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Intravenous Regional Anesthesia With 0.5% Articaine, 0.5% Lidocaine, or 0.5% Prilocaine

A Double-blind Randomized Clinical Study

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Background and Objectives. The purpose of this study was to compare the effectiveness of three local anesthetic agents for intravenous regional anesthesia in the upper limb. Side effects and plasma concentrations of the drugs in the doses administered for IVRA were also studied. **Methods.** Thirty patients in ASA groups I and II received intravenous regional anesthesia for surgery of the upper limb. In a double-blind prospective study, they were randomly allocated to receive one of three local anesthetics: articaine, lidocaine, or prilocaine. Patients received 40 mL of a 0.5% solution of the local anesthetic. The onset time of sensory block was assessed by pinprick and the extent of motor block was scored as 0-3. Plasma concentrations of local anesthetics were determined in all patients from serial arterial blood samples drawn at predetermined times before and after tourniquet release. **Results.** The onset time of sensory block was significantly shorter (2.5 minutes) in the articaine group than in the lidocaine group (11.1 minutes) or the prilocaine group (10.9 minutes) (Scheffe, $P < .05$). Development of motor block was equal in all three groups (score 2). Estimation of plasma concentrations by high performance liquid chromatography showed that the peak level in all 30 patients was reached immediately after release of the tourniquet; plasma concentrations thereafter gradually declined. Maximum concentrations of articaine, lidocaine, and prilocaine were, 1.85, 8.5, and 4.4 $\mu\text{g/mL}$, respectively. No signs of local anesthetic toxicity of the cardiovascular or central nervous systems were seen. **Conclusion.** Articaine had the fastest onset of sensory block and the lowest peak plasma concentration of the three local anesthetics when used for intravenous regional anesthesia. *Reg Anesth 1997; 22: 29-34.*

Key words: intravenous regional anesthesia, articaine, lidocaine, prilocaine.

Intravenous regional anesthesia (IVRA), first described by Bier (1) in 1908, remains a popular technique for brief operations in the hand and fore-

arm and to a lesser extent in the lower limb, especially when a tourniquet is applied for surgical indications. Good surgical anesthesia can be achieved rapidly following injection of the local anesthetic agent, and after release of the tourniquet, recovery is fast. This makes it a very useful technique for ambulatory surgery. The technique is generally safe (2), although complications resulting from technical failure (3,4) or the choice of an unsuitable local anesthetic agent have been reported. Bupivacaine, for example, is contraindicated because of its high potential for cardiotoxicity. In the Netherlands the two most frequently used local anesthetics for IVRA

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are lidocaine 0.5% and prilocaine 0.5%. Recently we introduced articaine 0.5% for IVRA in our clinic and experienced good clinical results.

The present report describes a double-blind prospective study, in which we compared the onset time of sensory and motor block and possible side effects and complications of articaine 0.5%, lidocaine 0.5%, and prilocaine 0.5% in IVRA. Plasma concentrations of local anesthetic were determined from arterial blood samples taken at regular intervals in order to investigate possible relationships between systemic blood levels and eventual toxic reactions.

Materials and Methods

The study was approved by the ethics committee of our hospital, and written informed consent was obtained from 30 patients (ASA classes I and II), who were scheduled for surgery of the hand or forearm. Our pharmacist, who did not directly participate in the trial, prepared a randomization table containing 30 numbers of which 10 were designated articaine, 10 lidocaine, and 10 prilocaine. Each of the 30 patients received a number chosen at random and then received a local anesthetic solution corresponding to that number. Neither the patient nor the anesthesiologist had any knowledge of the identity of the solution, so that the double-blind nature of the trial was ensured. The groups were subsequently identified as articaine, lidocaine, and prilocaine.

No premedication was given. An 18-gauge 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 suitable vein in the other arm, and the radial artery of that arm was cannulated for continuous invasive blood pressure monitoring and intermittent blood sampling.

Oxygen saturation via a Datex Satlite pulse oximeter (Datex, Division of Instrumentation Corp., Helsinki, Finland), three-lead electrocardiography, (I, II, and III via HP 78353 B) (Hewlett Packard, Andover, MA), pulse rate, 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 (ECG) was registered on a Hellige Multiscriptor E.K. (Hellige, Freiburg, Germany) 33 in all patients before injection of the local anesthetic agent and 5 and 15 minutes after deflation 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 mm Hg above normal systolic pressure or to 300 mm Hg, whichever was higher. Arti-

caine 0.5% (Ultracaine®) was obtained from Hoechst Pharmaceuticals (Frankfurt a M. Germany), prilocaine 0.5%, (Citanest) was obtained from Astra Pharmaceuticals (Rijswijk, the Netherlands), and lidocaine 0.5% was prepared by the production unit of the Department of Pharmacy of the Medisch Spectrum Twente, the Netherlands, as described in the Formulary of Dutch Pharmacists (5) and complied with the recommendations for lidocaine hydrochloride injection published in the U.S. Pharmacopoeia, 23rd edition (6). A total of 40 mL of the allocated local anesthetic solution was injected over a period of 30 seconds. Skin reactions or subjective complaints were noted. The development of sensory block over the distributions of the median, radial, and ulnar nerves was assessed by pinprick. Motor block was assessed on a scale of 0 to 3, as defined below:

- 0, No motor block at all
- 1, No pronation/supination of forearm possible, but wrist and finger movements present
- 2, No pronation/supination of forearm possible and no wrist movements but finger movements present
- 3, No movement at all of the upper extremity

The onset of surgical analgesia was defined as the period from the end of the injection of the local anesthetic to the loss of pinprick sensation in the distribution of all three nerves.

Arterial blood samples were taken before injection, 10 minutes after injection, and then at 10-minute intervals 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 minutes. In no case was the tourniquet released within 30 minutes of completing the injection, even when actual surgery was of less than half-hour duration. The blood samples were centrifuged, and the plasma was frozen and stored at -20°C until analyzed.

Analysis

The concentrations of lidocaine or prilocaine were determined by high-performance liquid chromatography as described by Lindberg and Pihlajmaki (7) and that of articaine by high-performance liquid chromatography as described by Vree et al. (8). The day-to-day coefficient of variance for articaine, lidocaine, and prilocaine was 1.5%, 5.1%, and 6.1%, respectively.

Statistics

All data were entered into a database and analyzed by SAS statistical procedures (SAS Institute,

Cary, NC) on a personal computer. Group means were compared in a one-way analysis of variance followed by Scheffe's procedure to detect intergroup significance. Chi-square analysis was used in incidence tables. In all tests, $P = .05$ was used as the level of significance.

Results

Patient demographic data are listed in Table 1. The three groups were of comparable age and weight. The mean onset time of surgical analgesia determined in this study was 2.5 minutes for articaine, 11.2 minutes for lidocaine, and 10.9 minutes for prilocaine (Table 2). The onset of surgical analgesia in the articaine group was significantly faster than in the lidocaine and prilocaine group (by the Scheffe procedure).

In all but two patients, (one in the lidocaine and one in the prilocaine group), satisfactory surgical conditions, evidenced by good sensory block, were reached within 20 minutes, and no additional analgesics were required. In order to include these two patients in the statistical calculations, their onset time was set arbitrarily at 20 minutes, although surgery could only be commenced after local infiltration of lidocaine 1%. There was no trend toward a fixed sequence for the development of sensory block in the radial, median, and ulnar nerves. Motor block was incomplete in all 30 patients (a score of 2 on the 0–3 scale), but patients were subjectively unaware of this.

None of the patients exhibited objective symptoms of toxicity, either local or systemic, during injection of the local anesthetic, nor were there any subjective complaints. No changes in blood

pressure, heart rate, or oxygen saturation were observed at any time during the procedure and after deflation of the tourniquet. Toxic symptoms and subjective complaints were similarly absent following cuff release, and no changes were recorded on the ECG in any of the 12 leads.

Mean plasma concentrations of the three local anesthetic agents at various times after cuff release are shown in Figure 1. Peak plasma concentrations were reached immediately after release of the tourniquet. Lidocaine exhibited the highest plasma concentration curve and articaine the lowest. Maximum concentrations of articaine, lidocaine, and prilocaine were 1.85, 8.5, and 4.4 $\mu\text{g}/\text{mL}$ respectively. Local anesthetic was not detected in the plasma samples before cuff release in any of the 30 patients.

Discussion

Articaine is a local anesthetic of the aminoamide type, which differs from other local anesthetics in possessing a thiophene instead of a benzene ring (Fig. 2). Articaine was introduced by Hoechst Pharmaceuticals in 1974. Early experiments in the isolated frog sciatic nerve model by Muschaweck and Rippel (9) demonstrated an anesthetic potency 1.5 times that of lidocaine. Its efficacy in topical anesthesia was low, but it was significantly superior to lidocaine for infiltration anesthesia. Since introduction, articaine has become popular, especially in eastern European countries, for central as well as peripheral neural block. Until recently its use in the Netherlands was restricted to dental procedures; however, the last 5 years it has begun to be used by Dutch anesthesiologists as well (10,11).

Table 1. Demographic Data for the Patients in the Three Local Anesthetic Groups

Anesthetic	Men	Women	Age (y) (Mean \pm SD)	Weight (kg) (Mean \pm SD)
Articaine	3	7	50.2 \pm 14.2	70.5 \pm 8.4
Lidocaine	3	7	42.6 \pm 12.8	72.9 \pm 12.5
Prilocaine	4	6	44.1 \pm 14.2	80.1 \pm 15.7

Table 2. Mean Onset Times of Surgical Analgesia Measured in the Three Local Anesthetic Groups

	Articaine	Lidocaine	Prilocaine
Onset time (min) \pm SD	2.5 \pm 1.07	11.2 \pm 5.12	10.9 \pm 6.01
Scheffe grouping*	A	B	B

*Only differences between Scheffe groups A and B are statistically significant.

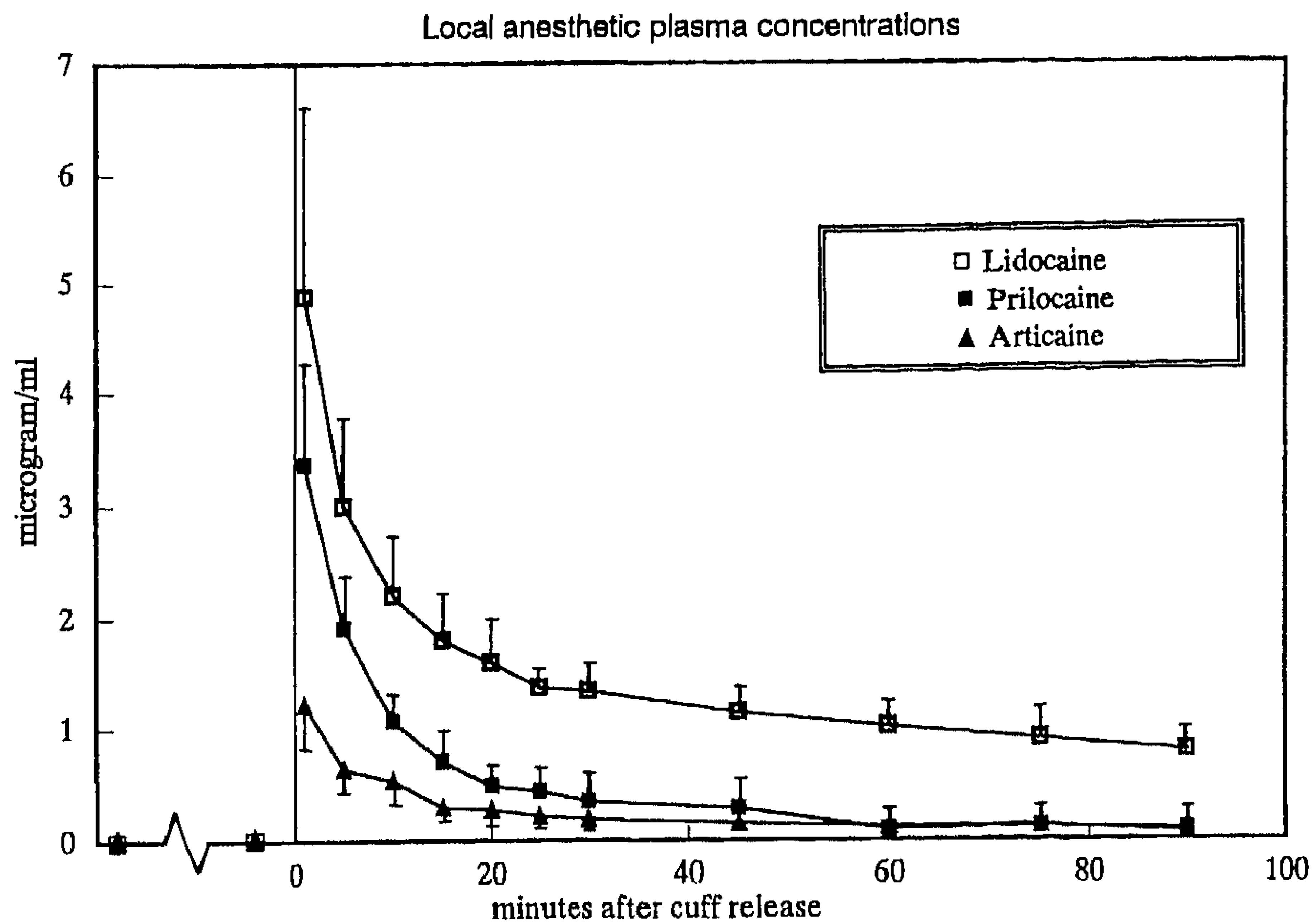


Fig. 1. Graphical presentation of the course of the mean local anesthetic plasma concentration. Bars represent standard deviation.

Hendolin and Mattila (12) and Baeder et al. (13) reported a relatively low incidence of side effects, and van Oss (14) also showed that large doses do not elicit toxic reactions.

The physicochemical properties of articaine, lidocaine, and prilocaine are listed in Table 3. These data

offer no convincing explanation for the faster onset time of articaine. There is very little difference between the pKa's of the three drugs, while the lipid solubility of articaine is lower than that of lidocaine or prilocaine. The vasodilatory effects of the three drugs are similar (9). Therefore, the more rapid

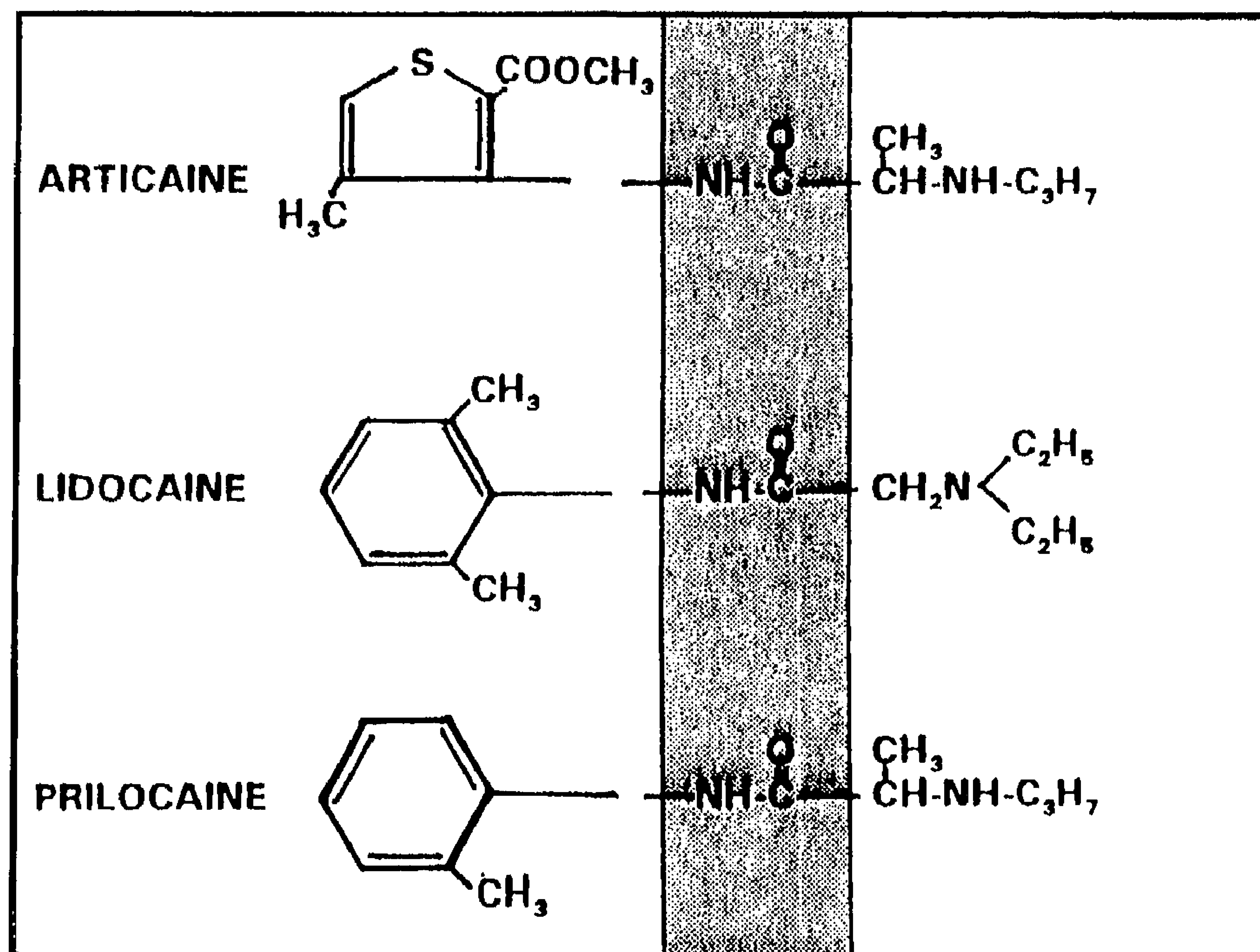


Fig. 2. Molecular structure of lidocaine, prilocaine, and articaine.

Table 3. Physicochemical Properties of Lidocaine, Prilocaine, and Articaine

Anesthetic	Molecular Weight	pK _a	Protein binding (%)	Lipid Solubility (log oct)*
Lidocaine	234.0	7.9	65	1.67
Prilocaine	220.0	7.9	55	1.31
Articaine	284.4	7.8	50–70	1.23

*Log oct (octanol) is the logarithm of the distribution ratio in a phase system where octanol and a buffer with pH 7.4 are used. A higher ratio reflects a better lipid solubility. Lidocaine and prilocaine pK_a from Tucker and Mather (25), articaine pK_a from Karzel (26), and lipid solubility data from Hansch and Leo (27).

onset time of articaine, as found in this study, cannot be explained on the basis of physicochemical differences.

The question remains: Did we use equipotent doses? Muschaweck und Rippel (9) derived their data from the isolated frog sciatic nerve model, but data obtained from this source may not be valid *in vivo*. Covino and Vassallo (15) note that while the intrinsic potency of chlorprocaine is four times that of procaine, *in vivo* the two drugs are equipotent. Similarly, the intrinsic potency of lidocaine has been shown to be 1.5 times to twice that of mepivacaine and prilocaine, but again, *in vivo* the agents appear to be equipotent. In spite of the findings of Muschaweck and Rippel (9), several clinical studies have shown articaine, prilocaine, and lidocaine to be equipotent *in vivo*. Hecksher-Sørensen (16), for example, was unable to demonstrate any clinical difference between 30 mL 1% lidocaine and 30 mL 1% articaine when used for brachial plexus block via the axilla. Reng and Auberger (17) reached the same conclusion when comparing 1% lidocaine plus epinephrine with 1% articaine plus epinephrine in epidural blocks for obstetric and gynecologic procedures. Hendolin and Mattila (12) and Brinkløv (18) also compared lidocaine and articaine during epidural anesthesia and apart from a longer duration of action of articaine, found no significant clinical difference between the two drugs. Eerola and Eerola (19) compared 2% solutions of articaine and prilocaine during epidural anesthesia and were similarly unable to demonstrate any significant difference in their anesthetic properties.

If, as stated by Lagermann et al. (20), the partition coefficient is a predictor of local anesthetic potency in the subarachnoid model, articaine should be the least potent drug. Covino and Vassallo (15) also referred to this correlation between partition coefficient and local anesthetic potency, but there are conflicting reports in clinical studies, and no consistent *in vivo* picture emerges.

Two studies, one in rats (21) and the other in humans (22), failed to reveal a significant differ-

ence in potency between prilocaine and articaine. On the basis of this work and the above-cited literature reports, we are led to the conclusion that despite Muschaweck and Rippel's findings (9), the drugs we investigated are equally potent *in vivo*. Despite apparent equivalence in dosage, we observed a faster onset time when articaine was used. Similarly, Eerola (23) showed that onset of analgesia in IVRA was more rapid with articaine than with prilocaine, although the quantitative difference in his series was less marked than in ours. The low plasma levels of articaine may be explained by rapid hydrolysis to its 2-carboxy metabolite by plasma esterase activity (8). Although our plasma determinations produced values that were higher than those of Brader et al (24) the results are not directly comparable because they used a different method.

On the basis of our results we conclude that articaine has a significantly faster onset than either prilocaine or lidocaine in IVRA.

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References

1. Bier A. Über einen neuen Weg Lokalanästhesie an den Gliedmassen zu erzeugen. Arch Klin Chir 1908; 86: 1007–1016.
2. Ware RJ. Intravenous regional analgesia: The debate continues. Anaesthesia 1982; 37: 958–959.
3. Rosenberg PH, Kalso EA, Tuominen MK, Linden HR. Acute bupivacaine toxicity as a result of venous leakage under the tourniquet cuff during a Bier block. Anesthesiology 1982; 58: 95–98.
4. Hallett G. Inaccuracies in measuring tourniquet pressures. BMJ 1983; 286: 1287–1288.
5. Formulary of Dutch Pharmacists. Den Haag, Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie, 1983: 53.

6. The United States Pharmacopeia XXIII. The National Formulary XVIII. Rockville, MD, The United States Pharmacopeial Convention, 1994: 888.
7. Lindberg RLP, Pihlajmaki KK. High-performance liquid chromatographic determination of bupivacaine in human serum. *J Chromatogr* 1984; 360: 369–374.
8. Vree TB, Baars AM, van Oss GECJM, Booij LHDJ. High-performance liquid chromatography and preliminary pharmacokinetics of articaine and its 2-carboxy metabolite in human serum and urine. *J Chromatogr* 1988; 424: 440–444.
9. Muschaweck R, Rippel R. Ein neues Lokalanästhetikum (Carticain) aus der Thiophenreihe. *Prakt Anasth* 1974; 9: 135–146.
10. Van Oss GECJM, Vree TB, Baars AM, Termond EFS, Booij LHDJ. Pharmacokinetics, metabolism, and renal excretion of articaine and its metabolite articainic acid in patients after epidural administration. *Eur J Anaesthesiol* 1989; 6: 49–56.
11. Van Oss GECJM, Booij LHDJ. Articaine 4% met adrenaline 1:200.000 (Ultracaine®DS) voor peridurale anesthesie: Enige gegevens. *Ned Tijdschr Anaesth* 1988; 2: 12–16.
12. Hendolin H, Mattila M. HOE 40045, ein neues Lokalanästhetikum, verglichen mit Lidocain bei Epiduralanästhesie. *Prakt Anasth* 1974; 9: 178–182.
13. Baeder C, Bähr H, Benoit W, Doerr BJ, Engelbart K, Hergott J, Kramer M, Schütz E, Schultes E, Scholz J, Springman FR, Wolf GL. Untersuchungen zur Verträglichkeit von Carticaine, einem neuen Lokalanästhetikum. *Prakt Anasth* 1974; 9: 147–152.
14. Van Oss GECJM. Articaine 4% met adrenaline 1:200.000 (Ultracaine®DS) voor peridurale anesthesie. Lecture, October 1987, Veldhoven, Netherlands.
15. Covino BG, Vassallo HG. Local anesthetics. Mechanisms of action and clinical use. Orlando, Grune & Stratton, 1976.
16. Hecksher-Sørensen S. Carticaine bei der axillären Blockade des Plexus brachialis. *Prakt Anästh* 1974; 9: 168–171.
17. Reng B, Auberger H.-G. Klinische Doppelblindstudie mit den Lokalanästhetika HOE 40045 (Carticaine) und Lidocaine. *Prakt Anästh* 1974; 9: 175–178.
18. Brinkløv MM. Clinical effects of Carticaine, a new local anesthetic. A survey and a double-blind investigation comparing carticaine with lidocaine in epidural analgesia. *Acta Anaesthesiol Scand* 1977; 21: 5–16.
19. Eerola R, Eerola M. A comparative study of carticaine and prilocaine in epidural anaesthesia. *Ann Clin Res* 1978; 10: 102–104.
20. Langerman L, Bansinath M, Grant GJ. The partition coefficient as a predictor of local anesthetic potency for spinal anesthesia: Evaluation of five local anesthetics in a mouse model. *Anesth Analg* 1994; 79: 490–494.
21. Wolff AP, Dirksen R, Gielen MJM, Booij LHDJ. The intrathecal effectiveness of four short acting local anesthetics in rats: A single concentration-response relationship. *Reg Anesth* 1993; 18(suppl): 25.
22. Wolff AP, Megens JH, Gielen MJM, Knape HT. Articaine 4% and Prilocaine 2% in lumbar epidural anesthesia. (submitted for publication)
23. Eerola R. A comparative study of carticaine and prilocaine in regional intravenous analgesia. *Prakt Anästh* 1974; 9: 171–175.
24. Brader AM, Conception M, Hurley RJ, Arthur GR. Comparison of lidocaine and prilocaine for intravenous regional anesthesia. *Anesthesiology* 1988; 69: 409–412.
25. Tucker GT, Mather LE. Properties, absorption, and disposition of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural blockade in clinical anesthesia and management of pain*. Philadelphia, Lippincott Raven, 1988: 47–110.
26. Karzel KMH. Lokalanästhetika und Lokalanästhesie. *Dtsch Apothek Zeitung* 1981; 4: 151–160.
27. Hansch C, Leo A. Substituent constants for correlation analysis in chemistry and biology. New York, Wiley-Interscience, 1979:270–285.