Effects of triprolidine and dipipanone in the cold induced pain test, and the central nervous system of healthy volunteers

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1 Twelve healthy volunteers took part in a study of the interaction between the antihistamine triprolidine and the opioid dipipanone in the cold induced pain (CP) test and tests of sedation. They received placebo, triprolidine 2.5 mg, dipipanone 8 mg or the combination of the two active treatments according to a double-blind, randomised, balanced, crossover design.

2 Antihistamine activity was demonstrated by triprolidine reducing the size of wheals and flares produced by intradermal histamine 1.6 µg. However, triprolidine produced no analgesia in the CP test, nor did it enhance the analgesia produced by dipipanone alone.

3 Neither treatment alone produced statistically significant sedation, assessed by visual analogue scales (VAS), side effect check list, body sway and reaction times. However, the combination did cause significant sedation.

4 Dipipanone reduced pupil size, depressed respiration, and decreased salivation. Triprolidine had no effects on pupil size and respiration, but reduced salivation slightly. It was concluded that histaminergic (H₁) mechanisms are unlikely to be involved in pain produced by cold.

Keywords pain volunteers antihistamines cold opioids

Introduction

The role of antihistamines in pain perception appears to be complex, for the results of experiments to investigate the analgesic action of these drugs have been contradictory. H₁-receptor blockers have been found to be antinociceptive or to enhance opioid antinociception in several animal models: e.g. rat tail electrical stimulation (Morichi & Pepeu, 1978); mouse tail clamp (Hanig *et al.*, 1981) and mouse hot plate (Bluhm *et al.*, 1982). However, other workers have found no effects (Westrick & Spratto, 1981; Hough *et al.*, 1984) or even antagonism of morphine analgesia (Mattila & Saarnivaara, 1968). Similarly, in human volunteers (Hougs & Skouby, 1957) and patients (Beaver & Feise, 1976; Bellville *et al.*, 1979) some antihistamines have been found to

produce analgesia or to enhance opioid analgesia, but in the same models others do not (Hougs & Skouby, 1957; Rumore & Schlichting, 1986).

Two problems recur in these experiments: the sedative effects of antihistamines might interfere with analgesic measures; and many of the drugs have effects on other transmitter systems (e.g. cholinergic) (Douglas, 1985).

We have, therefore, chosen to examine the actions of triprolidine 2.5 mg, a non-sedating dose of a relatively specific and potent H₁-receptor blocker (Hamilton *et al.*, 1982). We have used the cold induced pain test in volunteers to search for analgesic effects of the drug, alone and in combination with the opioid dipipanone 8 mg, a dose which has been shown to

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produce demonstrable analgesia in this test system (Posner *et al.*, 1985).

Methods

After approval by an independent protocol review committee, twelve healthy volunteers of both sexes (aged 23–37 years, weighing 48–79 kg) were recruited from the staff of Wellcome Research Laboratories, Beckenham. All were in good general health with no history of alcohol or drug abuse, and with no abnormal findings on physical and psychiatric examination, electrocardiogram, full blood count, plasma biochemistry or urinalysis. After a full explanation of the study protocol, the subjects gave informed consent in writing. They received an honorarium on completion of the study.

Study design

Groups of four subjects attended the laboratory at the same time of day on the same day of the week at weekly intervals. They performed a test battery prior to the drug and three more times at 60, 120 and 180 min post-drug. Subject times were staggered by 15 min intervals. The tests were performed in the following order: body sway, salivation, visual analogue scales (VAS), reaction time, pupil size, cold induced pain test and respiration test. The histamine skin test was performed 3.75 h post drug.

Dosages and formulations

The following treatments were administered orally as two identical capsules, according to a double-blind, randomised, balanced cross over design:

- (1) dipipanone 8 mg + lactose placebo = D
- (2) triprolidine 2.5 mg + lactose placebo = T
- (3) dipipanone 8 mg + triprolidine 2.5 mg = DT
- (4) lactose placebo + lactose placebo = P

Cold induced pain test

The subjects sat facing a computer monitor with their dominant hand immersed in water at 37° C for 2 min. At a computer generated signal, this hand was rapidly transferred to a bath of stirred water at 1° C. Pain intensity was then continually rated by the subject using a games paddle in the non dominant hand to move a cursor along a 200 mm VAS marked no pain at the left end, and maximum pain at the right end. Every second of the 3 min cold immersion, the computer measured the distance in mm of the cursor from the no pain end (Posner *et al.*, 1985).

Pupillometry

Pupil photographs were taken using a camera of fixed focal length with a ring flash. Pupil diameters (mean of the two eyes) were measured from colour transparencies using a magnifying lens and graticule (Posner *et al.*, 1985).

Subjective assessments

These were measured using computer generated 200 mm horizontal VAS as previously validated (Posner *et al.*, 1985). The 200 mm length is appropriate to the monitor screen. The order of presentation of the VAS was randomised at each test of every subject.

1. Drowsiness group: alert–drowsy; attentive–dreamy; muzzy–clearheaded; and mentally slow–quick witted.
2. Mood group: calm–excited; troubled–tranquil; happy–sad; and depressed–elated.

Reaction times

These were obtained using the Hobbs–Strutt portable reaction time meter. This device measures the response delay between the illumination of a light and pressing a switch. The mean of 25 to 30 reactions presented at irregular intervals over 5 min was obtained (Cohen *et al.*, 1985).

Body sway

This was measured using a Wright–Codoc ataxiometer. The subjects stood with their feet together wearing a blacked out mask for 3 min. Antero-posterior sway was measured for 3 min (Posner *et al.*, 1985).

Salivary secretion

Salivation was measured using three dental rolls inserted into the buccal cavities and under the tongue for 2 min. The difference in weight before and after insertion represents salivary flow (Bye *et al.*, 1979).

Side effects

Subject completed a check list, score 0 = absent, 1 = mild, 2 = moderate and 3 = severe, at the time of assessment of histamine antagonism.

Respiratory drive

End tidal P_{CO_2} was measured using a 'Gould Capnograph IV' for 2 min breathing room air.

Ventilatory response to rebreathing CO₂ was then measured using the Read (1967) technique, with minute ventilation measured with a 'Gould Pneumotachograph'. The regression line of ventilation against end tidal P_{CO₂} was calculated from at least five points between P_{CO₂} 50 mm Hg and 65 mm Hg; and ventilation at exactly 60 mm Hg was estimated from this line.

Assessment of histamine antagonism

At 3.75 h post-treatment histamine (acid phosphate) 0.1, 0.4, and 1.6 µg was injected intradermally in 100 µl of saline using a 'pan-jet' syringe. These doses were administered into three separate rows (top, middle and bottom respectively) on the subject's back. Four injection sites within each row were allocated randomly to the different treatments for each subject.

Twenty minutes later, the longest and narrowest orthogonal axes of the resultant wheals and flares were measured using a plastic ruler, and areas calculated assuming an elliptical shape (Peck *et al.*, 1975).

Data analysis

All measured variables were analysed by analysis of variance (ANOVA), and between treatment differences were then sought using Newman-Keuls test. Values of *P* < 0.05 were taken as significant. Results from the side effects check list were examined using the Sign test.

Results

Cold induced pain

Four features of the raw data were extracted for statistical analysis: the mean pain scores at 1, 2 and 3 min of cold water immersion; and the mean highest pain scores during the 3 min. One male subject could not keep his hand immersed in the cold water for more than a few seconds in the 2 and 3 h post-triprolidine 2.5 mg test sessions. His scores were assumed to be 200 (maximum pain on the VAS), in these two sessions. Table 1 shows the clear cut analgesia produced by dipi-

Table 1 Mean pain scores out of 200 for each treatment group in all four test sessions

Pain scores	Session	P	Treatment			S.E.D.
			T	D	DT	
60 s	pre-drug	129	140	138	131	7.7
	1 h	125	136	105	109	9.5
	2 h	130	147	106	105	10.4
	3 h	124	138	106	101	10.5
120 s	pre-drug	143	143	144	142	6.2
	1 h	148	145	117**	121**	7.9
	2 h	138	152	114*	113*	9.6
	3 h	137	146	120*	118*	7.6
180 s	pre-drug	144	143	146	143	6.2
	1 h	147	151	117**	123*	9.1
	2 h	139	151	115*	112*	10.3
	3 h	138	149	122	121	10.2
Greatest intensity	pre-drug	164	163	163	165	5.1
	1 h	164	169	133**	140**	6.9
	2 h	159	168	131*	132*	9.5
	3 h	157	166	135*	139*	8.3

The scores after 60, 120 and 180 s of cold water immersion are given, as well as the highest score obtained during the full 3 min immersion. Dipipanone 8 mg significantly reduced pain intensity at 120 and 180 s and also reduced the maximum pain perceived in a test. This effect was present in all three post-drug sessions. Triprolidine 2.5 mg never produced scores which differed significantly from placebo, and the scores after the combination of triprolidine 2.5 mg and dipipanone 8 mg were not different from those of dipipanone alone. Differences from placebo are shown by *P* < 0.01** and *P* < 0.05*. P = placebo; T = triprolidine 2.5 mg; D = dipipanone 8 mg; and DT = both triprolidine 2.5 mg and dipipanone 8 mg. S.E.D = standard error of difference.

panone 8 mg in all three post-drug sessions. There is no evidence for an effect of triprolidine 2.5 mg, either alone or in combination with dipipapone. Analysis of the data excluding the results of the subject who could not complete the test did not alter the significance values, nor did an analysis which included his other three occasions and estimated the missing values by the method of least squares.

Sedation

Evidence for sedation was sought using two objective (body sway, reaction time) and two subjective measures (VAS, side effect check list). The results of the objective measures are shown in Table 2 and the VAS in Table 3. Only the combination of active treatments had significant effects; these were present in all post-drug sessions for reaction time and VAS, but only at the third hour for body sway. On the check list of twenty-five possible side effects, only drowsiness was reported more often after an active treatment than after placebo. In confirmation of the above results, a significant effect was seen only with the combination of dipipapone and triprolidine (11 subjects vs 2 on placebo, $P < 0.001$; D alone = three subjects; T alone = five subjects).

Though the effect was not significant, there was a trend towards sedation with both active treatments alone. In all measures placebo tended to give the 'best' (i.e. least sedated) scores.

Opioid effects

Evidence for an antihistamine interaction in other opioid pharmacodynamic effects was sought by examining miosis and depression of respiratory response to inhaled CO₂ (Table 4). Dipipapone 8 mg produced a highly significant miosis at all post-drug sessions, and a clear cut respiratory depression, becoming pronounced by 2 h post-drug. Triprolidine 2.5 mg did not influence these opioid actions either alone, or in combination with dipipapone.

Histamine-induced wheals and flares

When assessed 3.75 h post-drug, triprolidine 2.5 mg produced significant reduction in the areas of wheals and flares produced by intradermal histamine 1.6 µg (Table 5). Dipipapone 8 mg has no effect, alone or in combination with triprolidine.

Salivary flow

The weighed dental roll technique is a good measure of reduced salivary flow (Bye *et al.*,

Table 2 Mean reaction times (RT) in ms and body sway (BS) in ° arc for the different treatments at each test. Other abbreviations as for Table 1

Measure	Session	P	Treatment			S.E.D.
			T	D	DT	
RT	pre-drug	258	255	270	255	8.7
	1 h	264	275	274	299*	12.5
	2 h	261	291	286	335**	16.3
BS	3 h	269	270	308	343**	20.3
	pre-drug	31.6	29.9	31.2	28.3	2.18
	1 h	29.2	31.8	30.1	30.6	2.50
	2 h	30.8	30.7	31.0	32.2	2.73
	3 h	30.3	31.2	28.6	36.8*	2.49

Table 3 These are the mean scores in mm from the left end of the 200 mm VAS. The first four scales assess drowsiness, the second four assess mood. Abbreviations as for Table 1

Scale	Session	P	T	D	DT	S.E.D.
Alert-drowsy	pre-drug	76	78	86	80	6.0
	1 h	79	88	88	106**	7.5
	2 h	74	91	88	117**	10.4
	3 h	77	88	88	126**	10.8
Attentive-dreamy	pre-drug	73	78	76	78	3.8
	1 h	75	83	80	100**	5.3
	2 h	76	91	87	106**	7.0
	3 h	76	82	89	110**	5.4
Muzzy-clear-headed	pre-drug	135	125	126	127	6.3
	1 h	125	116	112	96**	6.9
	2 h	124	109	106	86**	9.0
	3 h	122	114	105	80**	8.6
Mentally slow-quick witted	pre-drug	124	126	124	123	5.0
	1 h	119	116	120	108	5.1
	2 h	122	113	116	96**	6.4
	3 h	122	113	113	89**	6.7
Calm-excited	pre-drug	77	79	82	72	5.1
	1 h	80	80	77	71	7.7
	2 h	77	80	83	69	6.3
	3 h	75	80	81	74	6.5
Troubled-tranquil	pre-drug	121	121	117	116	5.1
	1 h	125	119	120	126	5.2
	2 h	122	120	121	126	5.6
	3 h	125	119	116	123	5.8
Happy-sad	pre-drug	77	79	87	79	5.7
	1 h	80	83	83	78	5.2
	2 h	78	77	78	75	5.8
	3 h	76	82	79	78	4.7
Depressed-elated	pre-drug	110	104	102	109	3.9
	1 h	107	110	104	112	4.8
	2 h	110	108	105	111	4.6
	3 h	110	110	102	108	4.3

1979). Both drugs significantly reduced salivation (Table 6). Once again there is no evidence for an interaction as the reduction in salivation produced by dipipanone 8 mg alone is the same as that caused by the combination of the two active treatments.

Discussion

The main aim of this study was to investigate the effects of H₁-receptor blockade in the cold induced pain test. Despite convincing evidence for triprolidine having actions in other systems (e.g. reduced wheals and flares after intradermal histamine), there was no evidence for pain reduction, by the drug at this dose, either alone or in combination with dipipanone. The cold induced

pain test is an extremely reliable way to demonstrate opioid analgesia in volunteers (De Jalon *et al.*, 1985; Posner *et al.*, 1985; Wolff *et al.*, 1976). Indeed the effect of dipipanone 8 mg was clearly demonstrated in this study. Previous work has suggested that antihistamine analgesia would be opioid in character or that the effect would be a potentiation of opioid analgesia (Rumore & Schlichting, 1986). Hence, the cold induced pain model should be an appropriate test for the detection of antihistamine pain relief. However, it remains possible that the drug produces a type of analgesia which cannot be detected in this model. For example, the CP test may not be appropriate for detecting non steroidal anti-inflammatory analgesics (De Jalon *et al.*, 1985).

Triprolidine 2.5 mg certainly had pharmacodynamic actions at the times the CP tests were

Table 4 Mean measures of opioid activity in the four treatment groups

Measure	Session	P	Treatment			S.E.D.
			T	D	DT	
P.D.	pre-drug	4.9	4.9	5.0	4.8	0.09
	1 h	4.8	4.9	3.8**	3.9**	0.15
	2 h	4.6	4.9	3.6*	3.7**	0.15
	3 h	4.9	5.0	3.7**	3.7**	0.21
PET CO ₂	pre-drug	42.6	42.4	42.4	41.9	0.71
	1 h	42.6	42.2	43.0	43.5	0.88
	2 h	42.8	43.4	44.6*	44.5*	0.54
	3 h	41.9	42.5	44.5**	44.4**	0.59
RMV60	pre-drug	19.5	19.7	19.4	22.1	1.70
	1 h	18.8	19.2	15.8	16.0	1.23
	2 h	19.0	19.1	13.8**	13.5**	1.11
	3 h	21.7	19.8	14.4**	13.7**	1.19
Slope	pre-drug	1.6	1.7	1.6	1.8	0.20
	1 h	1.6	1.7	1.2*	1.4	0.14
	2 h	1.5	1.6	1.2*	1.1**	0.12
	3 h	1.8	1.5	1.2**	1.2**	0.16

PD = pupil diameter in mm. PET CO₂ = resting end tidal partial pressure of CO₂ in mm Hg. Slope = gradient of regression line of ventilation against PET CO₂ during CO₂ rebreathing experiment, and RMV60 is the respiratory minute volume during this procedure at PET CO₂ = 60 mm Hg—calculated from the regression line. Other abbreviations as for Table 1.

Table 5 These are the areas of the wheals and flares produced by intradermal histamine injected into the skin of the back between the shoulders: triprolidine 2.5 mg consistently produces smaller wheals and flares

Histamine dose (µg)	Measure	P	Treatment			S.E.D.
			T	D	DT	
0.1	Wheal	71	47*	58	44*	7.8
	Flare	270	140	320	240	71
0.4	Wheal	79	70	90	66	8.1
	Flare	570	360	630	420	91
1.6	Wheal	153	103**	166	102**	15.2
	Flare	1040	790*	1170	770*	95

Abbreviations as for Table 1.

Table 6 These are the rates of saliva production in g over 2 min. Abbreviations as for Table 1 except † indicates significantly different ($P < 0.05$) from D and DT

Session	P	Treatment			S.E.D.
		T	D	DT	
pre-drug	1.2	1.4	1.4	1.5	0.14
1 h	1.5	1.5	1.1	1.1	0.23
2 h	1.9	1.4**	1.1**	1.1**	0.18
3 h	1.8	1.3**†	0.8**	1.0**	0.14

performed. This is shown by the marked sedation (both objective and subjective) produced by the dipipanone–triprolidine combination, and by

the reduction in salivary flow produced by triprolidine alone. In this study, the assessment of histamine antagonism was performed 0.75 h after the final CP test. However, previous work has shown such an oral dose to have activity at 1, 2, 3 and 4 h post-drug ingestion using the same test system (Hamilton *et al.*, 1982; Peck *et al.*, 1975).

The most striking finding in this study was the marked sedation produced by the combination of active treatments, with only non significant trends obtained with the individual drugs. In one previous study triprolidine 2.5 mg has been found to have small effects on reaction time and VAS at 1.5 h but not at 3 h (Cohen *et al.*, 1985). However, in another study only trends were seen in

these measures (Hamilton *et al.*, 1982). Similarly, dipipanone 8 mg has been shown to increase body sway and alter some VAS at 3 h but not earlier (Posner *et al.*, 1985). These effects were all small and of the same magnitude as the changes found in the present study. However, the effects of the combination of triprolidine and dipipanone were substantial; for example, the change in mean reaction time was greater than that obtained with 5 mg of triprolidine in the previous study (Cohen *et al.*, 1985). The mechanism of this drug induced sedation is not understood. However, the consistency of the observation on all four measures implies that the results are not artefactual. For example, it might be argued that incoordination and miosis might increase reaction time independently of sedation—but this would not account for the clear cut subjective effects.

In the present study, both drugs reduced salivation significantly. Dry mouth is a well-known side effect of opioids (Jaffe & Martin, 1985). Reduced salivation has not been demonstrated previously with triprolidine, though dry mouth has been reported by volunteers (Hamilton *et al.*, 1982). Presumably this indicates a mild anticholinergic action.

Triprolidine had no influence on respiration or pupil size, either alone or in combination with dipipanone. The opioid, however, had significant effects: raising resting end tidal P_{CO_2} and reducing the response to rebreathing CO_2 ; and constricting pupils.

The implication of all these results is that two different types of triprolidine-dipipanone interaction can occur. Neither drug affected the specific actions of the other drug. Thus, dipipanone did not affect the reduction (due to triprolidine) of intradermal histamine induced wheal and flare. Triprolidine did not influence opioid induced analgesia, miosis or respiratory depression. However, both drugs together produced substantial sedation while neither drug alone had a significant effect. If marked sedation is a typical finding of simultaneous treatments with an opioid and an antihistamine, this could explain studies in which antihistamines appear to enhance opiate analgesia. A reduction or delay in the response to painful stimuli would be measured as analgesia in many animal models (e.g. Bluhm *et al.*, 1982; Hanig *et al.*, 1981; Mattila & Saarnivaara, 1968) and some human volunteer studies (e.g. Houghs & Skouby, 1957). Similarly, it is conceivable that marked drowsiness (or even sleep) induced by opioids combined with antihistamines, would produce apparent pain relief in post operative patients (e.g. Beaver & Feise, 1976, but see Rumore & Schlichting, 1986).

In conclusion, these results provide no support for the use of an antihistamine, either alone or in conjunction with an opioid, to alleviate pain. The combination of the two drugs may, in fact, have important adverse consequences with markedly increased sedation.

References

- Beaver, W. T. & Feise, G. (1976). Comparison of the analgesic effects of morphine, hydroxyzine, and their combination in patients with post-operative pain. *Adv. Pain Res. Ther.*, **1**, 553–557.
- Bellville, J. W., Dorey, F., Capparell, D., Knox, V. & Bauer, R. O. (1979). Analgesic effects of hydroxyzine compared to morphine in man. *J. clin. Pharmacol.*, **19**, 290–296.
- Bluhm, R., Zsigmond, E. K. & Winnie, A. P. (1982). Potentiation of opioid analgesia by H_1 and H_2 antagonists. *Life Sci.*, **31**, 1229–1232.
- Bye, C. E., Clubley, M., Henson, T., Peck, A. W., Smith, S. A. & Smith, S. E. (1979). Changes in the human light reflex as a measure of anticholinergic effect of drugs. A comparison with other measures. *Eur. J. clin. Pharmacol.*, **15**, 21–25.
- Cohen, A. F., Hamilton, M., Phillipson, R. & Peck, A. W. (1985). The acute effects of acrivastine (BW825C), a new antihistamine, compared with triprolidine in measures of central nervous system performance and subjective effects. *Clin. Pharmacol. Ther.*, **38**, 381–386.
- De Jalon, P. D. G., Harrison, F. J. J., Johnson, K. I., Kozma, C. & Schnelle, K. (1985). A modified cold stimulation technique for the evaluation of analgesic activity in human volunteers. *Pain*, **22**, 183–189.
- Douglas, W. W. (1985). Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In *The pharmacological basis of therapeutics*, 7th edition eds Gilman, A. G., Goodman, L. S., Rall, T. W. & Murad, F., pp. 605–638. New York: Macmillan Publishing Company.
- Hamilton, M., Bush, M., Bye, C. & Peck, A. W. (1982). A comparison of triprolidine and cyclizine on histamine (H_1) antagonism, subjective effects and performance tests in man. *Br. J. clin. Pharmacol.*, **13**, 441–444.
- Hanig, J. P., Hui, F. W. & Sun, C. L. (1981). The role of H_1 and H_2 agonists and antagonists and morphine in antinociception. *Fed. Proc.*, **40**, 282.
- Hough, L. B., Su, K. L., Goldschmidt, R. C., Khan-delwal, J. K., Newton, M. V. & Glick, S. D. (1984). No evidence for histamine mediated mor-

- phine analgesia. *Neuropharmacology*, **23**, 705–709.
- Hougs, W. & Skouby, A. P. (1957). The analgetic actions of analgetics, antihistaminics and chlorpromazine in volunteers. *Acta pharmac. tox.*, **13**, 405–409.
- Jaffe, J. H. & Martin, W. R. (1985). Opioid analgesics and antagonists. In *The pharmacological basis of therapeutics*, 7th edition, eds Gilman, A. G., Goodman, L. S., Rall, T. W. & Murad, F., pp. 491–531. New York: Macmillan Publishing Company.
- Mattila, M. J. & Saarnivaara, L. (1968). Modification by antihistaminic drugs of the morphine analgesia in rabbits. *Ann. Med. exp. Fenn.*, **46**, 72–77.
- Morichi, R. & Pepeu, G. (1978). A study of the potentiation of morphine antinociception by hydroxyzine in the rat. *Br. J. Pharmac.*, **62**, 391–392P.
- Peck, A. W., Fowle, A. S. E. & Bye, C. (1975). A comparison of triprolidine and clemastine on histamine antagonism and performance tests in man: Implications for the mechanism of drug induced drowsiness. *Eur. J. clin. Pharmac.*, **8**, 455–463.
- Posner, J., Telekes, A., Crowley, D., Phillipson, R. & Peck, A. W. (1985). Effects of an opiate on cold induced pain and the CNS in healthy volunteers. *Pain*, **23**, 73–82.
- Read, D. J. C. (1967). A clinical method of assessing the ventilatory response to carbon dioxide. *Aust. Annals Med.*, **16**, 20–32.
- Rumore, M. M. & Schlichting, D. A. (1986). Clinical efficacy of antihistaminics as analgesics. *Pain*, **25**, 7–22.
- Westrick, M. L. & Spratto, G. R. (1981). The effect of antihistamines on the analgesic response in the morphine treated rat. *Fed. Proc.*, **40**, 282.
- Wolff, B. B., Kantor, T. G. & Cohen, P. (1976). Laboratory pain induction methods for human analgesic assays. *Adv. Pain Res. Ther.*, **1**, 363–367.

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