Regional metabolism of articaine in 10 patients undergoing intravenous regional anaesthesia during day case surgery

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Aims To study the pharmacokinetics of articaine and its metabolite articainic acid, in patients undergoing intravenous regional anaesthesia.

Methods Ten patients (three male, seven female, ASA class 1–2), scheduled for surgery of the hand or forearm were included in the study. Articaine (40 ml, 0.5% solution (200 mg) was injected over 30 s. In total fifteen arterial blood samples were taken, one before injection and then at 10 min intervals, starting 10 min after completion of injection, until the tourniquet was released; thereafter blood samples were drawn at intervals of 1, 5, 10, 15, 20, 25, 30, 45, 60, 75 and 90 min. The tourniquet was released 30 min after completing the injection.

Results During tourniquet application and regional analgesia of 30 min duration, 55% of articaine was hydrolysed by plasma (20%) and tissue (35%) esterase activity to the metabolite articainic acid. After releasing the tourniquet, articaine and its metabolite appeared in the blood; articaine was rapidly eliminated with a t1/2 of approximately 60 min. The plasma concentration of the metabolite articainic acid was the sum of the amount formed during IVRA (55%) and the amount formed after tourniquet release (45%).

Conclusions Articaine is a safe agent for intravenous regional anaesthesia (IVRA) with rapid onset of good surgical anaesthesia. During tourniquet application and regional analgesia, 55% of the administered dose is already hydrolysed, thus reducing the chance of side effects after tourniquet release.

Keywords: articaine, pharmacokinetics, articainic acid, regional metabolism

Introduction

For intravenous regional anaesthesia (IVRA), different local anaesthetics have been used [1]. At the beginning of the 20th century, Bier used 40 ml 0.5% procaine [2]. Ligocaine was first used in 1963, and prilocaine in 1964 [3]. The use of chloroprocaine may lead to thromboembolitis [1], venous irritation and urticaria [4]. Bupivacaine is contraindicated because of potential cardiotoxicity and fatal complications have been reported following intravenous injection [5–8], a situation that exists with this technique when the tourniquet is released at the end of the surgical procedure.

The ideal agent for IVRA provides rapid onset of good surgical anaesthesia with a low cardiotoxicity. Articaine is a safe local anaesthetic agent as previously reported [9, 10] and its metabolite has no effect on heart rate and blood pressure [11, 12]. Articaine ((±)-3-n-propylamine-proponylamido-2-carbomethoxo-4-methylthiophen hydrochloride) was first investigated clinically in 1974 [13–16] and is now used (4% with adrenaline 1: 200 000) in dentistry for infiltration and conduction anaesthesia. The very fast onset of the block, the excellent quality of the anaesthesia, the reduced toxicity and the short duration of action, owing to hydrolysis of the parent drug, are responsible for its wide utilization [17, 18]. There are only limited data on the pharmacokinetics of articaine and no report is available relating to IVRA. The aim of this investigation was to study the pharmacokinetics of articaine and its metabolite, articainic acid, in 10 patients undergoing intravenous regional anaesthesia.

Methods

Protocol

The study was approved by the Ethics Committee of the Medisch Spectrum Twente, and written informed consent was obtained from 10 patients (ASA class 1–2, classification according to the American Society of Anesthesiologists), scheduled for surgery of the hand or forearm. Three men and seven women were included in the study. The mean (± s.d.) body weight was 70.5 ± 8.4 kg, and age 50.2 ± 14.2 years.

Patient preparation

No premedication was given. An 18G cannula was introduced into a suitable vein in the dorsum of the hand of the arm to be treated. A similar cannula was introduced into a vein in the other arm, and the radial artery of that
The arm was cannulated for continuous invasive blood pressure monitoring and intermittent blood sampling. Oxygen saturation via a Datex ‘Satlite’ pulse-oximeter. Blood was collected in tubes containing lithium-heparin (Datex, Division of Instrumentarium, Helsinki, Finland), ECG, pulse rate (3 lead, I, II and III via HP 78353 B, Hewlett-Packard, Andover, USA) and continuous invasive arterial blood pressure were monitored from the time of the first venous cannulation until withdrawal of the final blood sample. A 12-lead electrocardiogram was registered on a Hewlett-Packard Multiscriptor EK 33 (Hellige, Freiburg, Germany) in all patients, before injection of articaine, and 5 and 15 min after definition of the tourniquet.

The arm was exsanguinated by means of an Esmarch bandage, after which a pneumatic tourniquet, placed around the arm above the elbow was inflated to 150 Torr above normal systolic pressure or 300 Torr, whichever was higher. Articaine 0.5% (Ultracaine®) was obtained from Hoechst Pharmaceuticals (Frankfurt am Main, Germany). Forty (40) ml of the articaine 0.5% solution (40 × 5 mg ml⁻¹ = 200 mg=0.704 mmol) were injected over a period of 30 s. Any skin reactions or subjective complaints were noted. The development of sensory blockade over the distributions of the median, radial and ulnar nerves was assessed by pinprick. Onset of the surgical analgesia was defined as the period from the end of the injection of the local anaesthetic to the loss of pinprick sensation in the distribution of all three nerves.

In total fifteen arterial blood samples were taken; one before injection and then at 10 min intervals, starting 10 min after completion of injection, until the tourniquet was released; thereafter blood samples were drawn at intervals of 1, 5, 10, 15, 20, 25, 30, 45, 60, 75 and 90 min. The tourniquet was released 30 min after completing the injection. Blood was collected in tubes containing lithium-heparin and 1 mg edrophitobate to inhibit plasma esterase. The samples were centrifuged at 3,000 g and the plasma separated and stored until analysis.

**Drug analysis**

The plasma concentrations of (±)-articaine (CAS number 23964–58–1; MW 284; C₁₃H₂₀N₂O₃S; HCl salt CAS number 23964–57–0, MW 320.8) and metabolite (±)-articainic acid (C₁₂H₁₈N₂O₃S, MW 270) were determined by h.p.l.c. as described earlier. Briefly, the method is as follows: Column: Spherisorb 5 ODS, 250 mm x 4.6 mm. u.v. detection was achieved at 275 nm. Mobile phase: (4 g H₃PO₄, 0.6 g TMACl in 1 l water) and acetonitrile (40 56, v/v) at 1.5 ml min⁻¹ flow rate. Plasma (0.3 ml) was deproteinized with acetonitrile (0.3 ml), vortexed and centrifuged at 3,000 g. 50 µl was injected onto the column.

The recovery of articaine added to human plasma in the concentration range 0.04–8.0 mg ml⁻¹ was 64.5 ± 2.8% (mean ± s.d., n=8). The recovery for the metabolite was 82.9 ± 3.7% in the concentration range 0.1–20.0 mg ml⁻¹. The inter- and intra-day coefficients of variance for articaine (0.040 mg ml⁻¹–8.0 mg ml⁻¹) and articainic acid (0.1–20.0 mg ml⁻¹) were less than 5%.

The lowest limit of quantitation for both compounds in serum was 0.04 µg ml⁻¹ at a signal-to-noise ratio 3:1.

**Figure 1** Mean plasma concentration-time curves of articaine and its metabolite articainic acid after a regional i.v. dose of 200 mg articaine. During tourniquet application there were no measurable plasma concentrations of parent drug and metabolite. After tourniquet release, the plasma concentrations of the metabolite articainic acid were higher than that of the parent drug, indicating regional metabolism. Also the constructed plasma concentration-time curve of articainic acid formed after tourniquet release is shown. The difference between the AUC of total articainic acid and the AUC of plasma formed articainic acid represents the AUC of the metabolite formed during regional analgesia in the well exsanguinated arm.

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Regional metabolism of articaine

Pharmacokinetics

Pharmacokinetic parameters were calculated from the fitted plasma concentration-time curve ($R^2 > 0.98$) according to a two-compartment model using the MW/Pharm computer package (Medware® Groningen, The Netherlands) [20].

The elimination half-life ($t_{1/2,z}$) values were calculated from $\ln 2/\lambda_z$, where $\lambda_z$ is calculated by log-linear regression analysis of the terminal log-linear phase.

$AUC(0,t)$ was the area under the plasma concentration-time curve and was calculated using the linear trapezoidal rule to $t = 90$ min.

Total body clearance (CL) is described as $CL = \frac{Dose}{AUC(0, t)}$. The volume of distribution in the central compartment $V_d = \frac{Dose}{C_0}$. $V_z$ = the volume of distribution during elimination $= \frac{CL}{\lambda_z}$. $V_{ss}$, the volume of distribution at steady-state $= \frac{Dose . AUMC(0, t)}{AUC(0, t)^2}$.

Mean residence time (MRT) $= \frac{AUMC(0, t)}{AUC(0, t)}$, where $AUMC(0, t)$ is the area under the moment curve from zero to $t = 90$ min.

$C_{max}$ = maximum plasma concentration, $t_{max}$ = time at which $C_{max}$ occurs, $t_{lag}$ = lag time, $t_{1/2,abs}$ = half-life of absorption, $t_{1/2,a}$ = half-life of distribution phase, $t_{1/2,z}$ = half-life of elimination phase.

Results

Clinical response

The onset time of the local anaesthetic action of articaine was $2.5 \pm 1.1$ min.

In all patients satisfactory surgical conditions, evidenced by good sensory blockade, were reached within 10 min, and no additional analgesics were required. There was no trend towards a fixed sequence, radial-median-ulnar in the development of sensory blockade. None of the patients exhibited objective symptoms of toxicity, either local or systemic, during injection of articaine, nor were there any subjective complaints. No changes in blood pressure, heart rate or oxygen saturation were observed at any time during the procedure, nor after deflation of the tourniquet. Toxic symptoms and subjective complaints were absent following tourniquet release, nor were any changes recorded on the ECG when analyzed from the 12-lead registration.

Pharmacokinetics

Figure 1 shows the mean plasma concentration-time curves of articaine and its metabolite articainic acid in 10 patients after releasing the tourniquet. Plasma concentrations of both compounds were zero before releasing the tourniquet.

The plasma concentration-time curve of the metabolite articainic acid showed, during the first 100 min after tourniquet release, a plateau value with a mean concentration of $3 \pm \text{mg} \text{l}^{-1}$.

Table 1 shows the individual and mean values of the pharmacokinetic parameters of articaine. Articaine is eliminated biexponentially with a $t_{1/2,a}$ of $4.6 \pm 2.5$ min and a $t_{1/2,z}$ of $58.8 \pm 38.7$ min (mean ± s.d.). Table 2 shows the individual and mean values of the pharmacokinetic parameters of the metabolite articainic acid. The difference

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Constant</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Mean ± s.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0,90min) (mg l$^{-1}$ min)</td>
<td>40.6 ± 10.6</td>
<td>18.0</td>
<td>17.8</td>
<td>12.7</td>
<td>33.2</td>
<td>21.0</td>
<td>29.1</td>
<td>23.2</td>
<td>44.8</td>
<td>19.7</td>
<td>26.0 ± 10.6</td>
</tr>
<tr>
<td>Percentage of total AUC</td>
<td>14.8 ± 7.1</td>
<td>4.76</td>
<td>7.39</td>
<td>4.05</td>
<td>9.36</td>
<td>6.43</td>
<td>7.89</td>
<td>9.39</td>
<td>12.16</td>
<td>5.84</td>
<td>7.91 ± 3.36</td>
</tr>
<tr>
<td>CL (l min$^{-1}$)</td>
<td>4.92 ± 3.46</td>
<td>11.1</td>
<td>11.2</td>
<td>15.8</td>
<td>6.02</td>
<td>9.52</td>
<td>8.63</td>
<td>6.88</td>
<td>4.47</td>
<td>10.17</td>
<td>8.87 ± 3.46</td>
</tr>
<tr>
<td>V_d (l)</td>
<td>130 ± 71.6</td>
<td>202</td>
<td>325</td>
<td>171</td>
<td>106</td>
<td>238</td>
<td>111</td>
<td>106</td>
<td>116</td>
<td>186</td>
<td>169.0 ± 71.6</td>
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<tr>
<td>V_{ss} (l)</td>
<td>733 ± 360</td>
<td>544</td>
<td>550</td>
<td>618</td>
<td>418</td>
<td>1449</td>
<td>216</td>
<td>325</td>
<td>257</td>
<td>316</td>
<td>543.0 ± 360</td>
</tr>
<tr>
<td>V_{z} (l)</td>
<td>1042 ± 380</td>
<td>671</td>
<td>619</td>
<td>823</td>
<td>478</td>
<td>1449</td>
<td>338</td>
<td>450</td>
<td>449</td>
<td>348</td>
<td>564.0 ± 380</td>
</tr>
<tr>
<td>t_{1/2,a} (min)</td>
<td>6.2 ± 2.5</td>
<td>3.4</td>
<td>4.8</td>
<td>2.4</td>
<td>5.6</td>
<td>4.8</td>
<td>7.89</td>
<td>5.6</td>
<td>21.2</td>
<td>4.6</td>
<td>4.6 ± 2.5</td>
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<tr>
<td>t_{1/2,z} (min)</td>
<td>146 ± 38.7</td>
<td>35.0</td>
<td>28.4</td>
<td>30.1</td>
<td>49.0</td>
<td>105</td>
<td>31.2</td>
<td>31.1</td>
<td>31.2</td>
<td>31.2</td>
<td>31.2 ± 12.2</td>
</tr>
</tbody>
</table>

Table 1: Pharmacokinetic parameters of articaine after i.v. administration of 40 ml 0.5% = 200 mg of articaine. The removal model, intravenous administration Total AUC = AUC articaine + AUC articainic acid.
Table 2  Pharmacokinetic parameters of articaine acid after iv. administration of 40 ml 0.5% = 200 mg = 0.704 mmol of articaine.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>1</th>
<th>2</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Mean ± s.d.</th>
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<tbody>
<tr>
<td>$t_{lag}$ (min)</td>
<td>9.06</td>
<td>9.83</td>
<td>9.78</td>
<td>8.74</td>
<td>8.91</td>
<td>8.71</td>
<td>8.99</td>
<td>9.12</td>
<td>9.53</td>
<td>6.09</td>
<td>8.78 ± 1.04</td>
</tr>
<tr>
<td>$t_{max}$ (min)</td>
<td>99.4</td>
<td>99.5</td>
<td>99.5</td>
<td>99.5</td>
<td>99.5</td>
<td>99.5</td>
<td>99.5</td>
<td>58.8</td>
<td>99.5</td>
<td>61.0</td>
<td>91.5 ± 16.7</td>
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<tr>
<td>$t_{1/2,abs}$ (min)</td>
<td>6.08</td>
<td>153</td>
<td>23.5</td>
<td>24.0</td>
<td>20.7</td>
<td>322</td>
<td>263</td>
<td>2.29</td>
<td>16.1</td>
<td>28.2</td>
<td>20.1 ± 7.2</td>
</tr>
<tr>
<td>$t_{1/2,metabolised}$ (min)</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5</td>
<td>36.5 ± 36.5</td>
</tr>
<tr>
<td>$C_{max}$ (mg l$^{-1}$)</td>
<td>0.98</td>
<td>3.74</td>
<td>1.22</td>
<td>2.61</td>
<td>2.48</td>
<td>2.88</td>
<td>2.34</td>
<td>2.06</td>
<td>2.48</td>
<td>2.44</td>
<td>2.32 ± 0.79</td>
</tr>
<tr>
<td>AUC$\text{total}$* (mg l$^{-1}$ min)</td>
<td>223.0</td>
<td>342.5</td>
<td>212.9</td>
<td>281.9</td>
<td>305.3</td>
<td>290.5</td>
<td>323.2</td>
<td>293.7</td>
<td>307.3</td>
<td>301.3</td>
<td>299.3 ± 123.4</td>
</tr>
<tr>
<td>AUC** (mg l$^{-1}$ min)</td>
<td>223.0</td>
<td>342.5</td>
<td>212.9</td>
<td>281.9</td>
<td>305.3</td>
<td>290.5</td>
<td>323.2</td>
<td>293.7</td>
<td>307.3</td>
<td>301.3</td>
<td>299.3 ± 123.4</td>
</tr>
<tr>
<td>AUC$\text{formed}$ (mg l$^{-1}$ min)</td>
<td>71.38</td>
<td>159.4</td>
<td>71.07</td>
<td>140.1</td>
<td>143.8</td>
<td>147.1</td>
<td>140.8</td>
<td>135.6</td>
<td>150.4</td>
<td>164.8</td>
<td>132.4 ± 33.5</td>
</tr>
<tr>
<td>AUC$\text{IVRA metabolised}$ (mg l$^{-1}$ min)</td>
<td>32.0</td>
<td>46.5</td>
<td>33.4</td>
<td>49.2</td>
<td>46.0</td>
<td>49.5</td>
<td>43.6</td>
<td>48.2</td>
<td>46.9</td>
<td>54.7</td>
<td>44.9 ± 7.1</td>
</tr>
<tr>
<td>AUC$\text{IVRA metabolised}$/AUC$\text{formed}$ (mg l$^{-1}$ mm)</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* calculated from total plasma concentrations = AUC$\text{total}$ = AUC$\text{formed}$ + AUC$\text{IVRA}$. ** calculated from corrected plasma concentrations = AUC$\text{formed}$ after tourniquet release; one compartment model AUC$\text{IVRA metabolised}$ = AUC$\text{IVRA}$ - AUC$\text{formed}$. 1 all values; 2 low values n = 7; 3 high values n = 3; P = 0.0067. Arithmetic mean.
in AUC values between total and plasma formed articaic acid represents the amount and percentage of articaic acid formed in the exsanguinated arm during tourniquet application (55.1 ± 7.1%).

Table 3 summarizes the AUC values of articaic and its metabolite articaic acid, as well as the percentages of articaic acid formed during IVRA (55.1 ± 7.1%) and after tourniquet release (44.9 ± 7.3%).

### Discussion

The absorption of articaic from the exsanguinated forearm after releasing the tourniquet was so fast that the maximum plasma concentration was already achieved at the first sample at 1 min. Thereafter articaic was eliminated according to a biexponential decay after i.v. administration with $t_{1/2,α}$ of 4.6 ± 2.5 min, and a $t_{1/2,β}$ of 58.8 ± 38.7 min. At the first plasma sample at 1 min, the metabolite articaic acid was present at a relatively high concentration of 3.1 ± 0.46 μg ml$^{-1}$, which remained nearly constant during the whole sampling period of 90 min. A similar behaviour of articaic acid has been reported earlier [18, 19], the plasma concentration-time curve of the metabolite showed a broad maximum, which started to decline 2 h after administration of the parent drug. The intrinsic $t_{1/2,α}$ of the metabolite was 60 min [11, 12], when the metabolite was administered as the study compound.

The plasma concentration-time curve of the metabolite shows two processes. First there is the high initial concentration, which starts to decline for 10 min, thereafter the concentration rises again to an apparent ‘plateau’ value. When the intrinsic half-life of 60 min of articaic acid is inserted at the $C_0$ value of 3.08 μg ml$^{-1}$, and the concentrations of this line subtracted from the overall plasma concentration of articaic acid, the plasma concentration-time curve of the metabolite after tourniquet release emerges. When the areas under the ‘corrected’ plasma concentration-time curves are calculated (AUC[0,τ] μmol l$^{-1}$ min) the relative percentages of the different processes can be visualized as demonstrated in Table 2.

Thus when articaic is injected in the well exsanguinated arm, tissue and plasma esterase hydrolyse articaic to articaic acid for 55% of the administered dose. The $t_{1/2}$ of serum esterase hydrolysis of articaic was 1.25 h [19], thus during the 30 min of tourniquet application (≈ 0.40 $t_{1/2}$), approximately 20% is hydrolysed. The remaining 35% therefore must be attributed to tissue esterase activity.

This explains the high initial value of the plasma concentration of the metabolite. After i.v. and epidural administration of articaic, it takes 1 h to reach the $C_{max}$ of the metabolite [18, 19]. The metabolite is rapidly eliminated from the body by renal excretion (80%) and glucuronidation (20%) and shows an intrinsic $t_{1/2,α}$ value of 60 min [11, 12]. After tourniquet release the remaining articaic is further hydrolysed by plasma esterase (45%).

From the plasma concentration-time curve of articaic acid formed after tourniquet release, the calculated $t_{1/2,α}$ showed a large variation (6.08–321.7 min; 132% CV) which was due to three patients (numbers 2, 6, 7) having prolonged absorption times. In these three patients the $t_{1/2,α}$ (246.0 ± 85.6 min; 34.8% CV) was 12 times larger than in the other seven patients (20.21 ± 7.22 min; 35.7% CV; $P = 0.0167$). This difference may reveal a difference in the efficiency of intravenous injection or show substantially different tissue distribution. In the seven patients, the injection is purely intravenous, with relatively little diffusion in the tissues, so that after tourniquet release, the total amount is swept with the incoming blood stream into the general circulation. When in the other three patients the intravenous injection is less perfect (in part intramuscular), the absorption from tissues takes more time.

### Clinical implication

Articaic is a suitable and safe agent for IVRA with rapid onset of good surgical anaesthesia. During tourniquet application and regional analgesia, 55% of the administered dose is already hydrolysed, thus reducing the chance of side effects after tourniquet release. It has to be determined whether the metabolite articaic acid possesses analgesic and local anaesthetic properties, as this compound is present in high concentrations in plasma. After releasing the tourniquet, articaic is rapidly eliminated with a $t_{1/2,α}$ of approximately 60 min.

### References

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Table 3 AUC values (s.d.) of articaic, and its metabolite articaic acid (total and formed) after IVRA administration of 40 ml 0.5% (≈200 mg = 704 μmol).

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC [μmol l$^{-1}$ 90 min]</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articaic</td>
<td>91.5 ± 38</td>
<td>7.9 ± 3.4$^a$</td>
</tr>
<tr>
<td>Articaic acid</td>
<td>1070.0 ± 552</td>
<td>92.0 ± 3.4$^a$</td>
</tr>
<tr>
<td>total formed</td>
<td>1070.0 ± 552</td>
<td>92.0 ± 3.4$^a$</td>
</tr>
<tr>
<td>after tourniquet release</td>
<td>490.0 ± 124</td>
<td>44.9 ± 7.3$^a$</td>
</tr>
<tr>
<td>during tourniquet application</td>
<td>582.0 ± 60</td>
<td>55 ± 7.1$^a$</td>
</tr>
<tr>
<td>total A–Ac</td>
<td>1162.0 ± 552</td>
<td>100</td>
</tr>
</tbody>
</table>

Calculated from individual plasma concentration-time data (n = 10). $^a$of total articaic (A) + articaic acid (Ac). $^b$of total articaic acid.
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(Received 25 June 1996, accepted 3 March 1997)