Dipipanone and nifedipine in cold induced pain; analgesia not due to skin warming

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The mechanism of the pain relief produced by opiates in normal volunteers in the cold induced pain test has been investigated. In a double-blind placebo controlled study, hand skin temperature during a 3 min immersion in water at 1° C was not affected by either the opioid dipipanone 8 mg or the vasodilator nifedipine 10 and 20 mg. During this immersion, dipipanone produced significant pain relief. Nifedipine reduced pre-immersion blood pressures and raised heart rates, however, it did not significantly alter pain scores. It is concluded that vasodilatation and local warming do not play a role in the relief of pain by opiates in the cold immersion test.

Keywords volunteers cold pain opioids vasodilatation

Introduction

A reliable and sensitive healthy volunteer pain model would be useful for the investigation of potential analgesics. One such model is the pain produced by local cooling of the hand, which can be reduced by opiates (Posner *et al.*, 1985; Wolff *et al.*, 1966). However, the intensity of cold induced pain depends upon skin temperature (Chery-Croze, 1983), and upon the degree of constriction of local blood vessels (Lewis, 1930; Wolf & Hardy, 1941; Kreh *et al.*, 1984). Opiates are vasodilators (Jaffe & Martin, 1985). It is possible, therefore, that the pain relief they produce in cold pain models may be due to vasodilatation and local heating, rather than analgesia in a conventional sense. Similarly, new chemical entities thought to be analgesic because of their effects in the cold pain test could, in fact, be acting as vasodilators.

The following experiment was performed to determine whether the relief of cold induced pain in healthy volunteers by dipipanone 8 mg was associated with raised skin temperatures. In addition, the effects of nifedipine 10 and 20 mg, in this model were investigated. Nifedipine is a Ca²⁺ antagonist vasodilator which has been

used as a therapy for the cold induced pain of Raynaud's disease (Gjørup *et al.*, 1986).

Methods

After protocol approval by an independent review committee, twelve volunteers (nine female, three male) were recruited. They were aged 21 to 44 years (mean 26.5), and weighed 53 to 80 kg (mean 62.4). All were in good health, with no abnormal findings on physical and psychiatric examination. Electrocardiogram, blood count, plasma biochemistry and urinalysis were all normal. Urine screens for drugs of abuse were negative. The subjects gave informed consent prior to the study and received an honorarium afterwards.

Study design

The subjects received nifedipine 10 and 20 mg (N10, N20), dipipanone 8 mg (D8), and lactose placebo (P) as identical capsules. The treatments were administered double blind, according to a

randomised, balanced, crossover design. A test battery was performed twice on each occasion, 90 and 180 min post drug administration, in the following order: pre test heart rate and blood pressure; cold induced pain test with monitoring of hand skin temperature; post test heart rate and blood pressure. The schedule for each subject was staggered by 15 min so that six subjects could be studied per morning, but individual subjects were always studied on the same week days at the same times.

Cold pain test (CPT)

The method of Posner *et al.* (1985) was used. Briefly, pain was induced by transfer of the dominant hand from stirred water at 37° C to water at 1° C, where it was kept immersed for 3 min. Pain intensity was measured every second as the position of a cursor on a computer generated 200 mm visual analogue scale marked 'No pain' at the left end and 'Max pain' at the right end. The subjects used a games paddle held in the non-dominant hand to adjust the cursor position. The cursor was placed at the 'No pain' end prior to every test.

Three parameters were extracted for analysis from the raw data: (1) Maximum pain score. This was the greatest intensity of pain perceived by a subject. (2) Area under the curve of pain score against time. This was equivalent to the average pain intensity perceived during the 3 min test. (3) Pain score at 30 s. This was analysed in case vasodilators have transient pain relieving effects by slowing the rates of hand cooling.

Hand skin temperature

This was measured using three T type copper-constantin thermocouples applied to the skin of the dorsum and palm of the hand, and to the volar surface of the middle finger between the interphalangeal joints (Lewis, 1930). The junctions were held in place with 2 cm² of tape—thickness 1.0 mm. Temperature was recorded every 8 s using a Yokogawa hybrid chart recorder, (Matron, High Wycombe).

Cardiovascular effects

Heart rate, and systolic, diastolic, and mean blood pressures were obtained before and after every CPT using a 'Dinamap' automatic recorder.

Statistical analysis

Standard analysis of variance was used, with subject, occasion, treatment and time as factors. Two-tailed *t*-tests were used to establish treatment placebo differences. Throughout the text, * indicates $P < 0.05$ and ** $P < 0.01$.

Results

There were no significant treatment by time interactions, so all the results are expressed as the means of both test sessions.

Cold induced pain

D8 produced significant pain relief in all three submeasures (Table 1). Nifedipine did not produce detectable analgesia.

Table 1 Ratings of pain and cardiovascular effects

Measure	P	N10	Treatments		S.E.D.
			N20	D8	
Maximum pain	169	165	166	155*	5.0
Area under the pain curve $\times 10^3$	23.4	22.2	22.0	20.4**	0.89
Pain score at 30 s	87	81	81	73**	4.7
Pre test mean BP (mm Hg)	89.5	83.3**	85.2*	87.5	1.76
Pre test heart rate (beats min ⁻¹)	66.0	76.3*	83.0**	68.7	2.48
Post test mean BP (mm Hg)	94.4	97.9	87.7	91.3	4.69
Post test heart rate (beats min ⁻¹)	69.5	80.0**	83.2**	66.7	2.67

Means and standard error of differences (S.E.D.) between means for the four treatments. Abbreviations: placebo, P; nifedipine 10 and 20 mg, N10 and N20; dipipanone 8 mg, D8. For an explanation of the pain measures, see **Methods** section.

Table 2 Examples of the mean temperatures at the three sites during the cold water immersions. The least significant difference for detecting temperature differences between treatments and placebo ranges between 0.5 and 1.3° C depending upon duration of immersion and position on hand

	<i>P</i>	<i>N10</i>	<i>Treatments</i>		<i>S.E.D.</i>
			<i>N20</i>	<i>D8</i>	
Palm temperature (° C)					
60 s	9.9	10.0	9.6	9.3	0.64
120 s	7.8	8.0	7.7	7.2	0.57
180 s	7.2	7.4	7.3	6.4	0.55
Dorsum temperature (° C)					
60 s	8.5	8.3	8.3	8.3	0.67
120 s	6.7	6.0	6.2	6.1	0.61
180 s	5.7	5.2	5.4	5.3	0.43
Finger temperature (° C)					
60 s	5.9	5.0	5.9	6.3	0.64
120 s	3.6	3.0	3.4	3.8	0.39
180 s	2.6	2.3	2.5	2.7	0.26

Abbreviations as for Table 1. At no time during the immersion did any treatment cause a significant change in hand skin temperature.

Skin temperatures

The apparatus could sensitively detect the differences in temperature between the palm, dorsum and finger. However, alterations in skin temperature by the active treatments were not detected (Table 2).

Cardiovascular effects

Nifedipine produced a significant reduction in pretest mean blood pressures and this was associated with a significant tachycardia. The post test blood pressures were not significantly different from each other, though the heart rates were still significantly raised by nifedipine (Table 1).

Discussion

The most striking finding in this study is the lack of drug effect upon hand skin temperature during the 3 min cold immersions. Vasodilatation certainly can cause a rise of several °C in the skin temperature of digits immersed in water at 0° C—shown particularly clearly by Lewis (1930) using the technique adopted in this experiment.

References

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In our hands, temperature differences between the finger, the palm and the dorsum were clearly demonstrated, and the repeatability of the results was such that we could have detected drug induced rises in temperature of as little as 0.5–1.3° C. Since considerably greater changes in skin temperature than this are required to alter pain intensity (Chery-Croze, 1983), it is most unlikely that dipipanone produces analgesia in the CPT by skin warming.

It is, perhaps, surprising that doses of nifedipine sufficient to produce marked cardiovascular effects (lowered blood pressure, tachycardia) did not affect skin temperature during the cold water immersion. Presumably, the vasoconstrictor response is too intense to be blocked by this drug at these doses. Indeed, the observation that post test mean blood pressures were not significantly different between treatments provides some evidence for abolition of nifedipine vasodilatation by the CPT. Whether other vasodilators, alone or in combination, could overcome the vasoconstriction and warm the hand is not known. As nifedipine failed to alter hand skin temperature during the CPT we cannot conclude that a more potent vasodilator would not produce pain relief.

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