AN INTRADERMAL STUDY OF THE LOCAL ANAESTHETIC AND VASCULAR EFFECTS OF THE ISOMERS OF MEPIVACAINE

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SUMMARY

The duration of action and vascular effects of L(+) and D(-) and racemic mepivacaine were investigated in a double-blind study in 23 fit volunteers. Isosmolar 0.1-ml intradermal injections of a range of concentrations of each agent from 0.011% to 2.7%, and physiological saline were given in duplicate to at least 14 subjects. Local colour changes were observed 5-10 min after injection, and analgesia to pinprick was tested at 5-min intervals thereafter until full recovery. Both isomers were vasoconstrictor at concentrations of 0.3% and less; at greater concentration the L isomer produced more vasodilatation and haemorrhagic change. The duration of action of both isomers increased with concentration between 0.05 and 0.9%, but the L isomer was significantly longer acting than the D at 0.3%, and more. The log dose-duration curve could be interpreted as linear between 0.1 and 0.9%, with the slope of the L isomer being twice as steep as the D. The findings for racemic mepivacaine were between those of the two isomers. The longer duration of analgesia of L-mepivacaine was not associated with superior vasoconstrictor power.

The duration of action of a local anaesthetic is determined by the time for which an effective concentration is maintained within the axonal membranes of pain conducting neurones. Reduction in local blood flow slows the rate of removal and prolongs the action. Because of the disadvantages of adding vasoconstrictors, suitable local anaesthetics with intrinsic vasoconstrictor activity have been sought. Those developed since lignocaine possess an asymmetric carbon atom and exist as two stereoisomers, the L and D forms. The terms L and D denote the spatial configuration of the molecule, while laevo-rotatory (–) and dextro-rotatory (+) denote the optical activity, which does not necessarily correspond to spatial configuration and is of little importance biologically. Pairs of isomers have the same physicochemical properties and in vitro local anaesthetic potency (Akerman, Persson and Tegner, 1967; Åberg, 1972) and in clinical practice the racemic mixtures are used. However, it has been shown that the L(–) bupivacaine, L(+) prilocaine and L(+) mepivacaine are longer acting than the D isomers in vivo (Akerman, Persson and Tegner, 1967; Adler, Adler and Åberg, 1969; Luduena, Bogado and Tullar, 1972). In the case of bupivacaine, intradermal studies in man have shown that only the L isomer has local vasoconstrictor activity (Aps and Reynolds, 1978), and this may explain its longer duration of action. The L isomer of mepivacaine was shown to have greater vasoconstrictor activity than the D isomer on rat portal vein (Åberg and Wahlström, 1972).

The present work investigated the local anaesthetic and vascular effects of mepivacaine and its isomers given intradermally to human volunteers. Because vasoactivity of local anaesthetics has been shown to be concentration-dependent, vasoconstriction occurring at low and vasodilatation at high concentrations (Aps and Reynolds, 1976, 1978), a wide range of concentrations of mepivacaine has been investigated.

METHODS

Solutions

D(–), L(+) and racemic mepivacaine hydrochloride were made up to 2.7% and 0.9% (weight of base/vol.) using 0.9% saline and distilled water so that the resulting solutions were isosmolar with 0.9% saline. Serial dilutions to yield the lower concentrations were made using 0.9% saline. Gas–liquid chromatography was used to check that the concentrations of racemic, D- and L- mepivacaine solutions were equal.

Coded sterile ampoules were made up by passing the solution through a Millipore filter,
displacing air with nitrogen gas, sealing and auto-
claving. A check for leaking ampoules was incor-
porated into the autoclaving procedure, and any
leaky ampoules were discarded.

Subjects
The subjects were 23 fit adults, 13 male and 10
female, age range 19–30 yr. There were two studies
involving 14 subjects each; five subjects took part
in both studies. One subject was an author
(J. W. F.) and the rest medical students and
laboratory workers who gave informed consent.

Procedure
In the first study, the concentrations 0.1, 0.3 and
0.9% of D,L and DL (racemic) mepivacaine and
0.9% saline control, were tested. Pairs of 0.1-ml
injections of each solution were given intra-
dermally on the flexor surface of the forearms; thus
20 injections were given to each subject. Injections
were spaced at 4-cm intervals. The position of each
solution on the forearm varied at random between
subjects and was not known to either subject or
experimenter.

Between 5 and 10 min after the injection, colour
change in each bleb was assessed by J. W. F. in all
cases, and classified as pale, neutral or pink. From
these colour changes, a vasoactivity score for the
pair of blebs was calculated as follows:

<table>
<thead>
<tr>
<th>Colour changes</th>
<th>Vasoactivity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both blebs pale</td>
<td>2</td>
</tr>
<tr>
<td>One pale, one neutral</td>
<td>1</td>
</tr>
<tr>
<td>Both neutral</td>
<td>0</td>
</tr>
<tr>
<td>One pink, one neutral</td>
<td>-1</td>
</tr>
<tr>
<td>Both pink</td>
<td>-2</td>
</tr>
</tbody>
</table>

(Pink and pale did not occur)

Haemorrhagic changes (bleeding or bruising)
were noted. Ten minutes after injection, then
every 5 min for the first hour and every 10 min
thereafter until full recovery, analgesia was tested
by pricking the central area (0.3 mm diameter)
of the bleb with a lancet five times while the subject
looked away. The number of times a sharp sen-
sation was felt was recorded for each bleb. The
time to 50% recovery for each solution was taken
as the time at which the combined sharpness score
for the pair of blebs reached 5 out of 10. If this
occurred between timing intervals the time to 50%
recovery was taken as the mid-point of the interval.
If the score was 9 or 10 at the first test, the time to
50% recovery was taken as zero.

RESULTS

Analgesic activity
At concentrations less than 0.1% there was little
or no difference between the analgesic activities
of the two isomers and saline (fig. 1). At 0.1% there

![Fig. 1. Mean pinprick scores presented as % of recovery against
time for L-mepivacaine (●) and D-mepivacaine (○). A = 2.7%;
B = 0.9%; C = 0.3%; D = 0.1%; E = 0.05%; F = 0.033%;
G = 0.011%; H = NaCl. n = 14 for each point except NaCl and
0.3%, where n = 28.](https://academic.oup.com/bja/article-abstract/53/11/1211/246575)
was some analgesic activity which wore off within 20 min, but no discernible difference between the isomers. At 0.3, 0.9 and 2.7% concentrations, analgesic activity of the L isomer was greater, the discrepancy between the isomers increasing with concentration. Complete analgesia (0% recovery in all subjects) occurred at 0.3% only with L-mepivacaine, and at higher concentrations lasted longer with L- than with D-mepivacaine.

**Duration of action**

Recovery was complete or almost so within 2 h after the injection at all concentrations. The times to 50% recovery of all solutions are shown in figure 2. These form sigmoid log dose–duration curves for both the L and D isomers. The duration of action of both isomers was very brief at concentrations up to 0.1%. At higher concentrations, L-mepivacaine was longer acting than D-mepivacaine, and this difference increased with increasing concentration, making the slope of the log dose–duration curve steeper for L-mepivacaine. The upper asymptote of the log dose–duration curve for D-mepivacaine appears to lie at about 40 min, while that for L-mepivacaine is above 70 min. The duration of action of the racemic mixture, over the range of concentrations tested, lies between the two isomers.

The central regions of the log dose–duration curves were subjected to analysis of variance using the GLIM3 linear modelling computer program (Baker and Nelder, 1978) which can fit multiple regression lines to the data on the principle of least squares. Linearity of the log dose–duration curves was checked by demonstrating no significant difference in residual variance from a model which allowed curvature. There was considerable inter-subject variation in 50% recovery time, and this was found to be highly significant ($P<0.01$, $F$ test). Subjects appeared to respond to changes in concentration in much the same way, but differed in their susceptibility. This led to the parallel log dose–duration lines model shown in figure 3. However, the slopes did differ between the preparations of L-, D- and racemic mepivacaine (fig. 3D).

**Fig. 2.** Mean duration of action for L-mepivacaine (—), D-mepivacaine (---), and racemic mepivacaine (—). Vertical bars represent SEM. Differences between L- and D-mepivacaine at given concentrations: *$P<0.05$; ****$P<0.0001$ (paired sample two-tailed $t$ tests).

**Fig. 3.** Time to 50% recovery over middle range of concentrations. Regression lines calculated by GLIM3 linear modelling computer program. Panels A–C = 14 individual lines, taking account of subject variation, for L- (A), D- (B) and racemic (C) mepivacaine. Panel D = mean positions of lines for L-, D- and racemic mepivacaine. Slopes (min per log unit of concentration) (SEM = ± 2.58): $L$, $b = 22.67$; $D$, $b = 11.87$; DL, $b = 16.01$. 
Vascular effects

Vascular effects, as judged by local colour changes, were in all cases transient, and in no case did permanent tissue damage occur. Haemorrhagic changes occurred in 16 of 28 injections of 2.7% L-mepivacaine, and in eight of 28 injections of 2.7% D-mepivacaine. Haemorrhagic changes occurred only four times after the remaining 532 injections, and were apparently unrelated to dose and subject, although all four occurred with L-mepivacaine. The probability of this occurring by chance if the four haemorrhagic changes were equally likely to have been associated with any of the 532 injections is $P = 0.018$.

Vasoactivity varied with concentration as shown in figure 4. Vasodilatation was most frequent at the 2.7% concentration of L-mepivacaine. Comparing the vasoactivity scores within subjects, the vasodilator activity of L-mepivacaine was significantly greater than that of D-mepivacaine at 0.9 and 2.7% concentrations ($P < 0.01$), Wilcoxon's test for pair differences). Both L- and D-mepivacaine showed vasoconstrictor activity which appeared to be maximal at a concentration of 0.1%, but was still significantly greater than that of saline at 0.011% ($P < 0.05$).

No significant difference in vasoconstrictor activity was demonstrated between the L and D isomers at any of the concentrations tested individually, nor taking concentrations 0.011–0.3% as a group, although in four of the five vasoconstrictor concentrations, L-mepivacaine showed greater activity. Racemic mepivacaine produced colour changes similar to those caused by the L isomer.

DISCUSSION

The prolonged duration of action of L- compared with D-mepivacaine confirms the results of other investigations (Adler, Adler and Åberg, 1969; Åberg and Adler, 1970; Åberg, 1972). The sigmoid nature of the log dose-duration curves, the demonstration of a central linear region which varies in slope between isomers, and the existence of different asymptotes for maximal duration of action, show that there is some difference between the pharmacological activity profiles of the two isomers, rather than a general difference in potency which would have resulted in a parallel shift along the log dose axis.

It was postulated earlier that this difference lay in vascular activity, but the present results do not demonstrate a significant difference in vasoconstrictor activity which could account for the differences in duration of action. L-Mepivacaine was shown to be significantly more vasodilator than D-mepivacaine at high concentrations, but this should result in a more rapid washout, unless it is also associated with an increase in capillary permeability, local oedema and hence reduction of capillary circulation. This is known to occur with irritant concentrations of local anaesthetics (Luduena, 1969), and the high frequency of
haemorrhagic changes observed in the present study indicates that 2.7% mepivacaine may produce local irritation (Reynolds, Bryson and Nicholas, 1976) which is more common with the L isomer than with the D.

Comparing figures 2 and 4, it is evident that the occurrence of vasoconstriction does not coincide with maximum analgesic activity, but with lower concentrations. However, in the area around a high concentration, diffusion may produce the lower vasoconstrictor concentrations. This is supported by the fact that pale rings were frequently seen around the pink blebs as time went on. Where pallor (vasoconstriction) occurs at the centre of a bleb, a longer duration of action for a given drug and dose might be expected. This was tested by including the vasoactivity score as a covariate in the log dose-duration model. A small effect in the expected direction was noted, but this was not statistically significant. L- and D-mepivacaine did not differ significantly in this respect. However, there may be factors other than vasoactivity to explain the prolonged duration of action of L-mepivacaine. The rate of diffusion away from the injection site has been shown to be greater for tritiated D- than for L-mepivacaine in guineapig skin (Åberg, 1972), a difference still being present when the effect of capillary circulation washout was eliminated by killing the guineapig just before the injection. It was suggested that the L isomer may undergo greater tissue binding than the D. We carried out some preliminary observations on the oral absorption of the two isomers, using the method of Beckett and Triggs (1967). There was no obvious difference between the two isomers in their percentage absorption by the oral mucosa, over a range of isosmotic pH values from 5.4 to 9.0. Thus, absorption by oral mucosa does not demonstrate the postulated differences in tissue binding, but this may be because such absorption is principally influenced by lipid solubility and pKa.

We have demonstrated a clear difference in duration of action between the isomers of mepivacaine, which conforms with the findings of Luduena, Bogado and Tullar (1972). In the present study this difference increased with concentration, but the longer action of the L isomer was not associated with superior vasoconstrictor powers. This is surprising since, first, Åberg and Andersson (1972) showed that, in low concentration, L-mepivacaine had a contractile effect on rat portal vein while the D isomer caused relaxation. Second, there was a clear distinction between the isomers of bupivacaine when vasoactivity and duration were tested intradermally in man (Aps and Reynolds, 1978) while the distinction was less marked in the rat portal vein (Åberg and Wahlström, 1972).

That both isomers of mepivacaine can produce vasoconstriction accords with the superior vasoconstrictor properties of racemic mepivacaine over other local anaesthetics at concentrations used clinically (Reynolds, 1980).

ACKNOWLEDGEMENTS

We thank Mr A. V. Swan of the Department of Community Medicine, St Thomas’s Hospital, for statistical advice, the staff of the Sterile Products Unit, St Thomas’s Hospital Pharmacy, for making up the sterile ampoules, and Dr Gunnar Åberg, of the Ciba-Geigy Corporation, Summit, New Jersey, for the isomers of mepivacaine.

REFERENCES


ETUDE INTRADERMIQUE DE L'AGENT ANESTHESIANT LOCAL ET DES EFFETS VASCULAIRES DES ISOMERES DE LA MEPIVACAINE

RESUME
Nous avons fait des recherches au cours d'une étude à double inconnue portant sur 23 volontaires en bonne santé, pour déterminer la durée d'action et les effets vasculaires de L(+) et de la mepivacaine racémique. Des injections isomoléculaires intradermiques de 0,1 ml d'une gamme de concentrations de chaque agent—comprises entre 0,011% et 2,7%—et de soluté physiologique ont été administrées en double à au moins 14 sujets. On a observé des changements de couleur locaux entre 5 et 10 min après l'injection et l'analgesie à la piqure d'aiguille a été testée à intervalles de 5 min tout de suite après et jusqu'à la récupération totale. Les deux isomères ont été vasoconstricteurs aux concentrations de 0,3% et moins; à des concentration plus fortes, l'isomère L a produit davantage de vasodilatation et de changements hémorragiques. La durée d'action des deux isomères a augmenté avec les concentrations, entre 0,05 et 0,9%, mais l'isomère L a eu une durée d'action nettement plus longue que D à 0,3% et plus. Le logarithme de la courbe dose-duree peut être interprété comme étant linéaire entre 0,1 et 0,9%, la pente de l'isomère L étant deux fois plus prononcée que D. Les résultats obtenus pour la mepivacaine racémique se situent entre ceux des deux isomères. La durée d'analgesie plus longue de la mepivacaine L n'a pas été associée à une puissance vasoconstrictive supérieure.

EINE INTRADERMALSTUDIE DER LOKALANÄSTHESIE- UND GEFÄSSWIRKUNGEN DER ISOMERE VON MEPIVACAINE

ZUSAMMENFASSUNG
Wirkungsdauer und Gefässauswirkungen von L(+)- und D(-)-Mepivacain wurden in einer Doppelblindstudie an 23 gesunden Versuchspersonen untersucht.

BRITISH JOURNAL OF ANAESTHESIA

Isomolar 0,1 ml Intradermalinjektionen einer Reihe von Konzentrationen eines jeden Mittels, von 0,011% bis 2,7%, sowie eine physiologische Kochsalzlösung wurden im Duplicat an mindestens 14 Versuchspersonen verabreicht. Lokale Farbveränderungen wurden 5-10 Min nach der Injektion beobachtet, und anschließend wurde die Empfindlichkeit auf Nadelstiche in 5 Min-Intervallen bis zur völligen Erholung getestet. Beide Isomere waren gässverengend bei Konzentrationen bis zu 0,3%; bei Spitzenkonzentrationen bewirkte das L-Isomer mehr Gefässverweiterung und hämorrhagische Veränderungen. Die Wirkungsdauer beider Isomere stieg bei Konzentrationen zwischen 0,05 und 0,9%, wobei das Gefälle des L-Isomers doppelt so steil war wie das des D-Isomeres. Die Ergebnisse für racemisches Mepivacain lagen zwischen denen der beiden Isomere. Die längere Schmerzlinderungsdauer von L-Mepivacain hatte nichts mit einer überlegenen gässverengenden Kraft zu tun.

UN ESTUDIO INTRADERMAL DE LA ANESTESIA LOCAL Y DE LOS EFECTOS VASCULARES DE LOS ISOMEROS DE LA MEPIVACAINA

SUMARIO
Se investigó la duración de la actividad y los efectos vasculares de L(+) y D(-) y de la mepivacaina racémica, en un estudio de doble anonimato efectuado en 23 voluntarios sanos. Se administraron por duplicado a, por lo menos, 14 sujetos, inyecciones intradermales de 0,1 ml isomolar, en una gama de concentraciones entre 0,011% a 2,7%, para cada agente, así como soluciones salinas fisiológicas. Se observaron cambios locales de color después de los 5-10 min de la inyección y se comprobó la analgesia a los pequeños pinchazos a intervalos de 5 min hasta la recuperación total. A concentraciones de 0,3% e inferiores, ambos isómeros fueron vasoconstrictores; a la máxima concentración el isómero L produjo una mayor vasodilatación y un mayor cambio hemorrágico. La duración de la actividad de ambos isómeros aumentó con la concentración, entre 0,05 y 0,9%, pero la actividad del isómero L fue significativamente de mayor duración que la del D a concentraciones de 3% y de valores superiores. La curva logarítmica de dosis-duración podría interpretarse como lineal entre 0,1 y 0,9%, siendo la pendiente del isómero L doble que la del D. Los resultados para la mepivacaina racémica quedaron comprendidos entre los de los dos isómeros. La mayor duración analgésica de la mepivacaina L no vino asociada con una potencia vasoconstrictora superior.