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# Epidural Metabolism of Articaine to its Metabolite Articaic Acid in Five Patients after Epidural Administration of 600 mg Articaine

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## Abstract

The clinical pharmacokinetics, metabolism and renal excretion of articaine and its metabolite articaic acid have been investigated in man after epidural administration. ( $\pm$ )-Articaine and its metabolite ( $\pm$ )-articaic acid have different pharmacokinetic constants ( $P=0.0079$ ) except for lag-time ( $t_{lag}$ ; 0.06 min), first phase distribution of elimination ( $t_{1/2\alpha}$ ;  $0.49 \pm 0.21$  h), and elimination half life ( $t_{1/2\beta}$ ;  $2.19 \pm 0.98$  h), which are all the same for both compounds. The total body clearance of articaine ( $103 \pm 57$  L h $^{-1}$ ) is 10 times higher than that of the metabolite articaic acid ( $10.7 \pm 1.80$  L h $^{-1}$ ,  $P=0.0079$ ). With similar half-life ( $t_{1/2\beta}$ ) values (2 h), the volumes of distribution ( $V_{\beta}$ ) are 10 times higher for the parent drug than for the metabolite ( $329 \pm 212$  L compared with  $38.4 \pm 7.5$  L, respectively;  $P=0.0079$ ). The difference between the areas under the curves for total plasma articaic acid and that formed in the plasma gives an indication of the percentage metabolism during epidural transfer ( $5.38 \pm 1.51\%$ ). This percentage of metabolism corresponds to a mean epidural transfer time of 5 min. The main compound in the urine is articaic acid ( $64.2 \pm 14.4\%$ ), followed by articaic acid glucuronide ( $13.4 \pm 4.97\%$ ) and the parent drug ( $1.45 \pm 0.77\%$ ). In total,  $79.0 \pm 18.5\%$  of the dose is recovered in the urine. The renal clearance of articaine is  $22.5 \pm 13.9$  mL min $^{-1}$ , whereas that of articaic acid is  $119.6 \pm 30.1$  mL min $^{-1}$  ( $P < 0.0001$ ). The apparent renal clearance of articaic acid glucuronide was  $25.4 \pm 12.0$  mL min $^{-1}$ . This value does not differ from that of the parent drug ( $P > 0.8$ ). Articaic acid glucuronide is not present in plasma, but has an apparent renal clearance of 25 mL min $^{-1}$ .

These results suggest that articaic acid is glucuronidated by the tubular cells and then excreted.

Articaine (( $\pm$ )-3-*n*-propylamino- $\alpha$ -propionylamido-2-carbomethoxy-4-methylthiophen hydrochloride; MW 320.9, pK $_a$  7.8; CAS number 23964-57-0) is a local anaesthetic drug first clinically investigated in 1974 (Muschawek & Rippel 1974; Kirch et al 1983). Only small differences were found when lidocaine 2% or articaine 2%, both with adrenaline 1:200 000, were used for epidural anaesthesia. The articaine had a slightly faster onset of action and probably less toxicity, especially to the heart and brain (Hendolin & Mattila 1974; Brinklov 1977; Moller & Covino 1993; Simon et al 1996).

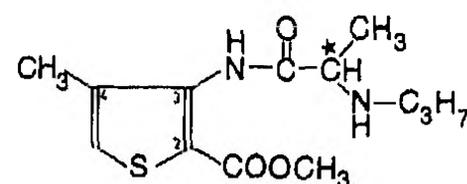
Articaine 4% with adrenaline 1:200 000 is widely used in dentistry for infiltration and conduction anaesthesia. The very fast onset of the block, the excellent quality of the anaesthesia, the reduced toxicity and the shorter duration of action, owing to hydrolysis of the parent drug, are responsible for its wide utilization (Ferber & Marxkors 1973; van Oss et al 1989).

Epidural anaesthesia with 4% articaine with adrenaline 1:200 000 has several advantages over commonly used local anaesthetics such as ( $\pm$ )-mepivacaine, lidocaine, ( $\pm$ )-prilocaine and ( $\pm$ )-bupivacaine: shorter time to onset (7 min); shorter sensory block (105 min) and motor block (65 min); more intense motor block (66% of patients completely paralysed); lower failure rate; no allergic reactions; lower toxicity; fewer post-operative complications (van Oss, personal observations).

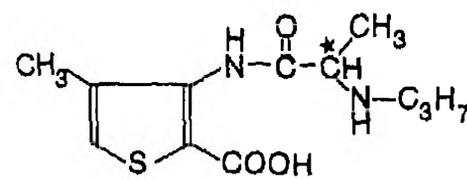
( $\pm$ )-Articaine is metabolized to ( $\pm$ )-articaic acid (Fig.

1). It was noted in a group of 18 patients receiving 600 mg epidurally that the yield of articaine hydrolysis showed a bimodal character (van Oss, unpublished results); although the time-course of the experiment (3 h) was sufficient to follow the kinetics of the parent drug, it was too short to study the metabolite which requires a study over 30 h.

van Oss et al (1989) investigated the pharmacokinetics of ( $\pm$ )-articaine in five patients undergoing epidural local anaesthesia. Their main kinetic parameters were half-life,  $t_{1/2}$ , percentage of the dose excreted, protein binding and renal clearance (van Oss et al 1989). Ongoing research on articaine by Simon et al (1996) showing regional metabolism of the drug suggested a more detailed re-investigation of the clinical pharmacokinetics of articaine after epidural administration.



Articaine



Articaic acid

The aim of this study was to re-investigate the clinical pharmacokinetics, metabolism and renal excretion of articaine and its metabolite articanic acid in man after epidural administration.

## Materials and Methods

### Drugs

Articaine and articanic acid were a gift of Hoechst Pharma (Amsterdam, The Netherlands).

### Patients

Five patients (ASA I-II, classification according to the American Society of Anesthesiologists) undergoing elective surgery gave their informed consent to participate in this study, which was approved by the hospital Ethics Committee. The demographic data of the patients are summarized in Table 1. Pre-medication was with lorazepam, 2.5 mg, given orally the evening before surgery and repeated 2 h before surgery. An epidural needle was placed at the site through which a catheter was inserted and passed 4 cm cranially. For this procedure 1.8 mL articaine 4% with adrenaline 1:200 000 was administered subcutaneously before the puncture.

Induction of anaesthesia consisted of atropine 3.5 mg kg<sup>-1</sup>, fentanyl 1.5 mg kg<sup>-1</sup>, thiopental 0.10 mg kg<sup>-1</sup>, etomidate 0.2 mg kg<sup>-1</sup>, and vecuronium 0.1 mg kg<sup>-1</sup>. All patients were endotracheally intubated and artificially ventilated to an end-tidal CO<sub>2</sub> concentration of 4.5–5%. A central venous catheter was placed in the right internal jugular vein and an arterial catheter in a radial artery. A urinary catheter was inserted. Anaesthesia was maintained with a mixture of 60% nitrous oxide in oxygen and additional doses of fentanyl and vecuronium were administered as needed. Occasionally, dehydrobenzperidol, midazolam, flucloxacillin, furosemide or heparin was administered as needed.

Articaine (Ultracain, Hoechst; 4% solution, 15 mL = 600 mg (2.112 mM)) with adrenaline 1:200 000 was administered during the operation via the epidural catheter.

### Sampling

Blood samples were taken just before administration, at the end of administration (0), and 1, 2.5, 5, 10, 15, 20, 30, 40 and 50 min and 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 12 h thereafter in glass tubes containing 1 mg ecothiopate to prevent esterase hydrolysis. Urine samples were collected at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32 and 36 h, after administration. The samples were kept at 4°C during surgery and centrifuged immediately

thereafter. Plasma and urine samples were kept at –20°C until analysis.

### Drug analysis

(±)-Articaine and its (±) metabolite were determined by high-performance liquid chromatography as described elsewhere (Vree et al 1988). In short, the separation was performed on a 250 × 4.6 mm Spherisorb 5 ODS column; the mobile phase was a 4:6 (v/v) mixture of (4 g H<sub>3</sub>PO<sub>4</sub>, 0.6 g TMACl in 1 L water) and acetonitrile at a flow rate of 1.5 mL min<sup>-1</sup>. UV detection was achieved at 275 nm. Plasma (0.3 mL) was deproteinized with acetonitrile (0.3 mL), vortex mixed and centrifuged at 3000 g; 50 µL was injected on to the column.

The inter- and intra-day coefficients of variance for articaine and articanic acid were less than 5%.

**Deglucuronidation.** Urine (10 µL) was incubated with β-glucuronidase (10 µL; 10 000 units mL<sup>-1</sup>; from *Escherichia coli* Type VII (Sigma, St Louis, USA) and phosphate buffer (pH 6.8; 100 µL). Reaction time was 16 h at 37°C.

Plasma (100 µL) was incubated with β-glucuronidase (100 µL; 10 000 units mL<sup>-1</sup>; from *Escherichia coli* Type VII (Sigma, St Louis, USA) and phosphate buffer (pH 6.8; 100 µL). Reaction time was 16 h at 37°C.

### Data analysis

Pharmacokinetic parameters were calculated from the fitted plasma concentration–time curve ( $r^2 > 0.98$ ) according to a 2-compartment model using the MW/Pharm computer package (Mediware, Groningen, The Netherlands; Proost & Meyer 1992). The elimination half-life ( $t_{1/2\beta}$ ) values were calculated from  $\ln 2/\beta$ , where  $\beta$  is calculated by log-linear regression analysis of the terminal log-linear phase. The area under the plasma concentration–time curve,  $AUC_{0-\infty}$ , was calculated using the linear trapezoidal rule with extrapolation of  $t$  to  $\infty$  using  $Ct/\beta$ , with  $Ct$  being the last measured concentration.

Total body clearance (CL) was calculated from  $CL = \text{dose}/AUC_{0-\infty}$ .  $V_d$ , the volume of distribution in the central compartment, was calculated from  $V_d = \text{dose}/C_0$ .  $V_{ss}$ , the volume of distribution at steady-state, was calculated from  $V_{ss} = \text{dose} \times AUMC_{0-\infty}/AUC_{0-\infty}^2$ , where  $AUMC_{0-\infty}$  is the area under the moment curve from zero to  $t = \infty$ . The volumes of distribution,  $V_\beta$ , were calculated from  $V_\beta = CL/C\beta$ . The mean residence time (MRT) after extravascular administration was calculated from  $MRT = AUMC_{0-\infty}/AUC_{0-\infty} + 1/k_a + t_0$ . The mean epidural transfer time (METT) was calculated from  $METT = AUC_t = AUC_0 e^{-kt}$ , where  $AUC_t$  is the AUC for plasma-formed articanic acid and  $AUC_0$  is the AUC for total

Table 1. Demographic data of the patients.

	Gender	Age (years)	Height (cm)	Body weight (kg)	Surgery
1	F	49	165	65	Kidney artery stenosis
2	F	42	157	62	Thorax reconstruction
3	M	66	175	67	Femoro-popliteal bypass
4	M	76	177	80	Amputation of rectum
5	F	71	166	82	Diaphragmatic hernia repair
Mean (± s.d.)		60.8 ± 14.6	168.0 ± 8.1	71.2 ± 9.1	

articainic acid. The renal clearance of articaine and articainic acid were calculated from  $\text{mg excreted}/\text{AUC}$  ( $\text{mg L}^{-1} \text{h}$ ). The renal clearance of articainic acid glucuronide was calculated from  $[\text{mg excreted acid} + \text{gluc}/\text{AUC}_{\text{acid}}] - \text{Cl}_{\text{R,acid}}$ . The percentage excreted was calculated from  $\text{mmol}_{\text{urine}}/\text{mmol}_{\text{dose}} \times 100\%$ .

Analysis of variance was performed according to standard procedures. The level of significance was set at  $P = 0.05$ .

## Results

Fig. 2 shows the plasma concentration-time curves and renal excretion rate-time profiles of articaine and its metabolite articainic acid in one patient after epidural administration of articaine (600 mg).

Fig. 3 shows the mean plasma concentration-time curves of articaine and its metabolite articainic acid in the five patients. In the first blood sample ( $t = 0$ ), the plasma concentration of the metabolite articainic acid ( $2.06 \pm 0.54 \text{ mg mL}^{-1}$ ) is already higher than that of the parent drug ( $0.60 \pm 0.27 \text{ mL}^{-1}$ ,

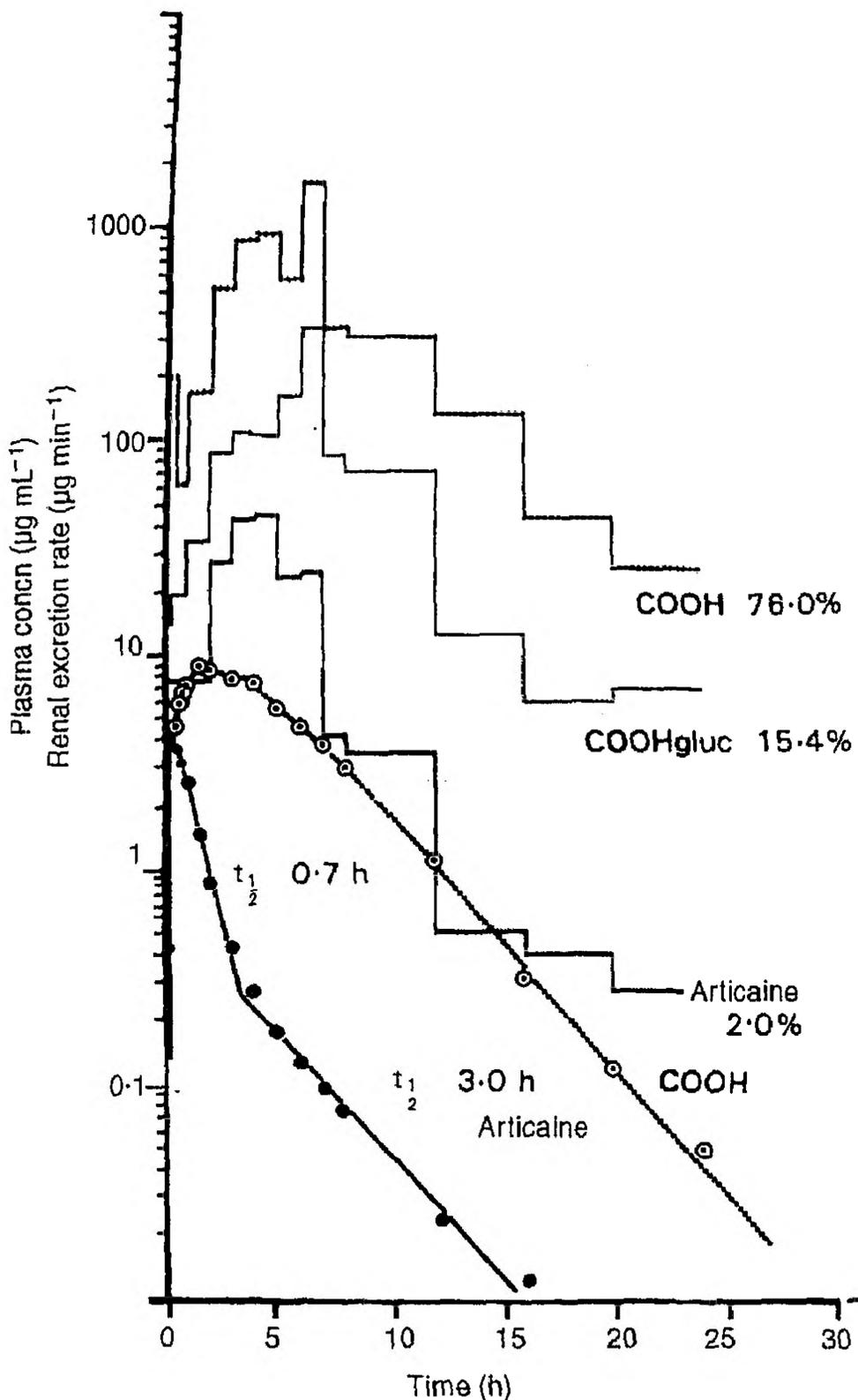


FIG. 2. Plasma concentration-time curves and renal excretion rate-time profiles of articaine, its metabolite articainic acid (COOH) and the corresponding glucuronide conjugate (COOHgluc) in one patient after epidural administration of 600 mg articaine.

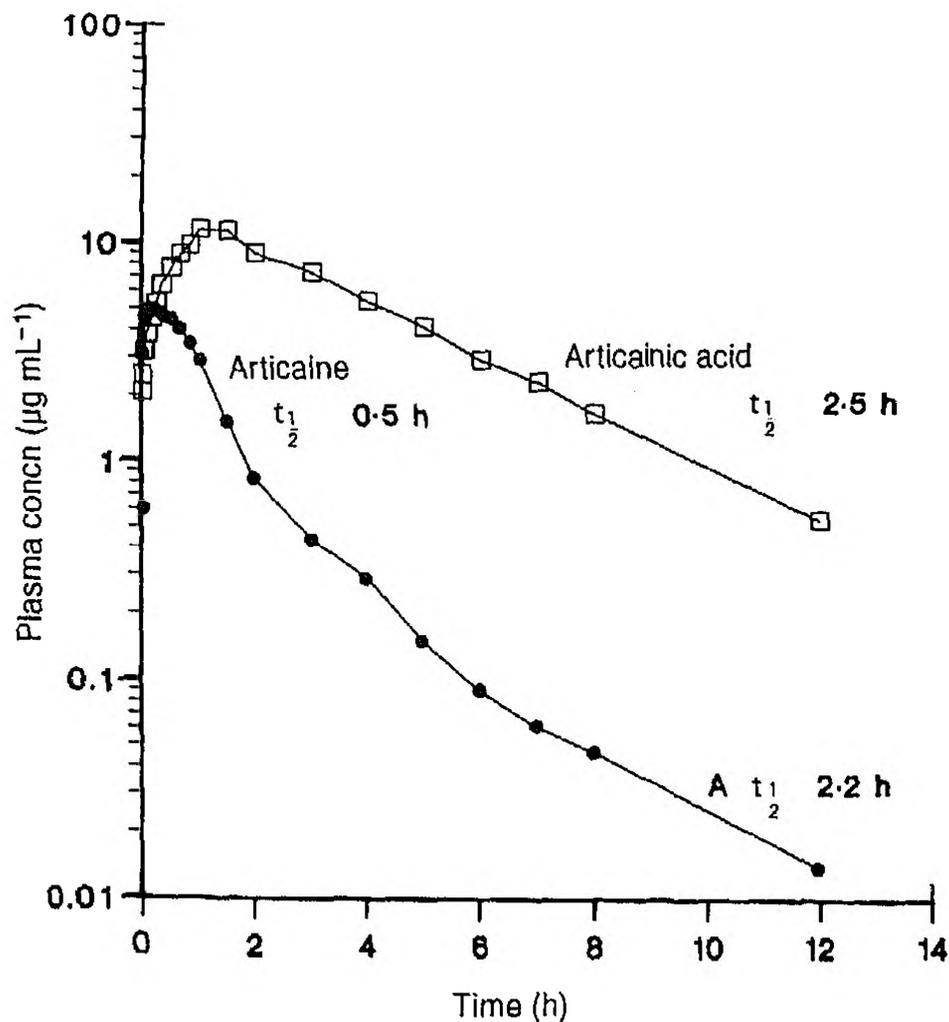


FIG. 3. Mean plasma concentration-time curves of articaine and its metabolite articainic acid in the five patients. The terminal half-lives of elimination run parallel.

Table 2. Mean plasma concentrations of articaine and articainic acid ( $\text{mg L}^{-1}$ ; mean  $\pm$  s.d.) after epidural administration of 600 mg ( $2.112 \text{ mM}$ ) articaine.

Time min	h	Articaine	Articainic acid	
			Total	Plasma-formed
0	0	$0.60 \pm 0.27$	$2.06 \pm 0.54$	$0.00 \pm 0.00$
1	0.017	$3.08 \pm 2.45$	$2.46 \pm 1.03$	$0.46 \pm 0.58$
2.5	0.042	$4.54 \pm 2.37$	$3.18 \pm 2.03$	$1.20 \pm 1.57$
5	0.083	$4.79 \pm 2.31$	$3.78 \pm 3.12$	$1.86 \pm 2.71$
10	0.166	$5.14 \pm 2.35$	$4.50 \pm 3.43$	$2.68 \pm 3.00$
15	0.25	$5.04 \pm 2.37$	$5.26 \pm 3.52$	$3.55 \pm 3.11$
20	0.33	$4.48 \pm 1.54$	$6.36 \pm 4.44$	$4.77 \pm 4.04$
30	0.50	$4.37 \pm 2.49$	$7.62 \pm 4.96$	$6.19 \pm 4.63$
40	0.66	$3.96 \pm 2.27$	$8.74 \pm 3.37$	$7.46 \pm 3.08$
50	0.83	$3.39 \pm 2.12$	$9.66 \pm 3.50$	$8.64 \pm 3.53$
60	1.0	$2.88 \pm 1.86$	$11.4 \pm 3.77$	$10.4 \pm 3.57$
90	1.5	$1.52 \pm 0.83$	$11.2 \pm 2.50$	$10.5 \pm 2.38$
120	2.0	$0.83 \pm 0.44$	$8.90 \pm 0.75$	$8.40 \pm 0.82$
180	3.0	$0.44 \pm 0.25$	$7.32 \pm 1.45$	$7.14 \pm 1.53$
240	4.0	$0.29 \pm 0.18$	$5.40 \pm 1.94$	$5.37 \pm 1.93$
300	5.0	$0.15 \pm 0.07$	$4.12 \pm 1.66$	$4.12 \pm 1.66$
360	6.0	$0.089 \pm 0.051$	$2.92 \pm 1.48$	$2.92 \pm 1.48$
420	7.0	$0.061 \pm 0.041$	$2.31 \pm 1.34$	$2.31 \pm 1.34$
480	8.0	$0.047 \pm 0.018$	$1.66 \pm 1.02$	$1.66 \pm 1.02$
720	12.0	$0.014 \pm 0.013$	$0.54 \pm 0.38$	$0.54 \pm 0.38$

$P = 0.0079$ ; Table 2). The terminal half-lives of elimination run parallel.

Fig. 4 shows the mean plasma concentration-time curves of articaine and its metabolite during the first hour after epidural administration. In the first plasma sample, the concentration of the metabolite is higher than that of the parent drug.

Table 3 summarizes the mean ( $\pm$  s.d.) pharmacokinetic constants derived from the plasma concentration-time curves in each volunteer. Articaine and articainic acid have different

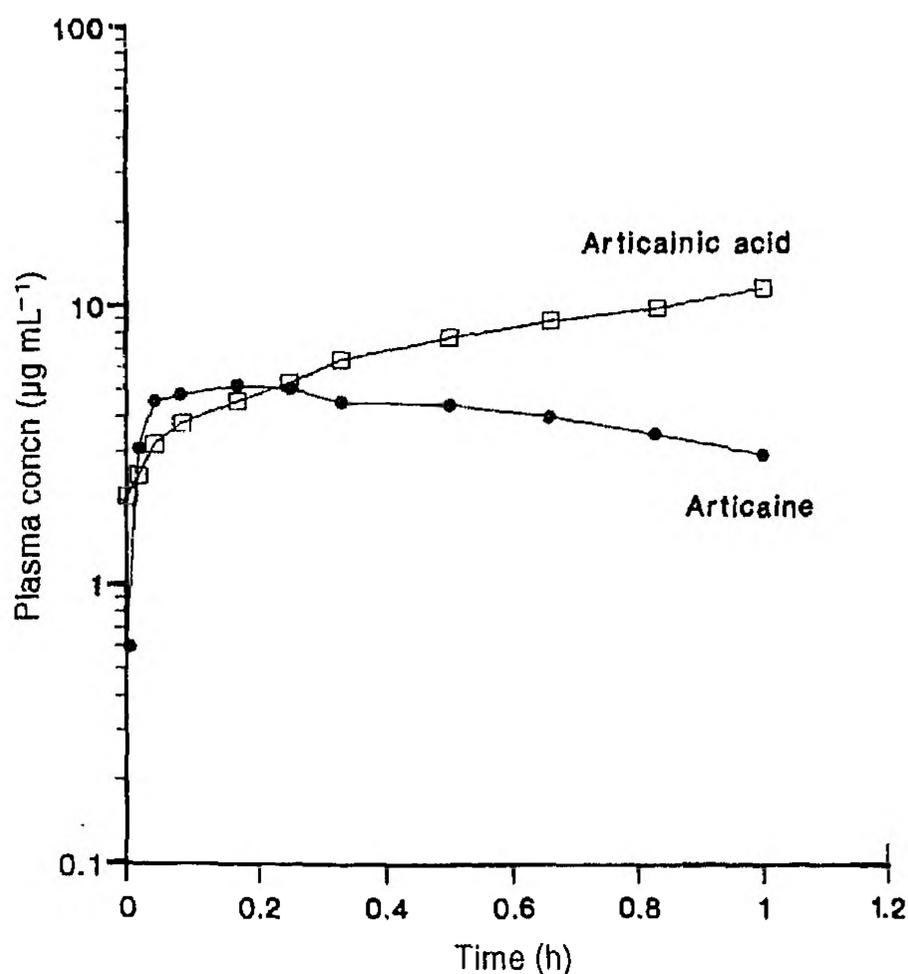


FIG. 4. Mean plasma concentration-time curves of articaïne and its metabolite articaïnïc acid during the first hour after epidural administration. In the first plasma sample the concentration of the metabolite is higher than that of the parent drug.

pharmacokinetic constants ( $P=0.0079$ ) except for  $t_{lag}$ ,  $t_{2\alpha}^1$  and  $t_{2\beta}^1$ .

Differences in the kinetics of the parent drug can be explained by differences in the rate of release from the epidural space, as reflected by the absorption half life ( $t_{2abs}^1$ ), which varies 10-fold from 54 s (0.015 h) to 9 min (0.152 h; mean  $0.063 \pm 0.052$  h = 3.8 min) (Table 3).

The rapid absorption showed short times for maximum plasma concentration ( $t_{max}$ ) of 12 min ( $0.203 \pm 0.101$  h) and relatively high maximum plasma concentration ( $C_{max}$ ) of  $5.30 \pm 2.02$  mg mL<sup>-1</sup>. Thereafter, the elimination of articaïne can be described by a two-compartment model with a  $t_{2\alpha}^1$  of 30 min ( $0.49 \pm 0.21$  h) and a  $V_d$  of  $99.0 \pm 41.7$  L followed by a  $t_{2\beta}^1$  of  $2.19 \pm 0.98$  h and a  $V_\beta$  of  $329 \pm 212$  L. The overall MRT is  $1.64 \pm 0.49$  h and the  $V_{ss}$  is  $154 \pm 72.6$  L.

The total body clearance of articaïne ( $103 \pm 57$  L h<sup>-1</sup>) is 10 times greater than that of articaïnïc acid ( $10.7 \pm 1.80$  L h<sup>-1</sup>;  $P=0.0079$ ). With identical  $t_{2}^1$  values, the volumes of distribution are also 10 times higher for the parent drug than for the metabolite ( $P=0.0079$ ).

Fig. 5 shows the mean plasma concentration-time curves of total articaïnïc acid and articaïnïc acid formed in plasma. The difference between the plasma AUC of total articaïnïc acid and that formed in plasma gives an indication of the percentage metabolism during epidural transfer ( $5.38 \pm 1.51\%$ ). This percentage metabolism corresponds with a mean epidural transfer time of 5 min.

Table 3. Pharmacokinetic parameters of articaïne and articaïnïc acid (mean  $\pm$  s.d.) after epidural administration of 600 mg (2.112 mM) articaïne.

Parameter	Articaïne	Articaïnïc acid	$P^*$	Articaïnïc acid glucuronide
Maximum plasma concentration (mg mL <sup>-1</sup> )	$5.30 \pm 2.02$	$13.81 \pm 3.23$	0.0079	
Time for maximum plasma concentration (h)	$0.203 \pm 0.101$	$1.31 \pm 0.62$	0.0079	
Lag-time (h)	$0.001 \pm 0.0$	$0.001 \pm 0.0$	1.0000	
Absorption half-life (h)	$0.063 \pm 0.052$	$0.65 \pm 0.35$	0.0079	
$t_{2\alpha}^1$ (h)	$0.49 \pm 0.21$	$0.90 \pm 0.61$	0.1508	
Elimination half-life (h)	$2.19 \pm 0.98$	$2.54 \pm 0.64$	0.8413	
Mean residence time (h)	$1.64 \pm 0.49$	$3.62 \pm 1.06$	0.0079	
Area under the plasma concentration time curve (mg L <sup>-1</sup> h)	$7.42 \pm 3.32$	$51.74 \pm 8.99$	0.0079	
( $\mu$ mol L <sup>-1</sup> h)	$26.14 \pm 11.71$	$191 \pm 33.4$	0.0079	
Total body clearance (L h <sup>-1</sup> )	$103 \pm 57.0$	$10.70 \pm 1.80$	0.0079	
Volume of distribution in the central compartment (L)	$99.0 \pm 41.7$	$19.35 \pm 9.89$	0.0079	
Volume of distribution at steady-state (L)	$154 \pm 72.6$	$28.24 \pm 5.96$	0.0079	
Volume of distribution (L)	$329 \pm 212$	$38.36 \pm 7.46$	0.0079	
Renal excretion				
% Dose excreted	$1.45 \pm 0.77$	$64.2 \pm 14.4$	< 0.0001	$13.4 \pm 4.97$
Total % excreted				$79.0 \pm 18.5$
Renal clearance				
mL min <sup>-1</sup>	$22.5 \pm 13.9$	$119.6 \pm 30.1$	< 0.0001	$25.4 \pm 12.0$
L h <sup>-1</sup>	$1.36 \pm 0.84$	$7.20 \pm 1.82$	< 0.0001	$1.52 \pm 0.71$ $P > 0.8$ with parent
Epidural metabolism				
% dose	$5.38 \pm 1.51$			

\*Unpaired non-parametric test, Mann-Whitney two-sample test.

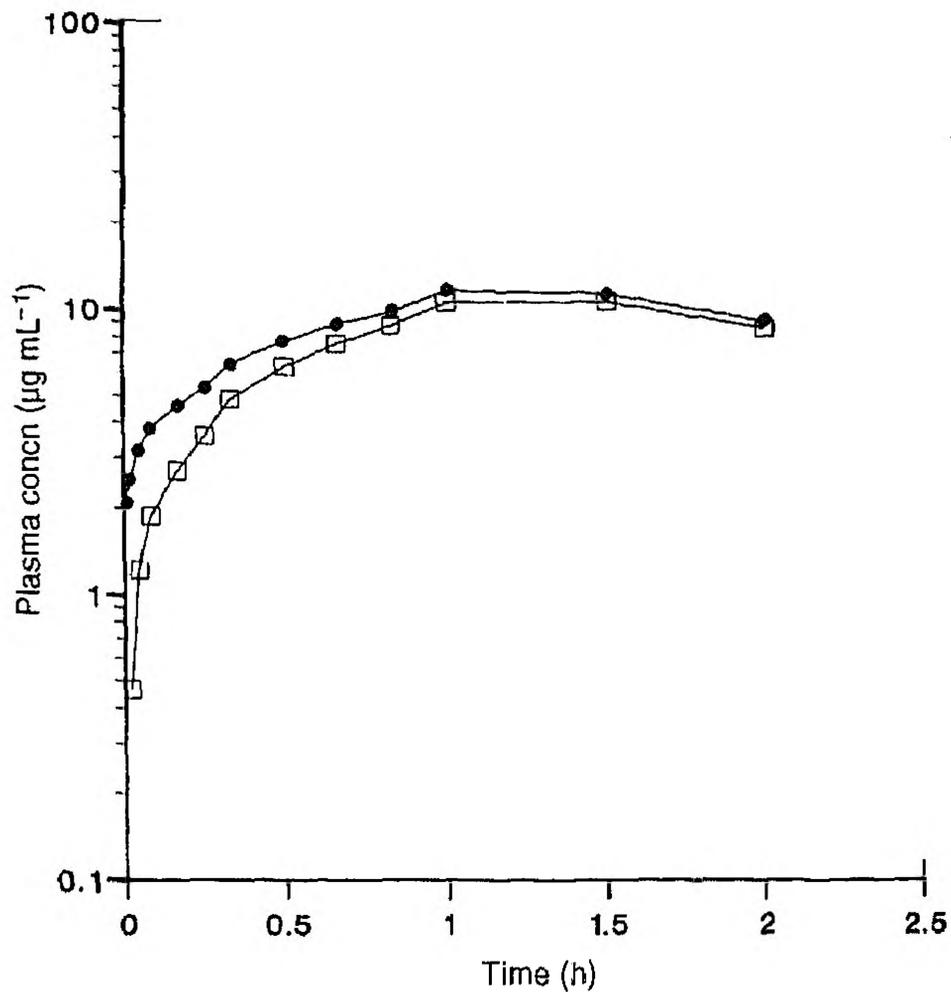


FIG. 5. Mean plasma concentration-time curves of total artocainic acid (●) and that formed in plasma (□). The difference in AUC reflects metabolism during epidural transfer of the parent drug.

The main compound in the urine is artocainic acid ( $64.2 \pm 14.4\%$ ), followed by artocainic acid glucuronide ( $13.4 \pm 4.97\%$ ) and the parent drug ( $1.45 \pm 0.77\%$ ). In total  $79.0 \pm 18.5\%$  of the dose is recovered from the urine. The renal clearance of artocaine is  $22.5 \pm 13.9 \text{ mL min}^{-1}$ , whereas that of its metabolite artocainic acid is  $119.6 \pm 30.14 \text{ mL min}^{-1}$  ( $P < 0.0001$ ). The apparent renal clearance of artocainic acid glucuronide was  $25.44 \pm 11.97 \text{ mL min}^{-1}$ . This value is not different from that of the parent drug ( $P > 0.8$ ).

### Discussion

The metabolic fate of artocaine and its nearest structural analogue, prilocaine, are different. Prilocaine is mainly hydrolysed to *o*-toluidine and *N*-propylalanine (Akerman et al 1966). The 2-carbomethoxy group in artocaine prevents this hydrolysis; instead, this group is hydrolysed by esterase activity to the 2-carboxy group and the drug is largely (40–80%) excreted in the urine as the metabolite artocainic acid. Only a small percentage (5–17%) is excreted as the glucuronide of artocainic acid. This ester-type glucuronide is stable in urine between pH 5 and pH 7 (van Oss et al 1989, 1988a, b).

When artocainic acid was administered as the study compound, 78% was excreted unchanged and 22% as glucuronide. In these circumstances, artocainic acid showed an intrinsic  $t_{1/2}$  of elimination of 1 h (van Oss et al 1988a, b). This implies that all artocainic acid formed after epidural absorption and hydrolysis is excreted immediately and that variations in the recovery of the artocainic acid metabolite must therefore reflect patient-dependent variation in the release of artocaine from the epidural space. The pharmacokinetics of drugs after epidural

administration are highly patient dependent (Koopman-Kimenai et al 1991, 1995; van Oss et al 1989).

### Epidural metabolism

In the first blood sample ( $t=0$ ), the plasma concentration of the metabolite is already higher than that of the parent drug (Table 2). This means that hydrolysis must have taken place during the epidural transfer. When the  $C_0$  of artocainic acid is considered as a fixed amount of drug entering the general circulation, this amount is eliminated with the intrinsic half-life of 1 h, as if the compound was administered intravenously (van Oss et al 1988a, b). When these extrapolated plasma concentrations were subtracted from the total plasma concentrations of artocainic acid, the plasma concentration-time curve of artocainic acid formed from hydrolysis by plasma esterase activity remains (Fig. 5). A similar observation was made with artocaine after a 30-min disposition time in an exsanguinated arm during intravenous regional anaesthesia (Simon et al 1996).

The difference between the 'total and corrected' plasma AUCs of artocainic acid gives an indication of the percentage metabolism during the epidural transfer (5%). This percentage metabolism corresponds to a mean epidural transfer time of 5 min.

The main compound excreted in the urine is the metabolite, which is also partly glucuronidated. Only 1.5% of artocaine is excreted unchanged.

### Renal clearance and glucuronidation

The apparent renal clearance of artocainic acid equals that of creatinine. When this renal clearance is corrected for protein binding of 77% (van Oss et al 1989), the metabolite is excreted by glomerular filtration and active tubular secretion (van Oss et al 1989, 1988a, b).

The apparent renal clearance values of artocainic acid glucuronide and of artocaine are similar. Both clearances differ significantly from that of artocainic acid ( $P < 0.0001$ ). Artocaine, as a basic compound, is subject to passive tubular reabsorption, and renal clearance will be dependent on urine pH and flow.

Artocainic acid glucuronide is not present in plasma, but has an apparent renal clearance of  $25 \text{ mL min}^{-1}$ . There are two possible explanations for this: either artocainic acid enters the renal tubule where it is partly glucuronidated and thereafter excreted, or artocaine is strongly reabsorbed by the kidney tubule, is hydrolysed in the tubule cell, then glucuronidated, and thereafter excreted. The first possibility seems less likely, because a compound that is actively excreted is unlikely to be conjugated at the same time. The second possibility seems more likely. After tubular reabsorption, the compound is hydrolysed by tissue esterases, glucuronidated and thereafter excreted. A similar renal conjugation process has been described for probenecid (Vree et al 1992), indomethacin (Vree et al 1994) and for the *N*-glucuronidation of sulphadimethoxine (Vree et al 1990a), sulphaphenazole (Vree et al 1990b) and furosemide (Vree et al 1995a, b). When artocainic acid was administered intravenously to a human subject, however (van Oss et al 1988a, b), artocainic acid glucuronide was present in the urine (22% dose). Thus the first possibility must, against all the odds, describe the actual situation.

*Clinical implications*

During epidural disposition, approximately 5% of the dose is lost owing to hydrolysis. This small and inevitable loss has no clinical implications. Measuring parent drug and metabolite always generates the question about whether the metabolite contributes to the overall local anaesthetic effect, especially when the metabolite concentrations are higher than those of the parent drug.

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