EFFECTS OF INTRADERMAL LIGNOCAINE AND MEPIVACAINE ON HUMAN CUTANEOUS CIRCULATION IN AREAS WITH HISTAMINE-INDUCED NEUROGENIC INFLAMMATION

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SUMMARY
The vasoconstrictive potencies of lignocaine and mepivacaine were studied in human skin. Lignocaine 0.5%, 0.25% mepivacaine (both plain and mixed with adrenaline or ornipressin), and saline (control) were injected intradermally into skin areas with enhanced perfusion (1% histamine prick). Flux was determined by scanning laser Doppler flowmetry and the size of any eventual pallor was measured. The artificially enhanced flux was increased further by saline, but not altered by the local anaesthetics. Mepivacaine produced a small pallor. Both vasoconstrictors reduced flux significantly and produced a larger pallor. We conclude that both local anaesthetics have only a mild constrictive effect on precapillary vessels. Mepivacaine has, additionally, a constrictor effect on the postcapillary vascular bed, causing pallor. An effective precapillary constriction which reduces the capillary clearance of both local anaesthetics can be achieved only by addition of a vasoconstrictor. (Br. J. Anaesth. 1993; 70: 167-172)

KEY WORDS
Anaesthetics, local: lignocaine, mepivacaine, vasoactivity. Skin: dermal blood flow.

Most modern local anaesthetics appear to be vasodilators in clinical concentrations and vasoconstrictor agents such as catecholamines or vasopressin derivatives are usually added. The same local anaesthetics in small concentrations, however, apparently constrict vessels [1].

The vasoactive properties of local anaesthetics have been examined by many different experimental approaches. Methods to estimate cutaneous circulation in human skin include visual inspection of colour changes [2-5], thermal clearance [6] and laser Doppler flowmetry [7, 8]. Results are generally inconsistent and difficult to interpret.

Although the skin is easily accessible for examination of vasoactivity of drugs, it presents several difficulties for the interpretation of the results. First, at rest, capillary perfusion of the skin is so low that vasoconstrictor effects are difficult to interpret [8]. Furthermore, even a minute injury such as the insertion of a fine needle [7, 9] or the injection of a small quantity of saline [7, 9] produces a rapid and marked increase in blood flow within a radius of up to several centimetres. This is caused by release of vasoactive substances (peptides, histamine) from stimulated nociceptors and mast cells (neurogenic inflammation; see [10] for a review). Consequently, the injection of a vasoconstrictive agent produces both dilatation and constriction in unpredictable proportions. For example, the intracutaneous (i.c.) injection of ropivacaine in a concentration thought to cause vasoconstriction enhances cutaneous perfusion, although the flux increase is less pronounced than that caused by saline [7].

In an attempt to find a stable and reproducible condition in which vasoconstriction can be measured, cutaneous vasodilatation induced by local heating has been used [8]. In this condition, the s.c. injection of 0.5% lignocaine causes a significant reduction in cutaneous blood flow, which is reduced further if adrenaline or ornipressin is added [8]. However, this does not pertain during regional anaesthesia, in which tissue is not heated, but rather stimulated by mechanical trauma and chemical irritation. Therefore a stable neurogenic inflammation of the skin seems to be a more natural condition to test local anaesthetics.

We have examined the vasoactive properties of 0.5% lignocaine and 0.25% racemic mepivacaine in skin areas with neurogenic inflammation induced by histamine. In these concentrations, lignocaine is thought to have vasodilator and mepivacaine vasoconstrictor properties [11]. Both drugs were used plain and in combination with adrenaline or ornipressin, and they were compared with saline as control. The induced changes in cutaneous circulation were determined by scanning laser Doppler flowmetry [12] and by the measurement of pallor and flare areas.

SUBJECTS AND METHODS
The following drugs were used: saline (0.9% NaCl, Braun Melsungen); lignocaine (0.5% Xylocain, Astra); mepivacaine (0.5% Scandicain, Astra); ornipressin (Por 8, Sandoz); adrenaline (Suprarenin 1:1000, Hoechst); histamine (1% histamine hydro-
chloride, Beecham Wülfing). Mepivacaine was diluted in saline; solutions containing vasoconstrictors were freshly prepared for each experimental day.

We studied 24 healthy volunteers (10 male) (mean age 25.6 yr, range 22–32 yr) who had given informed consent. In 12 subjects, lignocaine was examined; this group received saline (control), plain 0.5 % lignocaine (L), 0.5 % lignocaine with adrenaline 5 μg ml⁻¹ (L + A) and 0.5 % lignocaine with ornipressin 0.1 μg ml⁻¹ (L + O). In the other group (n = 12), mepivacaine was examined: saline (control), plain 0.25 % mepivacaine (M), 0.25 % mepivacaine with adrenaline 5 μg ml⁻¹ (M + A) and 0.25 % mepivacaine with ornipressin 0.1 μg ml⁻¹ (M + O).

Neurogenic inflammation was elicited by pricking 1 % histamine into the skin. Cutaneous perfusion was monitored by a two-channel laser Doppler flowmeter (Moore Instruments MFD3) combined with an automatic scanning device [12]. The approximate area of flare was estimated by measuring its long and short axes and calculating the area of an ellipse. The outline of a pallor was transferred to transparent film and its area determined by weighing the cutting.

Before an experiment, four test areas were selected on both dorsal forearms (fig. 1A); the test areas were not randomized as, in this region, basal capillary perfusion and the response to histamine are comparable. The scanning device was fixed to the area by double adhesive tape and flux was measured at a rate of one per 25 s at each of 10 points 2 mm apart (fig. 1B). After baseline flux had been recorded for 3 min, histamine was pricked at point 1. Flux recording was continued for another 5 min, then the axes of the flare were measured and the size of any eventual pallor was transferred to transparent film. After another 5 min, the final size of the pallor was recorded. All flux data were collected continuously by computer.

After an experiment, basal flux values, maximal flux after histamine prick and maximal deviation from histamine flux during the 5 min after injection of the test substances were determined for each measurement point. Maximal flux changes elicited by the administration of histamine or the test solutions were expressed as per cent of basal flux (= 100 %). In addition, the latencies of 50 % maximal flux reduction were determined for the solutions containing additives. For statistical analysis, the flux values at measurement point 4 were selected, because at this point neurogenic inflammation and the vasoconstrictor effects of the drugs combine without being disturbed by the tissue pressure of the histamine weal or of the injection. For each group, differences between histamine-enhanced flux and drug-induced flux responses and the differences in the size of pallors were tested by the Wilcoxon signed rank test for paired replicates. In order to
RESULTS

In all subjects, histamine caused a rapid increase in cutaneous perfusion which, on average, was more than 10-fold baseline flux near the prick; at increasing distance from the prick, flux values decreased and reached about four times baseline at point 10 (figs 2–4). There were great interindividual variations in the reactivity to histamine. The average flare size was 6.94 (SD 2.54) cm² in group L and 7.22 (2.22) cm² in group M. In both groups, the injection of saline produced a further statistically significant increase in perfusion (figs 3, 4). The injection of plain lignocaine caused a slight increase in perfusion in 11 of the 12 test subjects; no colour changes of the skin around the injection occurred. Plain mepivacaine did not change perfusion between the histamine prick and the injection; in the periphery of neurogenic inflammation, 10 of the 12 subjects produced a small flux reduction. Nine subjects developed a distinct pallor around the mepivacaine injection (fig. 5). Both adrenaline and ornipressin, when added to the local anaesthetic, caused a decrease in skin perfusion (statistically significant for L + A, L + O and M + A) which reached baseline values around the injection (figs 3, 4). In both groups, the flux decrease tended to develop more rapidly with adrenaline than with ornipressin (fig. 6) and it was accompanied by a marked pallor. Five minutes after the injection, the pallor had reached almost its final size, which was the same for adrenaline and ornipressin, when added to lignocaine; however, when added to mepivacaine, ornipressin produced, in all cases, a smaller pallor (fig. 5). The pallor produced by plain mepivacaine was in all cases smaller than that elicited by the two vasoconstrictors.

DISCUSSION

Histamine-induced neurogenic inflammation of the skin has proved to be a good experimental method for studying vasoactive properties of local anaesthetics. It provides a stable condition of enhanced blood flow lasting up to 1 h and allows observation of both vasodilatation and vasoconstriction. The vascular effects of small quantities of local anaesthetics, when injected into the skin with artificially enhanced blood flow, result from three separate mechanisms: the initial mechanical trauma and chemical irritation stimulate nociceptors and cause additional vasodilatation; the local anaesthetic blocks sympathetic axons and reduces the thermoregulatory vasoconstrictor tone (true for hands and feet); the local anaesthetic has intrinsic effects on vascular smooth muscle, either direct or through mediators.

Assuming that the injection of saline causes only neurogenic inflammation, a local anaesthetic without intrinsic vasoactivity should cause a comparable increase in blood flow. In this study, 0.5 % lignocaine increased flux less than saline and 0.25 %
mepivacaine even tended to reduce flux in the periphery of neurogenic inflammation. This indicates that both local anaesthetics in the concentrations used have a mild intrinsic constrictor effect on the precapillary side of human skin circulation. A decrease in cutaneous blood flow caused by s.c. 0.5% lignocaine has been observed earlier in a study with heat-induced vasodilatation [8]. Mesnil du Rochemont and Hensel [6], using a thermal clearance method with intradermal injection of 1% lignocaine or 1% mepivacaine, found a reduction in flow following an initial increase of about 20 min duration (probably the effect of the injection trauma). Other studies using laser Doppler flowmetry found, in comparison with saline, larger flux increases with 1% lignocaine [7, 11]; conversely 0.5% mepivacaine produced smaller flux increases [11].

Although we found that 0.5% lignocaine and 0.25% mepivacaine did not alter artificially enhanced perfusion to a significant extent, both drugs differed in one important aspect: in the majority of cases, mepivacaine produced a small pallor whereas lignocaine did not. This is puzzling, because flux in the pallor area was still considerably enhanced and it was far from the baseline values which were reached when vasoconstrictors were...
added. The dissociation between flux and colour is probably caused by the fact that the flowmeter measures the volume of blood per minute passing through the vertically arranged capillary loops, whereas skin colour is determined mainly by the volume of blood present within the deeper horizontal networks of the venous plexus. If a drug has a differential effect on precapillary and postcapillary vessels, a large flux in a pale skin could result. Therefore it is possible that 0.25% mepivacaine has a stronger constrictive effect on venules and veins than on arterioles and precapillary sphincters. When a small concentration of mepivacaine is injected into untreated skin, trauma-elicited neurogenic inflammation overcomes the mild constrictor action on precapillary vessels, leading to a flux increase [6, 11]. Simultaneously, in the postcapillary vascular bed, vasoconstriction prevails; the resulting pallor has been observed in several studies [3, 5]. In this study, no pallor was observed with 0.5% lignocaine, indicating that the constrictor effect on the postcapillary vessels was less marked. A differential effect on the arterial and venous vascular beds has also been observed when lignocaine and mepivacaine were infused into the brachial artery of human volunteers [13]; no direct effects on vascular resistance occurred, whereas venous tone was increased markedly. The differential effects of mepivacaine on arterial and venous vascular beds could be explained by the existence of two different routes of action. When injected in small concentrations into the extracellular space, the local anaesthetic penetrates the adventitia and has a direct constrictor effect on vascular smooth muscle. At the same time, the local anaesthetic is leaking through the capillary walls and drains away through venules and veins of the venular plexus. There, it could exert an additional indirect effect on venous smooth muscle mediated by the endothelium; it could either stimulate the release of endothelins or inhibit the release of endothelium-derived relaxing factor (EDRF). In man, the i.a. injection of an inhibitor of EDRF synthesis reduces arterial flow [14], but the i.v. injection does not by itself have a vasoconstrictor effect [15]. In contrast, the intradermal injection of endothelin 1 causes a reduction in cutaneous perfusion, together with a small pallor [16]. Therefore, it could be that mepivacaine stimulates the endothelium to release endothelins. However, the absence of an increase in vascular resistance during i.a. infusion of mepivacaine when the sympathetic system is blocked [13] does not support a simple endothelium-mediated action of local anaesthetics.

When added to 0.5% lignocaine, both adrenaline and ornipressin caused a rapid decrease in flux to baseline values and they produced a pallor of comparable size. In combination with 0.25% mepivacaine, both vasoconstrictors produced a similar rapid flux decrease; ornipressin, however, produced a significantly smaller pallor. A similar difference could not be seen in the amplitude of the spatial extent of flux reduction (compare figures 3 and 4). Thus we conclude that mepivacaine antagonizes the action of ornipressin mainly in the postcapillary bed. The existence of an antagonism between various local anaesthetics and vasoconstrictors, including felypressin, has been observed in several studies [17, 18].

The ratio between dilator and constrictor effects on precapillary vessels may be different in other vascular beds in which nociceptor density and vasoactivity of local anaesthetics may differ. In the extradermal space of the dog, plain 2% lignocaine causes a marked depression in spinal blood flow (microsphere flowmetry [19]), whilst in man the addition of adrenaline significantly reduces the leakage of the drug into the circulation and prolongs anaesthesia [20].

The present data give further support to the view of Covino [21] that vasoconstrictive and anaesthetic potency of a local anaesthetic are unrelated.

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