COMPARISON OF THE VASOACTIVITY OF AMIDE AND ESTER LOCAL ANAESTHETICS

An Intradermal Study

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The intrinsic vasoactivity of a local anaesthetic agent is one of the factors determining its rate of removal from the site of action. Lignocaine, and other amide local anaesthetics, have been shown to possess vasoconstrictor properties, especially at low concentrations (Aps and Reynolds, 1976; Reynolds, Bryson and Nicholas, 1976). Cocaine, an ester-linked agent, produces marked vasoconstriction by inhibition of noradrenaline uptake (Iversen, 1965), although alternative mechanisms such as the mobilization of Ca\(^{2+}\) (Daniel and Wolowyk, 1965) and the release of endogenous catecholamines (Vohra, 1970) may contribute to cocaine-induced smooth muscle contraction in other tissues. The intrinsic vasoactivity of other ester-linked anaesthetics, such as procaine and amethocaine, is less reliably documented.

The intradermal method of measuring local anaesthesia and vasoactivity gives results which are consistent with other methods (Äberg, 1972; Luduena, Bogado and Tullar, 1972; Aps and Reynolds, 1978; Fairley and Reynolds, 1981). Previous intradermal studies in human volunteers (Aps and Reynolds, 1976; Fairley and Reynolds, 1981) have demonstrated the direct action of amide local anaesthetics on cutaneous blood vessels and the effect this may have on the relationship between concentration and duration of action. The present study was designed to compare the vasoactivity, at various concentrations, of two ester-linked local anaesthetics with that of four amide-linked agents, using the intradermal route.

SUBJECTS, MATERIALS AND METHODS

**Solutions**

Each of the six local anaesthetics was prepared as an aqueous solution of the hydrochloride salt, containing 0.1% sodium metabisulphite (to stabilize the esters) and sufficient sodium chloride to render it isosmotic with physiological saline. Ampoules of the solutions were randomly coded and sterilized by autoclaving. The following solutions were administered:

- Procaine hydrochloride
- Amethocaine HCl
- Cinchocaine HCl
- Lignocaine HCl
- Racemic mepivacaine HCl
- Racemic prilocaine HCl
- Sodium chloride

**Subjects**

The subjects were 10 fit adults (eight male) whose ages ranged from 21 to 40 years. One subject was an author (D.G.W.); the others were medical students or medical and laboratory colleagues. All gave informed consent.

**Procedure**

The study was carried out in two parts. In the first, amethocaine, lignocaine and prilocaine (each
at three concentrations) and physiological saline (control solution) were tested in each of the 10 subjects. In the second part, procaine, cinchocaine and mepivacaine each in three concentrations, and saline were tested on the same 10 subjects. The solutions were injected intradermally on the flexor surface of both forearms; each subject received a pair of 0.1-ml injections of each of the 10 solutions, spaced at 40-mm intervals. The position of each solution varied randomly between the subjects and was known to neither subject nor investigator. The appearance of each bleb was noted 5–10 min after injection, by which time the initial distension had disappeared. Colour changes were classified as pink, nil or pale. Any haemorrhagic changes were recorded.

Ten minutes after injection, every 5 min for the first 1 h and subsequently every 10 min until complete recovery, analgesia was assessed by pricking the central area of each bleb with a lancet 5 times while the subject looked away. For each solution, the number of times out of 10 that the prick felt sharp was recorded; the time of 50% recovery was taken as the time at which the sharpness score reached 5 out of 10. If this occurred between two time intervals, the mid-point of the interval was taken. If the initial score at 10 min was 6, 7 or 8, the 50% recovery time was recorded as 5 min; with an initial score of 9 or 10, 50% recovery time was taken to be zero. The results for the control solution from the two parts of the study were combined.

Differences in proportions were analysed using the Chi-squared test with Yates’ correction. The GLIM3 linear modelling computer program (Baker and Nelder, 1978) was used to calculate the slopes of the linear regression lines of log concentration v. duration of action for each drug in each subject; the significance of the differences between the mean slopes for each drug was evaluated by a one-way analysis of variance, with logarithmic transformation of the slopes to decrease differences in their standard deviations. A value of $P$ less than 0.05 was considered statistically significant.

**RESULTS**

**Vascular effects**

All local colour changes were transient and no permanent tissue damage occurred. Only two haemorrhagic changes were observed, one with 1.0% lignocaine, the other with 0.1% prilocaine.

The vasoactivity of the six agents, expressed as
percentage frequency of local colour changes at different concentrations, is shown in figure 1. Procaine and amethocaine both showed vasodilator activity, which was significantly greater than that produced by saline \((P < 0.05)\), at both intermediate and highest concentrations. No vasoconstriction occurred with procaine at any concentration; that shown by amethocaine was not concentration-dependent and did not differ significantly from the effects of the saline.

There was a marked difference in appearance between the procaine and amethocaine injection sites. In all instances where procaine produced vasodilatation, the area of redness was well demarcated and showed no local oedema. In contrast, the vasodilatation produced by amethocaine extended over a larger area with irregular margins — a typical “flare” response; in addition, weal formation occurred at 12 injection sites at the lowest amethocaine concentration, 16 at the intermediate and 16 at the highest concentration.

The four amide local anaesthetics all produced less vasodilatation at all concentrations than did saline. All three concentrations of lignocaine and mepivacaine produced vasoconstriction significantly more frequently than saline \((P < 0.05\) for lignocaine; \(P < 0.001\) for mepivacaine). Significant vasoconstriction was only observed for cinchocaine at 0.01\%, \(P < 0.05\) and prilocaine at 1.0\% \((P < 0.001)\), compared with saline. Vasoconstrictor activity declined with increasing concentration for lignocaine, mepivacaine and cinchocaine, although this trend was not significant.

Taking the results for both ester agents together, 108 out of 120 blebs showed vasodilatation, compared with 49 out of 240 blebs for the four amide agents combined \((P < 0.001)\).

**Analgesic activity**

For each time of testing, the mean pinprick score for the 10 subjects was converted to a percentage (full recovery = 100\%). Figure 2 is a graphical representation of these results with time, for all three concentrations of the six agents, and for saline. The analgesic activity of 0.1\% prilocaine and 0.01\% cinchocaine differed little from that produced by saline. There was no difference between the analgesic activity of 0.1\% and 0.3\% procaine, but in all other instances analgesic activity increased with concentration. Only 1.0\% lignocaine produced complete analgesia (0\% recovery in all subjects at 10 min). A comparison of figures 1 and 2 demonstrates that there was no relationship between vasoactivity and initial analgesic activity.

**Duration of action**

Complete recovery from all injections (permanent pinprick score of 5 in all subjects) had occurred by 80 min. The mean 50\% recovery times of the different concentrations of the six agents plotted against the concentration on a logarithmic scale is shown in figure 3. The concentrations used were chosen to lie on the central linear portion of the respective log dose–duration curves; this appears to have been achieved with all agents except procaine, although the lowest concentration of procaine still had a 50\% recovery time well above that of the control solution.

Figure 4 shows the regression lines of log concentration \(v\). duration of action for each agent; concentration is expressed as a multiple of the lowest concentration to eliminate differences in potency. There was a highly significant difference between the slopes \((P < 0.001; F\) test). In general, the steepness of the slope reflected the observed vasoactivity of the agent; there was a significant difference \((P < 0.05)\) between the slopes of procaine and mepivacaine, cinchocaine and prilocaine, and between those of amethocaine and mepivacaine.

**DISCUSSION**

The relationship between the vasoactivity of a local anaesthetic agent and its duration of action is not straightforward. Using the intradermal route, in which systemic, reflex and regional effects are eliminated, Aps and Reynolds (1976) found a greater incidence of vasoconstriction with 0.125\% bupivacaine than with 0.25\% bupivacaine; the duration of action was not significantly different, indicating that the effect of increasing concentration was counteracted by the reduced vasoconstriction. \(L(-)\) Bupivacaine was longer acting than \(D(+)\) bupivacaine in concentrations of 0.48–3.84 mmol litre\(^{-1}\) (0.16–1.25\%), and over this range, the \(L(-)\) isomer showed significantly greater vasoconstriction (Aps and Reynolds, 1978). Luduena (1969), also, concluded that the increased duration of action of \(L(+)\) prilocaine, \(L(+)\) mepivacaine and \(L(-)\) bupivacaine, compared with their optical isomers, was solely attributable to the production of greater vasoconstriction. In contrast Fairley and Reynolds...
(1981), comparing L(+) and D(−) mepivacaine, found that the increase in the duration of action of the L(+) isomer in concentrations of 0.1–0.9% was not associated with greater vasoconstriction; indeed, at the highest concentration L(+) mepivacaine was the more potent vasodilator. In the present study, the vasoconstriction seen with mepivacaine, was associated with differences in the mean slope of the log dose–duration plots in the expected direction compared with cinchocaine, lignocaine and prilocaine, with which the vasoactivity was less marked and more variable. With none of the six agents was the vasoactivity as concentration-dependent as in previous intradermal studies (Aps and Reynolds, 1976; Reynolds, Bryson and Nicholas, 1976; Fairley and Reynolds, 1981). This may have been the result of the presence of sodium metabisulphite in the solutions; certainly, the saline–metabisulphite control solution produced a much higher incidence of vasodilatation (65%) than had been observed previously with plain 0.9% saline (0–10%). The addition of metabisulphite also appeared to increase the pain of the injection.

There are few reports of the effects of the intradermal administration of ester-linked local anaesthetics in man. Padfield (1967) compared 2%
prilocaine, 2% lignocaine and 2% procaine intradermally in human volunteers and found that these agents were equi-analgesic shortly after injection, with procaine having the shortest, and prilocaine the longest duration of action. There was a 60% incidence of vasodilatation with procaine. The action of ester-linked local anaesthetics on other vascular tissues, as well as on smooth muscle from other organs, appears to vary. In the rabbit aortic strip preparation, the contraction produced by acetylcholine, histamine, noradrenaline or 5-hydroxytryptamine was inhibited in a dose-dependent manner by procaine and amethocaine in concentrations ranging from 1 μmol litre⁻¹ to 1 mmol litre⁻¹, although the potencies for these inhibitory actions were not related to local anaesthetic potency (Altura and Altura, 1974). It was postulated that these effects

Fig. 4. Mean regression lines for duration of action calculated by the GLIM3 linear modelling computer. Concentration expressed as multiples of the lowest concentration for each agent. Slope values (min per log unit of concentration) ± SEM: Procaine, \( b = 11.41 ± 2.31 \); amethocaine, \( b = 12.77 ± 2.12 \); lignocaine, \( b = 18.47 ± 2.53 \); cinchocaine, \( b = 21.05 ± 2.94 \); prilocaine, \( b = 22.70 ± 3.09 \); mepivacaine, \( b = 31.12 ± 5.51 \).
might be mediated by “alteration in intracellular metabolism”.

Jacobs and Keating (1974) demonstrated that procaine, in concentrations up to 20 mmol litre$^{-1}$, facilitated or induced electrical and mechanical activity in sheep carotid artery strips, but in high concentration (80 mmol litre$^{-1}$) blocked electrical activity and caused contraction followed by relaxation. Blockade of Ca$^{2+}$ entry channels was thought to be the mechanism for the relaxant effect; procaine is known to inhibit Ca$^{2+}$ exchange in uterine smooth muscle (Feinstein, 1966). Åberg (1972) suggested that the smooth muscle relaxant effect of high concentrations of local anaesthetics is the result of inhibition of Ca$^{2+}$ release by stabilization of the membrane surrounding Ca$^{2+}$ stores.

The local oedema that we observed frequently with amethocaine may have decreased capillary blood flow and retarded absorption (Luduena, 1969). However, our results do not support this; any such effect may have been counteracted by the vasodilatation observed; in no instance was the weal blanched.

The duration of action of procaine and amethocaine might be decreased by plasma cholinesterase acting locally. However, Foldes and McNall (1952) found that the duration of action of procaine and chlorprocaine, given via the intradermal route in man, was not prolonged by the addition of a plasma cholinesterase inhibitor either with or without adrenaline. This indicates that, intradermally, in situ hydrolysis of ester-linked local anaesthetics is not a factor determining the duration of action.

It would appear that vasodilatation is a feature of ester-linked local anaesthetics even at low concentrations, in contrast to amides. In the clinical setting, intrinsic vasoconstriction enhances local anaesthetic activity while diminishing toxicity and, thus, contributes to the superior performance of the amides.

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REFERENCES