Dose–response relation of ornipressin with regard to vasoconstriction in human skin

H. FRUHSTORFER AND M. HEISLER

SUMMARY

We have studied the vasoconstrictor potency of ornipressin in the skin of 30 volunteers. Subjects received intradermal injections (50 μl) of five different concentrations of ornipressin (10⁻⁴, 10⁻³, 10⁻² u. ml⁻¹ in 0.9% saline) and plain 0.9% saline as a control. Immediately before injection, basal cutaneous blood flow in the test field was enhanced with 1% histamine. Capillary flux was measured by laser Doppler flowmetry and the size of pallor was determined. Ornipressin was effective at 10⁻⁴ u. ml⁻¹ and had its largest constrictor effect at concentrations of 10⁻² and 10⁻¹ u. ml⁻¹. Larger concentrations were less effective in reducing capillary flux. Interindividually, the most effective concentration varied between 10⁻³ and 10⁻¹ u. ml⁻¹. The size of pallor grew in a dose-dependent manner but 10⁻¹ u. ml⁻¹ always caused reddening in its centre. Capacitance vessels (skin colour) were more sensitive to ornipressin than resistance vessels (capillary flux). The shortest latency of vasoconstriction was obtained with concentrations of 10⁻³ and 10⁻¹ u. ml⁻¹. The results of this study suggest that for haemostasis of the skin a concentration of ornipressin 10⁻² u. ml⁻¹ is useful; this low concentration would reduce total dosage and unwanted side effects. (Br. J. Anaesth. 1994; 73: 220–224)

KEY WORDS


Ornipressin (ornithine-8-vasopressin) is a synthetic vasopressin with low antidiuretic activity [1]. It is used as a vasoconstrictor in surgery for haemostasis and in regional anaesthesia for prolongation of nerve block. When introduced, the advantage of ornipressin over catecholamines was thought to be its lower local and systemic toxicity [2–4]. Although there are few controlled clinical studies on the effectiveness of ornipressin, its vasoconstrictor potency is generally regarded as similar to that of adrenaline [5–7] whereas its latency has been found to be somewhat longer [7]. Clinical experience with ornipressin has generally been favourable, but this has been marred by recent reports of fatal cardiovascular complications [8].

According to the manufacturer’s recommenda-

H FRUHSTORFER, M.D., M. HEISLER, M.D., Institute of Physiology, University of Marburg, D-35033 Marburg, Germany. Accepted for Publication: January 29, 1994.

Correspondence to H. F.
Fig. 1. Basal flux, increase in flux after the 1% histamine prick and vasoconstriction elicited by injection of 50 μl of ornipressin 10⁶ u. ml⁻¹. On the right, the measurement line (length 18 mm) shows the two treatment points and the outlines of pallor and reddening (dark) produced by ornipressin within the histamine-elicited flare.

of each of the five concentrations of ornipressin and saline (control) using needles with a diameter of 0.36 mm (Becton Dickinson Micro-fine IV). Six test areas were selected on both dorsal forearms, three on each side. The six solutions were allocated randomly over the test areas between the subjects, who did not know which solution they received.

In each test area, cutaneous blood flow was monitored at 10 points along a longitudinal line of 18 mm in length by a laser Doppler flowmeter (Moore MBF 3D) combined with an automatic scanner ([11] see fig. 1). On each day, the system was calibrated with a motility standard. After having recorded basal flux for 3 min, 1% histamine was pricked into the skin near to the most distal recording point (= point 1). After neurogenic inflammation had developed fully, the test solution was injected intradermally between points 5 and 6, 9 mm proximal to the histamine prick. Then, flux monitoring was continued for another 15 min. The flux data from each of the 10 points were stored in a computer. After each recording, the outline of any eventual pallor within the histamine-elicited flare was transferred to transparent film; its size was determined by weighing the cutting.

With every experiment, for each of the 10 recording points, maximal flux after histamine prick and minimal flux after injection of the test solution were determined and expressed as percentage of basal flux (= 100). Additionally, the time between injection and the moment of 50% reduction in flux was measured. A dose–response curve was compiled from the average minimal flux values measured at points 5 and 6. As at the outset of the study the real form of the dose–response curve was unknown, a hypothesis concerning the most effective concentration could not be stated. Therefore, the differences in constrictive effects between all pairs of successive concentrations were tested using the Wilcoxon matched pairs signed rank test. Because of the explorative character of the study, the calculated P values should not be interpreted in a statistically confirmative sense.

RESULTS

Histamine caused a rapid increase in flux which, near the prick, reached about 10 times baseline values and which, on average, decreased to four times baseline.

FIG. 2. Median maximal flux after the histamine prick (---) and median minimal flux after injection of saline (Control) and the ornipressin solutions (u. ml⁻¹) (--). Data from each of the 10 measurement points are percentage of basal flux (= 100%). Histamine prick is at point 1, injection is between points 5 and 6 (n = 30).
Fig. 3. Mean latency of 50% reduction in flux for the different concentrations of ornipressin near the point of injection (means from points 5 and 6) (figures are SD) (n = 30).

Fig. 4. Mean (SD) area of the ornipressin elicited pallor and reddening (dark) for the different concentrations of ornipressin (n = 30).

Fig. 5. Mean (SD) minimal flux (means from points 5 and 6) after injection of saline (Control) and ornipressin solutions. P values (Wilcoxon signed rank test) are shown (n = 30).

Fig. 6. Mean (SD) minimal flux (means from points 5 and 6) as a function of ornipressin concentration, for five ornipressin-sensitive (------) and 13 ornipressin-insensitive (-----) subjects.

values 18 mm distant from it (figs 1 and 2). Injection of saline did not alter the increase in flux caused by histamine (fig. 2). Ornipressin caused a reduction in flux even with the lowest concentration (10^{-4} u. ml^{-1}), fig. 2). Concentrations of 10^{-3} and 10^{-1} u. ml^{-1} were most effective and reduced flux close to baseline values. The largest concentration (10^{0} u. ml^{-1}) was less effective and minimal flux was more than three times baseline (fig. 2). With concentrations of 10^{-2} and 10^{-1} u. ml^{-1}, a 50% reduction in flux was reached after about 30 s near the injection point. This latency was longer with both larger and smaller concentrations and at more distant recording points (fig. 3). Ornipressin caused a pallor, which was larger with higher concentrations (fig. 4). A distinct reddening in the centre of the pallor was produced by the two largest concentrations (10^{-1} u. ml^{-1} in six subjects and 10^{0} u. ml^{-1} in all subjects) (figs 1 and 4). This reddening was not reflected in a correspondingly large increase in flux. The injection of the largest concentration caused strong stinging pain in all subjects.

Compiling a dose–response curve for recording points 5 and 6, the greatest mean reduction in flux was obtained with ornipressin concentrations of 10^{-2} and 10^{-1} u. ml^{-1} (fig. 5). Differences in flux between adjacent concentrations of ornipressin were significant (P < 0.05), except for the difference between 10^{-1} and 10^{-2} u. ml^{-1} (fig. 5). Twelve subjects had peak vasoconstriction at 10^{-2} u. ml^{-1}, 13 subjects at 10^{-1} u. ml^{-1}, whereas in five subjects peak vasoconstriction was obtained with 10^{-3} u. ml^{-1} (fig. 6).

DISCUSSION

The results of this study showed that in human skin, ornipressin was effective at concentrations as low as 10^{-4} u. ml^{-1}. The concentrations with the largest constrictor effect were 10^{-2} and 10^{-1} u. ml^{-1}; higher concentrations were less effective. As ornipressin diffused away from the point of injection, the spread of the vasoconstrictor concentration was dose-dependent (i.e. the greater the concentration the larger was the area of constriction). In its centre, however, high concentrations may reduce and even delay vasoconstriction.

The U-shaped dose–response relationship may be explained by two inverse actions of ornipressin: low concentrations constrict both resistance and capaci-
tance vessels causing a decrease in capillary flux and skin pallor. When ornipressin concentration increases, the constrictor effect becomes maximal. Finally, with still higher concentrations the opposite effect appears and vasodilatation is superimposed causing a moderate increase in flux and conspicuous reddening. Blood vessels probably have two receptor subtypes for the antidiuretic hormone arginine-8-vasopressin: V1 receptors mediate constriction whereas extraenal V2-like receptors situated in smooth muscle or endothelial cells mediate dilatation [13]. Therefore, in human muscle, in a vascular bed with predominantly V2 receptors, arginine-8-vasopressin causes a dose-dependent increase in blood flow whereas the same plasma concentrations reduce blood flow in the fingers [14], probably because the V1; V2 ratio is in favour of V1 receptors. In contrast with the natural antidiuretic hormone, ornithine-8-vasopressin has a reduced V2 receptor affinity and is therefore mainly a vasoconstrictor [1]. With excessively high concentrations, when V1 receptors are saturated, V2-mediated vasodilatation becomes evident.

An alternative explanation for the U-shaped dose–response relation could be the dose-dependent release of vasodilator substances from mast cells and nociceptors. Ornipressin is a cationic peptide which may directly stimulate mast cells by receptor-independent activation of G-proteins [15]. In addition, ornipressin stimulates nociceptors (which can be inferred from the pain it elicits) at the largest concentration (10⁶ u. ml⁻¹), the solvent or the preservative could have a similar effect.

It is noticeable that in the skin, small volumes of ornipressin produced colour and flux changes which did not correspond in size: at small concentrations the area of pallor exceeded the area of reduced flux, whereas large concentrations produced within the pallor a reddening without a correspondingly large increase in flux (see fig. 1; compare figs 2 and 4). This phenomenon can be explained by greater response of capacitance vessels which determine the colour of the skin by the amount of blood contained. Ornipressin, injected into the extracellular space, penetrates the adventitia and has a direct effect on the smooth muscle of both resistance and capacitance vessels; simultaneously, it is drained away by the capillaries and reaches the venous plexus, where it could exert an additional effect via endothelium. Alternatively, capacitance vessels could have a greater sensitivity to ornipressin. The frequent clinical observation of facial pallor without conspicuous cardiovascular changes after administration of ornipressin supports the latter assumption.

Although ornipressin has a high vasoconstrictor potency over a wide concentration range, sensitivity to it differs between individuals: sensitive subjects show peak vasconstriction at a concentration of 10⁻³ u. ml⁻¹, whereas insensitive subjects need 10⁻² u. ml⁻¹. Consequently, in an ornipressin-sen- sitive patient, a concentration of 10⁻¹ u. ml⁻¹ would not produce optimal haemostasis. Attempts to improve it by increasing the concentration would only worsen bleeding, increase capillary clearance of the drug and thus heighten the danger of side effects.

Thus ignorance of the U-shaped dose–response curve of ornipressin may have been implicated in some of the reported cardiovascular complications.

In summary, for rapid powerful vasoconstriction of cutaneous vessels, a concentration of 10⁻² u. ml⁻¹ seems to be appropriate for most individuals. Concentrations of 2.5 x 10⁻² u. ml⁻¹ have also been reported to be satisfactory in regional anaesthesia [10] and in gynaecological surgery [16]. However, it is not known if this concentration is also optimally effective in other vascular beds. The use of low concentrations together with exclusion of patients at risk (old age [8], malfunctioning cardiovascular reflex system [17]) should improve the safety of ornipressin without reducing its efficacy.

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