (Woodbury *et al.* 2002; Bagonluri *et al.* 2005). In a limited survey of harvested velvet antlers, lidocaine was detected in 50% of samples at concentrations greater than the maximum permitted residue level of 0.1 mg/kg set by the New Zealand Food Safety Authority (Clear and Morris 2005). Lidocaine is metabolised by N-dealkylation in the liver to active metabolites, which are further metabolised to an aromatic amine, 2,6-dimethylaniline (DMA) (Duan *et al.* 2008). DMA is classified as potential carcinogen in humans (Anonymous 1993) and is hepatotoxic in rats (Duan *et al.* 20086). It has been reported to

increase the incidence of various types of tumours in rats and humans (Anonymous 1990; Beland *et al.* 1997; Duan *et al.* 2008).

Articaine hydrochloride (4-methyl-3-(2-propylaminopropionamido) thiophene-2-carboxylic acid methyl ester hydrochloride) is a unique amide-type local anaesthetic. It is widely used in humans where it is considered to be safe and effective (Oertel *et al.* 1997; Vree and Gielen 2005; Su *et al.* 2016). It is rapidly metabolised to inactive metabolites (mostly articainic acid) by plasma cholinesterases, thus decreasing systemic toxicity to the cardiovascular and central nervous systems which is common to all local anaesthetics (Snoeck 2012). Toxicity studies of articaine in rats and dogs also showed no pathomorphological systemic changes, even after administration of systemically toxic doses, and during *in vitro* and *in vivo* studies no mutagenic properties were associated with articaine, even at cytotoxic concentrations or the maximum tolerated dose (Leuschner and Leblanc 1999).

Given concerns regarding lidocaine residue in harvested antlers and the reported advantages of articaine hydrochloride, we propose that articaine hydrochloride may be preferable to lidocaine as a local anaesthetic for velvetting in red deer (*Cervus elaphus*). However it must be noted that articaine hydrochloride is not yet approved for use in veterinary medicine and no studies have been conducted in animals to evaluate the carcinogenicity of articaine or its metabolites.

The objectives of this study were to develop and validate a simple and sensitive method using liquid chromatography-mass spectrometry (LC-MS) for the quantification of articaine and its metabolite articainic acid in plasma of red deer, and to determine the pharmacokinetic parameters of articaine hydrochloride following S/C administration as a complete ring block around the base of the antlers in red deer.

Materials and methods

Reagents and drugs

Articaine hydrochloride standard (99.9%) was purchased from SCI Pharmtech (Taoyuan, Taiwan) and the purity was confirmed using nuclear magnetic resonance crystallography at Massey University (Palmerston North, NZ). Articainic acid standard (97%) was obtained from Toronto Research Chemicals (Toronto, Canada). Acetonitrile, methanol, water and formic acid were LC-MS grade and were purchased from Fisher Scientific (Auckland, NZ). Reagent grade perchloric acid was obtained from BDH (Auckland, NZ). Articaine hydrochloride solution (40 mg/mL) was prepared freshly on the day of use by weighing an appropriate amount of standard and dissolving it in milliQ water. The solution was then filtered through a syringe filter (0.45 μm, Phenomenex Inc, Auckland, NZ) and made up to 40 mg/mL with sterile normal saline.

Preparation of standards and quality control samples

Standard stock solutions (1 mg/mL) of articaine hydrochloride and articainic acid were prepared by dissolving in water and methanol, respectively. Equal volumes of both stock solutions were mixed and working solutions were then prepared by dilution with water. Standard solutions for the construction of calibration curves and quality control samples were prepared freshly by adding working solutions of either articaine or articainic acid to ice cold pooled plasma obtained from untreated red deer.

Sample preparation

A 0.5-mL aliquot of ice cold plasma was added to a 1.5 mL microcentrifuge tube and 25 µL of perchloric acid was then added and mixed using a vortex mixer for 10 seconds to precipitate proteins. After 10 minutes, the samples were mixed again using the vortex mixer then centrifuged at 20,800g for 10 minutes and 5 µL of supernatant was injected on to the chromatography column.

Liquid chromatography-mass spectrometry

Liquid chromatography was carried out using an ultra high performance liquid chromatography system equipped with a quaternary pump, a vacuum degasser, a column compartment and an autosampler (Dionex Ultimate 3000 System; Thermo Scientific, Germering, Germany). Chromatographic separations were achieved using a 2.6 µm particle size C-18 column (100 mm × 2.1 mm; Accucore, Auckland, NZ) coupled with a security guard column (Defender Guard Column; Accucore Auckland, NZ) maintained at a temperature of 30°C. The mobile phase consisted of 0.1% formic acid and acetonitrile (70:30, v/v) and was delivered at a flow rate of 0.3 mL/minute.

Mass spectrometric detection was performed using a hybrid quadrupole orbitrap mass spectrometer (Q Exactive Focus Hybrid Quadrupole-Orbitrap Mass Spectrometer; Thermo Scientific, Bremen, Germany) with an electrospray-ionization interface. Positive ion electrospray ionization-mass spectrometry was used for analysis of both articaine and articainic acid. Mass spectrometry conditions are given in Table 1. Data processing was performed using the Xcalibur data system (Thermo Scientific) and quantitation was performed in the full scan MS mode using peak-area ratios of the target ion of articaine (mass to charge ratio 285.16) and articainic acid (mass to charge ratio 272.11). Samples which exceeded the calibration limit were appropriately diluted with drug-free plasma and reanalysed.

Validation

The linearity of the LC-MS method was determined by linear regression analysis. Calibration curves were constructed using three replicates of pooled plasma obtained from untreated deer spiked with working solutions of either articaine hydrochloride or articainic acid, at concentration

ranging between 5–2,000 ng/mL and 10–1,000 ng/mL, respectively. The lower limit of detection and quantification of the compounds were set at signal to noise ratios of 3:1 and 10:1, respectively.

Recoveries of articaine hydrochloride and articainic acid from red deer plasma after extraction were calculated by measuring the peak areas for three replicate samples of plasma from untreated deer containing 20, 200 and 1,000 ng/mL of quality control standards, following the same sample preparation procedure described above. Specificity of the method was determined by comparing the chromatograms of blank plasma samples obtained from six untreated deer and a spiked plasma sample containing 20 ng/mL of articaine and articainic acid.

Intra-day and inter-day precision and accuracy of the method were determined by processing three replicates of plasma samples from untreated deer containing three concentrations (20, 200 and 1,000 ng/mL) of analytes six times on one day, and on six different days, respectively.

Carry-over from the system was assessed by injecting a drug-free plasma sample after injection of a plasma sample containing either articaine or articainic acid at concentrations equivalent to the respective upper limit of quantification.

Animals and experimental procedure

Six healthy 2-year-old male red deer weighing between 105–116 kg were used for this study. The experimental protocol was approved by Massey University Animal Ethics Committee (Palmerston North, NZ) and the study was conducted at Massey University Deer Research Unit (Palmerston North, NZ).

Each red deer was physically restrained in a hydraulic crush, the hair around the base of antlers was clipped and the pedicle circumference of each antler was measured using a measuring tape. The left or right facial vein was surgically prepared and a 20 gauge, 48 mm I/V catheter (BD Insyte, Sandy, UT, USA) was placed and secured with cyanoacrylate adhesive (Super Glue; Loctite, Auckland, NZ). The patency of the catheter was maintained using heparinised (10 USP/mL) saline.

Within 5 minutes of catheterisation, articaine hydrochloride (40 mg/mL) at a dose of 1 mL/cm of pedicle circumference was administered S/C as a complete ring block (4–5 injections) around the base of both the antlers using a 20 gauge needle attached to a 20 mL syringe. The syringe plunger was pulled back prior to infiltration to ensure the needle was not in a blood vessel. The time taken for drug administration did not exceed 2 minutes in any of the animals. Blood samples were collected, via the catheter in the facial vein, into heparinised vacutainers (BD Vacutainer, Plymouth, UK) prior to drug administration (0 minutes), and 10, 20, 30, 40 minutes and 1, 2, 4, 6, 8, and 12 hours following drug administration. Immediately after collection, blood samples were cooled on

ice and plasma was separated and stored at −20°C. LC-MS analysis was carried out within 1 month of sample collection.

For 2 hours after drug administration animals were visually observed for adverse signs such as muscle tremor, sedation or convulsion while unrestrained in a pen.

Pharmacokinetic analysis

Pharmacokinetic parameters were determined using non-compartmental analysis. The PKSolver add-on (Zhang *et al.* 2010) for Excel 2010 (Microsoft, Redmond, CA, USA) was used to calculate pharmacokinetic parameters using individual concentrations of articaine and articainic acid in plasma. The maximum concentration in plasma (C_{max}) and time to achieve C_{max} (T_{max}) were determined directly from the curves of plasma concentrations over time. The rate constant of the terminal phase (λ_z) was calculated by linear regression of the logarithmic plasma concentration and the terminal half life was calculated as:

$$t_{½\lambda z} = \ln 2/\lambda z$$

The area under the curve (AUC) and the area under the first moment curve (AUMC) were determined using the linear trapezoidal method. Mean residence time was calculated as:

$$MRT = AUMC/AUC$$

Results

LC-MS validation

Calibration curves (Supplementary Figure 1[1]) were linear with correlation coefficients of 0.997 for articaine and 0.998 for articainic acid. The lower limits of quantification were 5 ng/mL and 10 ng/mL, and the lower limits of detection were 1 ng/mL and 5 ng/mL, for articaine and articainic acid, respectively. The assay intra-day CV for articaine and articainic acid were <5.7 and 5.3%, respectively, and the inter-day CV for articaine and articainic acid were <12.8 and 10.7%, respectively. The extraction recoveries for articaine ranged from 72–79% and for articainic acid from 68–75% (Table 2). No carry-over effect was found when a drug-free plasma sample was injected after a sample containing concentrations of the analytes equivalent to the upper limit of quantification. Analysis of six blank plasma samples from untreated deer showed no interfering peak on the chromatograms at the retention times of articaine or articainic acid.

Representative chromatograms and electrospray ionization full scan MS mode are shown in Supplementary Figure 2[1] for plasma samples that were drug-free, or spiked with 20 ng/mL of

[1] https://doi.org/10.1080/00480169.2017.1391141

articaine and articainic acid, or from a red deer following S/C administration of 40 mg/mL articaine hydrochloride as a complete ring block around the antlers.

Pharmacokinetics

No signs of adverse effects were observed in any animal following administration of articaine hydrochloride. Mean concentrations in plasma of articaine and its metabolite articainic acid following S/C administration of articaine as a ring block are shown in Figure 1. Peak concentrations of articaine in plasma were detected in the sample collected 10 minutes after drug administration, which was the first sample collected. Concentrations in plasma of articaine hydrochloride and articainic acid were above the limit of quantification for 6 and 4 hours after administration, respectively. The pharmacokinetic parameters both compounds following S/C administration of articaine hydrochloride as a ring block are shown in Table 3.

Discussion

The LC-MS method described here for measurement of articaine and its metabolite articainic acid in the plasma of red deer is simple and sensitive with acceptable precision and accuracy. The sensitivity of the LC-MS method was greater than previously reported methods with a lower limit of quantifications of 5 ng/mL and 10 ng/mL for articaine and articainic acid, respectively. Richter and Oertel (1999) reported a lower limit of quantification of 10 ng/mL for articaine using an HPLC-based method and Hoizey *et al.* (2009) reported a lower limit of quantification of 78.1 ng/mL for articaine using a different LC-MS method. The sample preparation method used here involved a simple protein precipitation step which yielded good recoveries of the analytes. Previously reported extraction methods used liquid-liquid extraction or a solid phase extraction step followed by drying (Richter and Oertel 1999; Hoizey *et al.* 2009), which are more time consuming than the simple protein precipitation step used in our method.

This is the first study to investigate the pharmacokinetics of articaine hydrochloride and its metabolite articainic acid in red deer. Following S/C injection, articaine hydrochloride was rapidly absorbed with a mean C_{max} of 1013.9 ng/mL and T_{max} of 0.17 hours. The time when maximum concentrations were detected was when the first sample was collected after administration of articaine, therefore in future studies blood samples should be collected earlier than 10 minutes after administration to more accurately determine the C_{max} and T_{max}. Rapid absorption of the articaine hydrochloride can be attributed to its vasodilatory effect, similar to most other local anaesthetics (Snoeck 2012). The rapid absorption of articaine hydrochloride has also been reported in humans following oral nerve blocks and epidural administration (Muller *et al.* 1991; Vree *et al.* 1997).

The mean terminal half-life of 1.12 hours indicates that articaine is rapidly eliminated following S/C administration in red deer. Articaine was rapidly hydrolysed to its metabolite articainic acid, with maximum concentrations of articainic acid being detected 30 minutes after administration. Rapid hydrolysis has been reported to be due to the presence on the articaine molecule of an ester group, which makes it a suitable substrate for plasma esterases (Oertel *et al.* 1997). Articainic acid was also eliminated rapidly with a mean terminal half-life of 0.90 hours. Pharmacokinetic studies in humans found that articaine was excreted primarily as articainic acid (64%), and the glucuronide conjugate of articainic acid (13%). Only 1.5% was excreted as the parent drug, articaine hydrochloride (Vree *et al.* 1997).

No signs of toxicity associated with over-dose of local anaesthetic, such as muscle tremor, sedation or convulsion, were observed following administration of articaine hydrochloride in the current study. Rapid hydrolysis of articaine hydrochloride by plasma esterases to an inactive metabolite results in short half-life of the drug thereby reducing the risk of systemic toxicity (Oertel *et al.* 1997). In contrast, lidocaine hydrochloride is metabolized to active metabolites which require hepatic clearance. In addition, *in vitro* and *in vivo* preclinical toxicity studies in rats, rabbits and dogs indicated that articaine hydrochloride did not demonstrate any pathomorphological or mutagenic effects at doses up to 70 mg/kg (Leuschner and Leblanc 1999).

In conclusion, a method for the detection and quantification of articaine and articainic acid using LC-MS was developed and validated, and found to be simple, accurate and sensitive. Articaine hydrochloride was shown to have favourable pharmacokinetic properties in red deer including rapid absorption, hydrolysis and elimination. Moreover, we observed no adverse effects following S/C administration of articaine hydrochloride as a complete ring block around the antler pedicle in red deer. Articaine hydrochloride may therefore be a good alternative to the commonly used local anaesthetic lidocaine for velvetting in red deer. Use of articaine hydrochloride in animals has not been authorised in any animal species and further studies are required to evaluate the safety and efficacy of the drug at different concentrations, and to establish maximum residue limits, before it can be recommended for use as a local anaesthetic in red deer.

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Table 1. Mass spectrometry conditions for the quantification of articaine and articainic acid in the plasma of red deer (*Cervus elaphus*).

Parameter	Value
Resolution setting	70,000
Mass range	100.0–500.0 m/z
Spray voltage	3.3 kV
Sheath gas flow rate	30.0 arbitrary units
Auxiliary gas flow rate	5.0 arbitrary units
Capillary temperature	320°C
Heater temperature	350°C
Radio frequency lens level	50.0
HCD collision energy	35 eV

HCD=higher energy collisional dissociation; m/z=mass-to-charge ratio

Table 2. Mean (±SD) recovery (%) of articaine and articainic acid spiked into drug-free plasma from red deer (*Cervus elaphus*) at three different concentrations, after extraction and detection using liquid chromatography-mass spectrometry.

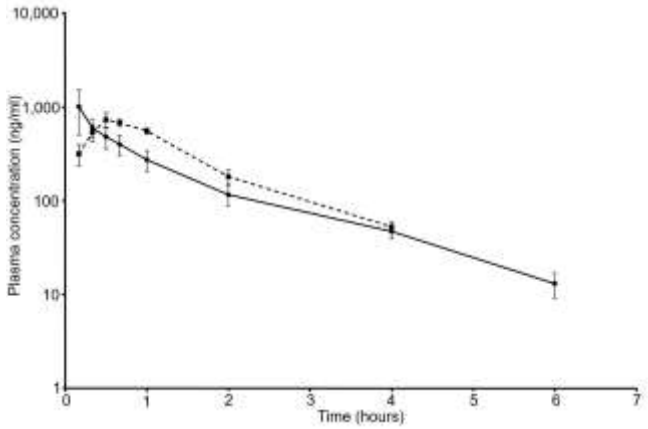
Concentration (ng/mL)	Articaine	Articainic acid
20	75.7±1.3	75.6±3.1
200	79.0±4.9	68.9±1.4
1,000	72.4±3.9	72.2±4.0

Table 3. Mean (±SD) pharmacokinetic parameters of articaine and articainic acid following S/C administration of 40 mg/ml articaine hydrochloride (1 mL/cm pedicle circumference) as a complete ring block around the antler pedicle of red deer (*Cervus elaphus*; n=6).

Parameter	Articaine	Articainic acid
Maximum plasma concentration (ng/mL)	1013.9±510.1	762.6±95.4
T_{max} (hours)	0.17±0.00	0.50±0.00
AUC (ng/mL.hour)	936.9±157.1	1196.0±80.7
AUMC (ng/mL.hour)	1326.5±151.0	1701.7±93.1
Terminal half life (hours)	1.12±0.17	0.90±0.07
Mean residence time (hours)	1.45±0.29	1.43±0.08

AUC=Area under the curve; AUMC= Area under the first moment curve; T_{max}=Time to reach maximum plasma concentration

Figure 1. Mean (±SD) concentrations of articaine (solid line) and articainic acid (dotted line) in plasma of red deer (*Cervus elaphus*; n=6) following S/C administration of 40 mg/mL articaine hydrochloride (1 mL/cm pedicle circumference) as a complete ring block around the antler pedicle. Note the log scale of the y-axis.



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