

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/25490>

Please be advised that this information was generated on 2021-03-01 and may be subject to change.

Comparison of the disposition kinetics of lidocaine and (\pm)prilocaine in 20 patients undergoing intravenous regional anaesthesia during day case surgery

M. A. M. Simon* MD, T. B. Vree† PhD, M. J. M. Gielen† MD PhD and L. H. D. J. Booij† MD PhD

*Department of Anesthesiology, Medisch Spectrum Twente, Haaksbergerstraat 55, 7513 ER Enschede; and †Institute for Anesthesiology, Academic Hospital Nijmegen Sint Radboud, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands

SUMMARY

Objective: The aim of this investigation was to compare the pharmacokinetics of lidocaine and prilocaine in two groups of 10 patients undergoing intravenous regional anaesthesia.

Method: The study had a randomized design. The patients were allocated to one of the two groups of 10. Each group received either lidocaine (200 mg = 0.855 mM) or prilocaine (Citanest[®], 200 mg = 0.909 mM), injected intravenously over a period of 30 s. 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.

Results: The mean onset time of surgical analgesia of lidocaine was 11.2 ± 5.1 min and that of prilocaine was 10.9 ± 6.0 min. After releasing the tourniquet, lidocaine is bi-exponentially eliminated with a $t_{1/2\alpha}$ of 4.3 ± 2.1 min and a $t_{1/2\beta}$ of 79.1 ± 31.2 min. Total body clearance was 0.86 ± 0.39 litres/min. Prilocaine is rapidly and bi-exponentially eliminated with a $t_{1/2\alpha}$ of 3.0 ± 1.6 min and a $t_{1/2\beta}$ of 29.9 ± 15.7 min. The total body clearance of prilocaine is higher than that of lidocaine, 4.15 ± 1.31 vs. 0.86 ± 0.39 litres/min, respectively ($P=0.0007$). Both compounds show comparable volumes of distribution (V_d , V_{ss} and V_β) and a comparable $t_{1/2\alpha}$ (4.3 ± 2.1 vs. 3.0 ± 1.6 min; $P=0.1780$). The $t_{1/2\beta}$ for the two compounds were different ($P=0.0031$); 79.1 ± 31.2 min for lidocaine and

29.9 ± 15.7 min for prilocaine. The mean residence time (MRT) of lidocaine (193 ± 233 min) also differed significantly from that of prilocaine (33.4 ± 19.9 min; $P=0.0022$).

Conclusion: Lidocaine is preferred for relatively long procedures and prilocaine for short procedures.

INTRODUCTION

Intravenous regional anaesthesia (IVRA), first described by Bier in 1908 (1), remains a popular technique for short-lasting surgical procedures on the hand and forearm and, to a lesser extent, on the lower limbs, especially if a tourniquet is to be applied.

Good surgical anaesthesia is achieved quickly following injection of the local anaesthetic agent and recovery after release of the tourniquet is rapid. The method is safe provided a suitable local anaesthetic agent is used. Bupivacaine, for instance, is contraindicated because of its cardiotoxicity (2–5). Lidocaine and prilocaine are considered to be very suitable agents for IVRA (6–14). It is considered to be important for patients to leave hospital free of anaesthetic drugs (15, 16).

Little has been published on the pharmacokinetics of lidocaine and prilocaine during IVRA. Both compounds are eliminated by hydrolysis of the amide bond, which is quicker with prilocaine than with lidocaine due to the 2,6-methyl substitution in the phenyl moiety of the latter drug. The aim of this investigation was to compare the pharmacokinetics of lidocaine and prilocaine in two groups of 10 patients undergoing intravenous regional anaesthesia.

Correspondence: Dr T. B. Vree, Institute for Anesthesiology, Academic Hospital Nijmegen Sint Radboud, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands.

MATERIALS AND METHODS

Patients

The study was approved by the Hospital Ethics Committee of the Medisch Spectrum Twente, and written informed consent to participate was obtained from 20 patients scheduled for surgery of the hand or forearm. All patients were classified according to the criteria of the American Society of Anesthesiologists as ASA I or II. Four men and six women received prilocaine. The mean (\pm SD) body weight was 80.1 ± 15.7 kg, and age 44.1 ± 14.2 years. Three men and seven women received lidocaine. The mean (\pm SD) body weight was 72.9 ± 12.5 kg, and age 42.6 ± 12.8 years. The study used a double-blind, randomized design.

Patient preparation

No pre-medication was given. An 18G cannula was introduced into a suitable vein in the dorsum of the hand of the arm to be treated. Two cannulae were introduced into the other arm, one into a suitable vein and the other into the radial artery. The latter was used for continuous monitoring of blood pressure and for intermittent blood sampling.

Oxygen saturation via a Datex 'Satlite' (Datex Division of Instrumentarium, Helsinki, Finland), pulse rate and EKG pulse-oximeter (three-lead, I, II and III via HP 78353 B, Andover, U.S.A.) and arterial blood pressure were measured continuously from the first venous cannulation until withdrawal of the final blood sample. A 12-lead electrocardiogram was registered on a Hellige Multiscriptor EK 33 (Hellige, Freiburg, Germany) in all patients prior to injection of the local anaesthetic and 5 and 15 min 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 Torr above normal systolic pressure or 300 Torr, whichever was higher. The local anaesthetic was injected intravenously in a randomized, double-blind fashion for establishing efficacy.

Drugs

Lidocaine 0.5% was prepared in the Department of Pharmacy of the Medisch Spectrum Twente (Enschede, the Netherlands) following the criteria of the Dutch

Pharmacopaea. Forty millilitres of the lidocaine 0.5% solution (40×5 mg/ml = 200 mg = 0.855 mM) were injected intravenously (i.v.) over a period of 30 s to each of the patients in the lidocaine group. Prilocaine 0.5% (Citanest[®]) was obtained from Astra Pharmaceuticals (Rijswijk, the Netherlands). Forty millilitres of the prilocaine 0.5% solution (40×5 mg/ml = 200 mg = 0.909 mM) were injected i.v. over a period of 30 s into each of the patients in the prilocaine group.

Side-effects

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.

Sampling

A total of 15 arterial blood samples were taken from each patient. One was drawn immediately before injection and subsequent samples at 10-min intervals, commencing 10 min after completion of the injection and ending at the moment of release of the tourniquet. The latter time was registered as $t=0$, and arterial blood samples were drawn at 1, 5, 10, 15, 20, 25, 30, 45, 60, 75 and 90 min. In no case was the tourniquet released within 30 min of completing the injection. Blood was collected in tubes containing Li-heparin. The samples were centrifuged at 3000 g, and the plasma separated and stored at -20°C until analysis.

Analysis

The plasma concentration of (\pm)prilocaine ($\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}$: CAS number 721-50-6, molecular weight = 220.31, $\text{pK}_a=7.9$; HCl salt: CAS number 1786-81-8, molecular weight = 256.8) was determined by high-performance liquid chromatography (HPLC) using a modification of the method described by Lindberg and Pilhlajmaki (17). Briefly, the method is as follows. Column: Spherisorb 5 ODS, 250×4.6 mm. UV detection was achieved at 230 nm. Mobile phase

(4 g H_3PO_4 , 0.6 g TMACl in 1 litre water) and acetonitrile (4:6 v/v) at 1.5 ml/min flow rate. Plasma (0.3 ml) was deproteinized with 0.33 M perchloric acid (0.3 ml), vortexed and centrifuged at 3000 g. Fifty microlitres were injected onto the column. The limit of quantitation was 0.1 μ g/ml. The inter- and intra-day coefficients of variance for prilocaine were less than 5%.

The plasma concentration of lidocaine ($C_{14}H_{22}N_2O$: CAS number 137-58-6, molecular weight = 234.33; HCl.H₂O salt: CAS number 73-78-9, molecular weight = 288.8) was determined by the same method. Ultra-violet detection was achieved at 210 nm. The inter- and intra-day coefficients of variance for lidocaine were less than 5%.

Pharmacokinetics

Pharmacokinetic parameters were calculated using a two-compartment model with the MW/Pharm computer package (Mediware[®], Groningen, the Netherlands) (18).

C_{max} was the maximum plasma concentration read from the fitted plasma concentration-time curve ($r^2 > 0.98$), and t_{max} the time at which C_{max} occurred. The elimination half-life ($t_{1/2\beta}$) values were calculated from $\ln 2/\beta$, where β was 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 and $C_t\beta$, with C_t ($t=90$) being the last measured concentration.

- Total body clearance (Cl) is described as $dose/AUC_{0-t}$.
- $V_d = dose/C_o$, the volume of distribution in the central compartment.
- $V_\beta = Cl/\beta$, the volume of distribution in the second compartment.
- $V_{ss} = dose \cdot AUMC_{0-t} / AUC_{0-t}^2$, the volume of distribution at steady state.
- Mean residence time (MRT) = $AUMC_{0-t} / AUC_{0-t}$, where $AUMC_{0-t}$ is the area under the moment curve from zero to $t=90$.

Statistical analysis

The Mann-Whitney two-tailed test for unpaired observations was used. Statistical significance was defined as $P < 0.05$.

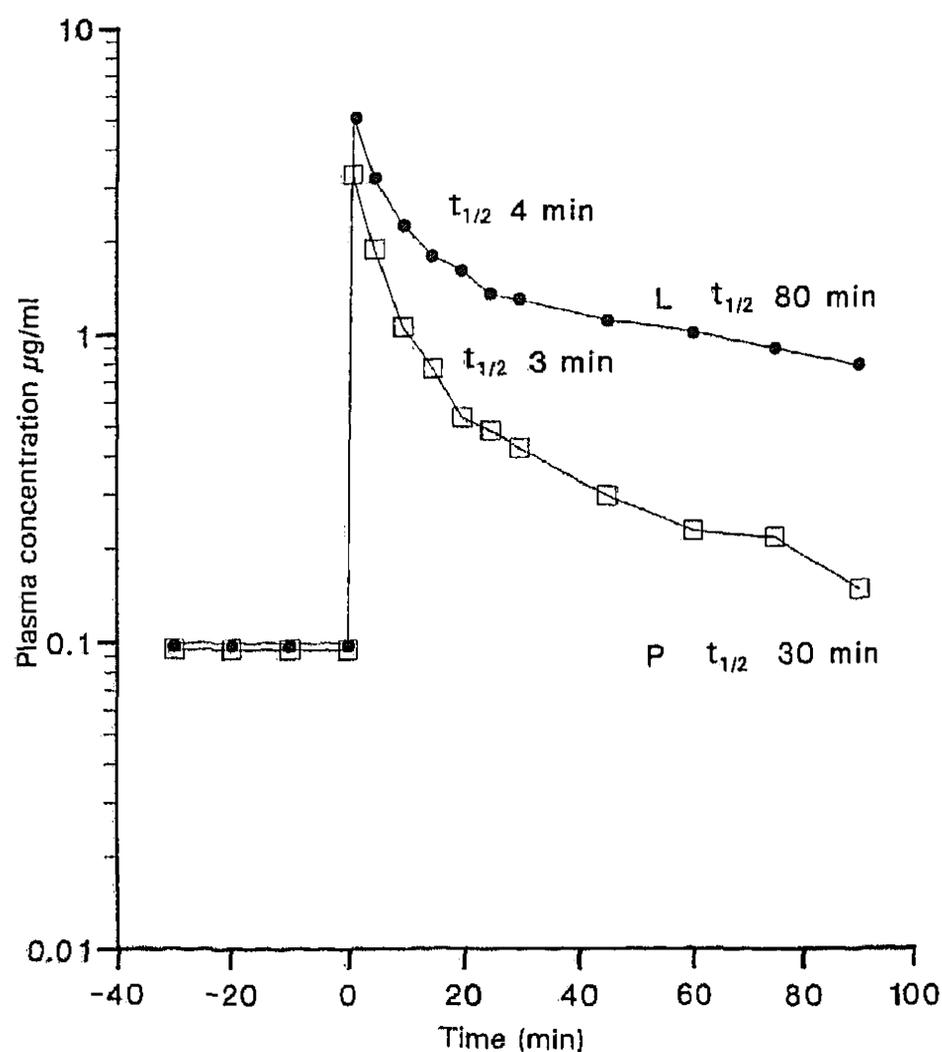


Fig. 1. Mean plasma concentration-time curves of lidocaine (L) and prilocaine (P) after a regional i.v. dose of 200 mg ($n=10$). During tourniquet occlusion there were no measurable plasma concentrations at the quantification limit of 0.1 μ g/ml.

RESULTS

Clinical response

The mean onset time of surgical analgesia of lidocaine was 11.2 ± 5.1 min and that of prilocaine 10.9 ± 6.0 min ($P=0.4236$). There was no trend towards a fixed sequence, radial, median, ulnar in the development of sensory blockade. In all patients satisfactory surgical conditions, evidenced by good sensory blockade, were reached within 20 min and no additional analgesics were required. None of the patients exhibited objective symptoms of toxicity, either local or systemic, during injection of the local anaesthetic, 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.

Pharmacokinetics

Figure 1 shows the mean plasma concentration-time curves of lidocaine and prilocaine in 10 patients after releasing the tourniquet. Plasma concentrations were

Table 1. Mean plasma concentrations ($\mu\text{g/ml} \pm \text{SD}$) of lidocaine and prilocaine after IVRA administration of 40 ml of 0.5% = 200 mg

Time* (min)	Lidocaine	Prilocaine
1	4.70 \pm 2.14	3.36 \pm 0.96
5	2.88 \pm 0.96	1.94 \pm 0.53
10	2.18 \pm 0.60	1.07 \pm 0.23
15	1.79 \pm 0.40	0.78 \pm 0.16
20	1.59 \pm 0.37	0.54 \pm 0.07
25	1.37 \pm 0.19	0.49 \pm 0.15
30	1.33 \pm 0.07	0.43 \pm 0.19
35	1.14 \pm 0.24	0.30 \pm 0.15
60	1.01 \pm 0.26	0.25 \pm 0.05
75	0.90 \pm 0.27	0.22 \pm 0.07
90	0.79 \pm 0.19	0.15 \pm 0.05

*Time = after tourniquet release.
Limit of quantification = 0.1 $\mu\text{g/ml}$.

zero before releasing the tourniquet and rose immediately to maximal concentrations after 1 min (Table 1). The elimination of lidocaine is bi-exponential, with a $t_{1/2\alpha}$ of 4.3 ± 2.1 min and a $t_{1/2\beta}$ of 79.1 ± 31.2 min. The elimination of prilocaine is bi-exponential, with a $t_{1/2\alpha}$ of 3.0 ± 1.6 min and a $t_{1/2\beta}$ of 29.9 ± 15.7 min.

Table 2 shows the mean values and statistical differences in the pharmacokinetic parameters of lidocaine and prilocaine. The total body clearance of prilocaine is higher than that of lidocaine, 4.15 ± 1.31 vs. 0.86 ± 0.39 litres/min, respectively ($P=0.0007$). Both compounds show comparable volumes of distribution (V_d , V_{ss} and V_β) and a comparable $t_{1/2\alpha}$ (4.3 ± 2.1 vs. 3.0 ± 1.6 min; $P=0.1780$). The $t_{1/2\beta}$ differs significantly between the two compounds ($P=0.031$); 79.1 ± 31.2 min for lidocaine and 29.9 ± 15.7 min for prilocaine. The MRT of lidocaine (193 ± 233 min) also differs significantly from that of prilocaine (33.4 ± 19.9 min; $P=0.0022$).

DISCUSSION

Diverse local anaesthetic agents have been used for IVRA. At the beginning of the 20th century, Bier (1) used 40 ml 0.5% procaine. The use of prilocaine was first reported by Lofgren and Tegner in 1960 (19). The use of chlorprocaine and lidocaine were first used in 1963 (20). Injection of chlorprocaine may lead to

Table 2. Comparison of the pharmacokinetic parameters (mean \pm SD) of lidocaine and prilocaine after IVRA administration of 40 ml of 0.5% = 200 mg

Parameter	Lidocaine	Prilocaine	P
Subjects M/F	3/7	4/6	
Body weight (kg)	72.9 \pm 12.5	80.1 \pm 15.7	0.5217
Age (years)	42.6 \pm 12.8	44.1 \pm 14.2	0.6238
Dose			
mg	200	200	
mM	0.855	0.909	
AUC (mg/litre/min)	127 \pm 23.1	45.4 \pm 11.5	0.0007
Cl (litres/min)	0.86 \pm 0.39	4.15 \pm 1.31	0.0007
V_d (litres)	36.2 \pm 3.91	51.4 \pm 22.8	0.1632
V_{ss} (litres)	104 \pm 37.7	120 \pm 49.4	0.5967
V_β (litres)	105 \pm 27.6	158 \pm 55.8	0.0723
$t_{1/2\alpha}$ (min)	4.30 \pm 2.12	3.04 \pm 1.62	0.1780
$t_{1/2\beta}$ (min)	79.1 \pm 31.2	29.9 \pm 15.7	0.0031
MRT (min)	193 \pm 233	33.4 \pm 19.9	0.0022

P = Mann-Whitney two-tailed test.

thrombophlebitis (21), venous irritation and urticaria (22). Bupivacaine is contraindicated because of potential cardiotoxicity, and fatal complications have been reported following intravenous injection (2-5), a situation which occurs with this technique when the tourniquet is released. The ideal agent for IVRA should achieve rapid onset of good surgical anaesthesia and, above all, be safe. Lidocaine and (\pm)prilocaine both fulfil these criteria, as reported by several authors (7, 12-14, 22-28).

The flushing and absorption of both lidocaine and prilocaine from the exsanguinated forearm after releasing the tourniquet was so fast that the maximum plasma concentration was detected in the first sampling time at 1 min. The maximum plasma concentrations of lidocaine were in agreement with those reported earlier (9, 29, 30) and stayed well below the toxic concentrations of 5-10 $\mu\text{g/ml}$, depending on the degree of anaesthesia (31).

Thereafter, lidocaine was eliminated according to a bi-exponential decay after i.v. administration with a $t_{1/2\alpha}$ of 4.3 ± 2.1 min and a $t_{1/2\beta}$ of 79.1 ± 31.2 min. Prilocaine was also eliminated according to a bi-exponential decay after i.v. administration with a $t_{1/2\alpha}$ of 3.0 ± 1.6 min and a $t_{1/2\beta}$ of 29.9 ± 15.7 min. The pharmacokinetic data shown in Table 2 correspond with those previously reported (32, 33).

The difference between the pharmacokinetics of lidocaine and prilocaine can be attributed solely to the difference in $t_{1/2\beta}$ values, which affects the AUC_t and thus the total body clearance. The rates of distribution and volumes of the two compounds are similar. The rate of metabolism/hydrolysis governs the overall rate of elimination, which is greater with prilocaine.

Comparison of metabolism

The metabolism of lidocaine proceeds via cytochrome P450 isoenzymes resulting in *N*-hydroxylation, *N*-dealkylation (MEGX, GX) and the principal reaction of 4-hydroxylation (32–36). The metabolism of prilocaine proceeds via cytochrome P450 isoenzymes resulting in *N*-hydroxylation, *N*-dealkylation (*N*-propylalanine) and hydrolysis of the amide bond (*O*-toluidine) (32–39). Unless tissue cytochrome P450 is capable of performing such reactions in measurable quantities, it is unlikely that a substantial amount of either lidocaine or prilocaine will be metabolized in the 30 min duration of exsanguination of the forearm.

CONCLUSIONS

It was concluded that both lidocaine and prilocaine are suitable and safe agents for IVRA with rapid onset of good surgical anaesthesia. This is in line with everyday practice in most institutions. After releasing the tourniquet, prilocaine is rapidly eliminated with a $t_{1/2\beta}$ of 30 min, while lidocaine is eliminated more slowly with a $t_{1/2\beta}$ of 80 min.

The longer elimination time of lidocaine results in a longer MRT than that of prilocaine. This apparently insignificant difference between the two drugs may well have important clinical consequences. Depending on the expected time-course of the surgical procedure ($2t_{1/2\beta}$), lidocaine or prilocaine can be the drug of choice for a local anaesthetic action. For a short-lasting surgical procedure (±)prilocaine is the local anaesthetic of choice ($2t_{1/2\beta}$ = 60 min), although administration of a racemic mixture is nowadays considered less favourably, while for a longer-lasting procedure lidocaine is preferred ($2t_{1/2\beta}$ = 160 min).

REFERENCES

1. Bier A. (1908) Über einen neuen Weg Lokalanästhesie an den Gliedmaassen zu erzeugen. *Archiv für Klinische Chirurgie*, **86**, 1007–1016.
2. Albright GA. (1979) Cardiac arrest following regional anaesthesia with etidocaine or bupivacaine. *Anesthesiology*, **51**, 285–286.
3. Davies JAH, Gill SS, Weber JCP. (1981) Intravenous regional anaesthesia using bupivacaine. *Anesthesia*, **36**, 1059–1060.
4. Heath ML. (1983) Bupivacaine toxicity and Bier blocks. *Anesthesiology*, **59**, 481.
5. Heath ML. (1982) Deaths after intravenous regional anaesthesia. *British Medical Journal*, **285**, 913–914.
6. Bartholomew K, Sloan JP. (1990) Prilocaine for Bier's block: how safe is safe? *Archives of Emergency Medicine*, **7**, 189–195.
7. Bader AM, Conception M, Hurley RJ, Arthur CR. (1988) Comparison of lidocaine and prilocaine for intravenous regional anaesthesia. *Anesthesiology*, **69**, 409–412.
8. Bell HM, Slater EM, Harris WH. (1963) Regional anaesthesia with intravenous lidocaine. *Journal of the American Medical Association*, **186**, 544–549.
9. Biscopig J. (1993) Die intravenöse Regionalanästhesie des Armes (IVRA). *Wiener Medizinische Wochenschrift*, **143**, 179–183.
10. Eriksson E. (1966) Prilocaine, an experimental study in man of a new local anaesthetic with special regards to efficacy, toxicity and excretion. *Acta Chirurgica Scandinavica*, **358** (Suppl.), 1–82.
11. Miles DW, James JL, Clark DE, Whitwam JG. (1964) Site of action of intravenous regional anaesthesia. *Journal of Neurology, Neurosurgery and Psychiatry*, **27**, 574–576.
12. Rawal N, Hallen J, Amilon A, Hellstrand P. (1993) Improvement in i.v. regional anaesthesia by re-exsanguination before surgery. *British Journal of Anaesthesia*, **71**, 462–463.
13. Wildsmith JAW. (1985) Prilocaine. An underutilized local anaesthetic. *Regional Anesthesia*, **10**, 155–159.
14. Thorn-Alquist AM. (1969) Blood concentrations of local anaesthetics after intravenous regional anaesthesia. *Acta Anaesthesiologica Scandinavica*, **13**, 229–240.
15. Schüle H. (1980) Klinisch-experimentelle Untersuchungen über die Verkehrstüchtigkeit nach zahnärztlichen Eingriffen. *Deutsche Zahnärztliche Zeitung*, **35**, 183–189.
16. Wörner H, Frank S, Stumpf H. (1980) Lokalanästhesie und Verkehrstüchtigkeit. *Deutsche Zahnärztliche Zeitung*, **35**, 377–384.
17. Lindberg RLP, Pihlajmaki KK. (1988) High-performance liquid chromatographic determination of bupivacaine in human serum. *Journal of Chromatography*, **360**, 369–374.
18. Proost JH, Meijer DKW. (1992) MW/Pharm, an integrated software package for drug dosage regimen calculation and therapeutic drug monitoring. *Computers in Biology and Medicines*, **22**, 155–163.

19. Lofgren N, Tegner C. (1960) Studies on local anesthetics. XX. Synthesis of some α -monoalkylamino-2-methyl propionanilides. *Acta Chemica Scandinavica*, **14**, 486–489.
20. Holmes CMcK. (1963) Intravenous regional analgesia. A useful method of producing analgesia of the limbs. *Lancet*, **A**, 245–247.
21. Dickler DJ, Friedman PL, Susman IC. (1965) Intravenous regional anesthesia with chlorprocaine. *Anesthesiology*, **26**, 244–245.
22. Pitkänen MT, Suzuki N, Rosenberg PH. (1992) Intravenous regional anaesthesia with 0.5% prilocaine or 0.5% chlorprocaine. A double blind comparison in volunteers. *Anaesthesia*, **47**, 618–619.
23. Borchard U, Niesel HC. (1994) Grundlagen der Pharmakologie der Lokalanästhetika. In: *Regionalanästhesie Lokalanästhesie Regionale Schmerztherapie*. ed. Niesel HC, pp. 35–68. Georg Thieme, Stuttgart.
24. Niesel HC. (1994) Klinische Pharmakologie und Toxikologie. Anwendung der Lokalanästhetika. In: *Regionalanästhesie Lokalanästhesie Regionale Schmerztherapie*. ed. Niesel HC, pp. 69–165. Georg Thieme, Stuttgart.
25. Solak M, Akturk G, Erciyes N, *et al.* (1991) The addition of sodium bicarbonate to prilocaine solution during i.v. regional anaesthesia. *Acta Anaesthesiologica Scandinavica*, **35**, 572–574.
26. Adams JP, Dealy EJ, Kenmore PI. (1964) Intravenous regional anesthesia in hand surgery. *Journal of Bone and Joint Surgery*, **46 A**, 811–816.
27. Eerola R. (1974) A comparative study of carticaine and prilocaine in regional intravenous analgesia. *Praktische Anästhesie*, **9**, 171–175.
28. Sorbie C, Chacha P. (1965) Regional anaesthesia by the intravenous route. *British Medical Journal*, **1**, 957–960.
29. Hargrove RL, Hoyle JR, Parker JBR, Beckett AH, Boyes RN. (1966) Blood lignocaine levels following intravenous regional analgesia. *Anaesthesia*, **21**, 37–41.
30. Merrifield AJ, Carter SJ. (1965) Intravenous regional analgesia: lignocaine blood levels. *Anaesthesia*, **20**, 287–303.
31. Deacock ARC, Simpson WT. (1964) Fatal reactions to lignocaine. *Anaesthesia*, **19**, 217–221.
32. Covino BG. (1984) Pharmacokinetics of local anaesthetic drugs: In: *Pharmacokinetics of Anaesthesia*. eds Prys-Robert C, Hug CG, pp. 270–292. Blackwell Scientific Publications, Oxford.
33. Pieper JA, Rodman JH. (1986) Lidocaine. In: *Applied Pharmacokinetics. Principles of Therapeutic Monitoring*. eds Evans WE, Schentag JJ, Jusko WJ, Harrison H, 2nd edn, pp. 639–681. Applied Therapeutics Inc., Spokane, WA.
34. Boyes RN. (1975) A review of the metabolism of amide local anaesthetic agents. *British Journal of Anaesthesia*, **47**, 225–230.
35. Tam YK, Tawfik SR, Ke J, *et al.* (1987) High-performance liquid chromatography of lidocaine and nine of its metabolites in human plasma and urine. *Journal of Chromatography*, **423**, 199–206.
36. Tucker GT, Mather LE. (1979) Clinical pharmacokinetics of local anaesthetics. *Clinical Pharmacokinetics*, **4**, 241–278.
37. Akerman B, Aström A, Ross S, Telc A. (1966) Studies on absorption, distribution and metabolism of labelled prilocaine and lidocaine in some animals. *Acta Pharmacologica Toxicologica*, **24**, 389–403.
38. Boyes RN. (1975) A review of the metabolism of amide local anaesthetic agents. *British Journal of Anaesthesia*, **47**, 225–230.
39. Geddes IC. (1965) Studies of the metabolism of Citanest C¹⁴. *Acta Anaesthetica Scandinavica*, Suppl XVI, 37–44.