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Experimental pain induced by electrical and thermal stimulation of the skin in healthy man: sensitivity to 75 and 150 mg diclofenac sodium in comparison with 60 mg codeine and placebo

G. STACHER, H. STEINRINGER, S. SCHNEIDER, G. MITTELBACH, S. WINKLEHNER & G. GAUPMANN
Psychophysiology Unit at the Departments of Psychiatry and Surgery I, University of Vienna, Vienna, Austria

1 Models with experimentally induced pain in healthy man might be useful for the screening for analgesic effects of new drugs.
2 Experimental pain models have been shown to discriminate reliably between the effects of opioid analgesics and placebo but their sensitivity to nonsteroidal anti-inflammatory agents is disputed.
3 This study investigated whether it would be possible by using electrically and thermally induced cutaneous pain to discriminate reliably the effects of single oral doses of 75 and 150 mg diclofenac sodium on the one hand and 60 mg codeine on the other from those of placebo.
4 Forty-eight healthy subjects participated each in four experiments in which they received, in random double-blind fashion, each of the treatments. Every experiment comprised eight series of measurements, two before and six after drug administration, carried out at 30 min intervals.
5 Diclofenac sodium produced significant dose-related increases of threshold and tolerance to electrically and threshold to thermally induced pain.
6 Codeine 60 mg was significantly superior to placebo in all pain measures. Its analgesic effects were stronger than those of diclofenac 75 mg but weaker than those of diclofenac 150 mg.
7 Neither 150 mg nor 75 mg diclofenac caused more side effects than placebo, whereas codeine 60 mg elicited a high frequency of side effects. No severe adverse effects occurred after any one treatment.
8 The results suggest that both electrically and thermally induced cutaneous pain are well suited to evaluate analgesic effects not only of opioids but also of nonsteroidal anti-inflammatory drugs.

Keywords experimentally induced pain diclofenac sodium codeine

Correspondence: Professor Dr G. Stacher, Psychophysiologisches Laboratorium, Psychiatrische Universitätsklinik, Währinger Gürtel 18–20, A-1090 Wien, Austria.

Introduction

Methods for the evaluation of the effects of analgesic drugs on clinical pain states have been shown to yield reliable and reproducible data. However, they often are time consuming and a large number of patients is needed, when more than two treatments are to be compared. To circumvent such difficulties, a number of models with experimental induction of pain in healthy subjects have been developed. With some of these models, effects of opioid analgesics could, under double-blind conditions, readily be differentiated from the effects of a pharmacologically inert placebo: tolerance to pain induced by cutaneous electrical stimulation of two fingers and by immersion of the hand into ice water increased significantly more after the administration of codeine 60 mg than after placebo (Wolff *et al.*, 1966b), and codeine 30 mg was found to be significantly superior to placebo in alleviating experimentally induced ischaemic fore-arm pain (Saarnivaara & Mattila, 1967). Threshold and tolerance to electrically and threshold to thermally induced cutaneous pain increased significantly more with codeine 60 mg than with placebo (Stacher *et al.*, 1982a). Using the same methods, a methionine-enkephalin analogue (Stacher *et al.*, 1979b), the opioid agonist/antagonist drugs meptazinol and pentazocine (Stacher *et al.*, 1983), as well as ceruletide, a decapeptide closely related to cholecystokinin (Stacher *et al.*, 1982b, 1984), could be shown to produce significantly more analgesia than placebo. For the detection of analgesic effects of nonsteroidal anti-inflammatory drugs, however, experimental pain models seemed much less suited. This might be due to the fact that most of the methods used for the induction of pain do not produce inflammation or substantial tissue damage and the mechanism, by which nonsteroidal anti-inflammatory agents mainly act, i.e., by inhibiting prostaglandin synthesis, thus might not come into play. It was possible to discriminate the effects of such drugs under double-blind conditions from those of placebo in only a few studies: acetylsalicylic acid 600 mg was found to alleviate ischaemic fore-arm pain induced by the submaximum effort tourniquet method (Smith *et al.*, 1966) significantly better than placebo (Smith & Beecher, 1969) and tolmetin 200 mg, as well as a combination of tolmetin 100 mg and paracetamol 400 mg, increased threshold and tolerance to electrically induced cutaneous pain significantly more than did placebo (Stacher *et al.*, 1979a). In a single-blind study on healthy volunteers, the sensation threshold to electrical stimulation of the tooth pulp was found to be significantly higher after administration of each proquazone 600 mg, indomethacin 100 mg, diclofenac 100 mg, naproxen 500 mg, and phenylbutazone 400 mg than after placebo (Gabka, 1979). In other studies, by contrast, no significant differences between the effects of acetylsalicylic acid 1000 mg and placebo (Graffenried *et al.*, 1978; Moore *et al.*, 1971; Wolff *et al.*, 1966a) and between the effects of naproxen sodium 550 mg and placebo (Stacher *et al.*, 1982a) could be detected. However, as the response to analgesic drugs is subject to substantial variability not only under clinical but also under experimental conditions, the negative findings of the latter studies might have simply been due to an insufficient number of subjects. The present investigation was carried out to evaluate, whether oral doses of 75 and 150 mg diclofenac sodium, a nonsteroidal drug with anti-inflammatory, anti-pyretic and analgesic properties (Brogden *et al.*, 1980), would, in comparison with placebo and 60 mg codeine, show any effects on electrically and on thermally induced cutaneous pain in a carefully designed study with a presumably sufficient number of healthy subjects. In addition, the study should assess the drugs' effects on psychomotor function and on the side effect profile.

Methods

Subjects

Twenty-four female and twenty-four male healthy subjects ranging in age from 19 to 30 years were studied. None of them took any drugs during the course of the study, with the exception of fourteen females, who were on oral sequential contraceptives. The subjects were given a short explanation of the purpose of the research and a description of the procedures to be followed. They were further given a description of any reasonably forseeable risks and discomforts. Written consent to participate was obtained from each subject. Before it was initiated, the investigation was approved by the Institutional Committee on Studies Involving Human Beings.

Assessment of analgesic efficacy

Electrical stimulation Chains of square wave constant current impulses of 1 ms duration and a pulse frequency of 100 s^{-1} were used to induce

pain (Lahoda *et al.*, 1977; Stacher *et al.*, 1979a,b, 1982a,b, 1983, 1984). The stimuli were administered by means of a pair of silver ball electrodes attached to the earlobule of the subjects' non-dominant side. Their intensity increased, in steps of 0.05 mA, linearly from zero to 6.4 mA, the maximum intensity being reached within 25.6 s. The subjects were given a handle fitted with two push buttons and instructed to press the left button as soon as they perceived the stimuli as painful and thereby to indicate pain threshold, and to press the right button when they felt they could not tolerate any further increase of stimulus intensity and thereby to indicate pain tolerance. Pressing of the second button stopped the stimulation. Eight chains of electrical stimuli were presented. The interval between the chains ranged randomly from 15–25 s. Pain threshold and pain tolerance values were stored on-line by a computer on magnetic disc.

Thermal stimulation Radiant heat of a constant intensity was used to induce pain (Stacher *et al.*, 1982a,b, 1983, 1984). On the volar surface of the subjects' dominant forearm, eight spots were marked and numbered from one to eight. The subjects were instructed to press the marked spots sequentially against a switch mounted at an aperture, 6 × 6 mm in size, on the stimulator. Without prior notice, a projection filament lamp mounted within the stimulator was then turned on by an experimenter. The subjects were instructed to pull their forearm away from the aperture as soon as they perceived the radiant heat stimulus as painful and thereby to indicate their pain threshold. The time elapsing between the turning on of the lamp and the withdrawal of the arm from the aperture, allowing the closure of the switch, was measured, in ms, by a digital clock and stored on magnetic disc. The intervals between the application of the radiant heat stimuli ranged randomly between 15 and 25 s.

Assessment of psychomotor function

Reaction time to acoustic stimuli as a measure of sensorimotor performance was recorded in response to ten tones presented with random intervals ranging from 2 to 10 s and stored by computer on magnetic disc.

Fine motor control as an index of motor function and behavioural co-ordination was measured by means of a tracking task. The subjects were required to achieve, with a pen in their dominant hand, as many correct hits as possible in a grid system within 15 s. Their performance was recorded and stored on-line on magnetic disc.

Assessment of subjective feelings and side effects

Subjective feelings of wakefulness, tiredness, fitness for work, well-being, warmth, and mouth dryness were assessed using visual analogue self-rating scales. Six pairs of polar statements were written on the right and the left edge of a display. Between the two statements there was a 10-cm line and the subjects were instructed to mark that point of the line, which they considered to indicate most correctly their feelings in the given moment. The positions of the marks were recorded and stored on-line on magnetic disc. The statements were 'I am entirely awake – I am nearly asleep', 'I feel very tired – I don't feel tired at all', 'I feel very fit for work – I don't feel fit for work', 'I definitely don't feel well – I feel very well', 'I feel very warm – I feel very cold', and 'My mouth is dry – my mouth isn't dry at all'.

Side effects as reported spontaneously by the subjects were recorded together with the experimenters' observations. In addition, a standardised questionnaire was used on which the subjects indicated the presence or absence of a side effect.

Experimental design and procedure

Each subject participated in four experimental sessions separated by intervals of two or three days. The sequence in which the subjects received the four treatments on the different days was randomised according to a plan with twelve 4 × 4 Latin squares. Half of the females and males, respectively, had their tests between 08.00 h and 12.30 h (forenoon), and the other half between 12.30 h and 17.00 h (afternoon). On each of the experimental days, three subjects were tested alternately in the forenoons and three in the afternoons. Thus, with 4 experimental days per week, the entire experiment could be carried out in 8 weeks. The subjects allocated to the forenoon experiments were instructed to come fasting to the laboratory at 07.30 h. The subjects allocated to the afternoon experiments were asked to have for breakfast one cup of mallow tea, i.e. herbal tea prepared of the petals of marsh mallows (family *Malvaceae*), and buttered bread at their usual time, and to come to the laboratory at 12.00 h. On arrival of the subjects, the electrodes were attached to the right earlobule and eight spots on the right forearm were marked for application of the thermal stimuli. Eight series of measurements, each lasting 8 min, were carried

out: 40 min and 10 min before, as well as 30, 60, 90, 120, 150, and 180 min after drug administration. In each of these series, threshold and tolerance to electrically induced pain, threshold to thermally induced pain, reaction time to acoustic stimuli, fine motor control, self-ratings, and side effects were recorded sequentially. The drugs were given as tablets of identical shape and colour, and, to assure optimal resorption, together with 100 ml of a pH 7.5 buffer solution. Immediately before as well as 30, 60, and 120 min after drug administration, blood was drawn from a forearm vein by means of an indwelling polyethylene cannula (Braunüle®, Braun Melsungen AG, Melsungen, West Germany) for the determination of the plasma concentrations of diclofenac sodium. Plasma concentrations were determined by Ciba-Geigy Limited, Basle, Switzerland. One hour after drug administration, the subjects were given a slice of buttered bread together with 200 ml mallow tea. Between the measurements, the subjects sat in a quiet room and were encouraged to read newspapers or books. After the end of each experiment, they were asked whether they had noticed any change in their mood or in any of their bodily functions.

Statistical analysis

An analysis of variance for repeated measures (Games, 1975) was performed on the differences between the data measured in the six periods after and the mean values of the data measured in the two periods before drug administration. The analysis investigated the influences of the fixed between-subjects factors 'sex' and 'time of day' (forenoon, afternoon), the fixed within-subjects factors 'treatment' (1 to 4), 'day' (experimental days 1 to 4), 'time' (six periods after drug administration), as well as of the random factor 'subject' (1 to 48). To evaluate differences between the mean effects of the four treatments, a sequentially rejective multiple test procedure (Holme, 1979) was used. In this procedure, which was based on the analysis of variance, directional tests were carried out and an overall significance level of $\alpha = 0.05$ was adopted.

Results

The analyses of variance revealed that, in general, neither the sex of the subjects, nor the time of day they had their tests, nor the sequence in which they received the treatments on the four experimental days had a significant influence on their responses to the administered treatments. A significant influence of the sex-factor was revealed only for reaction time, where the female subjects reacted slower than their male counterparts ($F_{(1,44)} = 4.20$, $P < 0.05$). A significant influence of the time-of-day-factor was found only for self-rated wakefulness and tiredness: the subjects rated themselves less wakeful and more tired in the afternoons than in the forenoons ($F_{(1,44)} = 5.13$, $P < 0.05$, and $F_{(1,44)} = 4.98$, $P < 0.05$, respectively). A significant influence of the factor 'experimental day' was found for the variables reaction time and fine motor control, where there were tendencies towards longer reaction times and decreasing fine motor control over the four experimental days ($F_{(3,720)} = 3.14$, $P < 0.025$, and $F_{(3,720)} = 5.41$ $P < 0.005$, respectively).

Analgesic efficacy

Threshold to electrically induced pain Threshold values increased with all of the active treatments but remained virtually unchanged after placebo. Maximum effects were reached 120 to 180 min after administration (Figure 1). Diclofenac 150 mg produced the most accentuated elevations of threshold, whereas codeine 60 mg and diclofenac 75 mg were less active. The analysis revealed that the treatment effects differed highly significantly ($F_{(3,720)} = 44.79$, $P < 0.001$). The increase in analgesic efficacy over time, which occurred after administration of all of the active drugs, was reflected by a significant F-ratio for the time-factor ($F_{(5,720)} = 9.14$, $P < 0.001$). The effects of the two doses of diclofenac as well as of codeine differed significantly from those of placebo. Diclofenac 150 mg was significantly

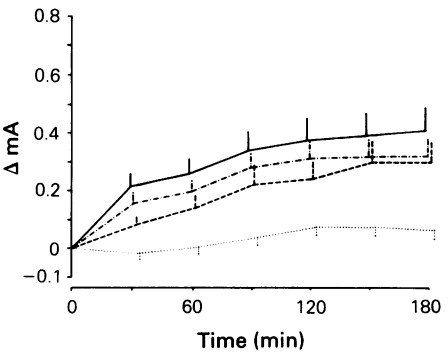

Figure 1 Threshold to electrically induced pain. Mean changes ± s.e. mean from basal values (ΔmA) 30, 60, 90, 120, 150, and 180 min after administration of diclofenac 150 mg (——), diclofenac 75 mg (-----), codeine 60 mg (—·—), and placebo (·····).

superior to 75 mg diclofenac and also to 60 mg codeine, whereas the effects of diclofenac 75 mg and codeine 60 mg did not differ.

Tolerance to electrically induced pain Tolerance increased markedly after the administration of the active drugs, but remained unchanged after placebo. With the two doses of diclofenac peak values were reached after 150 min and with codeine after 120 min (Figure 2). The analysis revealed that the treatments acted significantly differently ($F_{(3,720)} = 53.40$, $P < 0.001$). The increase in tolerance after the two doses of diclofenac and after codeine was reflected by a significant influence of the time-factor ($F_{(5,720)} = 9.88$, $P < 0.001$). All of the active drugs were significantly superior to placebo. Diclofenac 150 mg produced significantly higher elevations of tolerance than did diclofenac 75 mg and codeine 60 mg, codeine 60 mg being significantly more potent than diclofenac 75 mg.

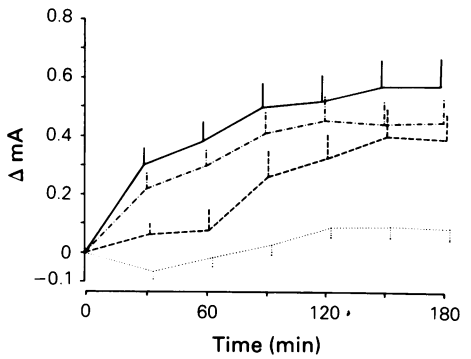

Figure 2 Tolerance to electrically induced pain. Mean changes ± s.e. mean from basal values (△mA) 30, 60, 90, 120, 150, and 180 min after administration of diclofenac 150 mg (——), diclofenac 75 mg (-----), codeine 60 mg (—·—), and placebo (·····).

Threshold to thermally induced pain Both doses of diclofenac and also codeine increased threshold markedly and peak levels were reached between 60 and 90 min after administration. Diclofenac 150 mg was most active, whereas the effects of 75 mg diclofenac and of codeine were weaker and differed only slightly from each other. After placebo, there was an initial increase of threshold which, however, was followed by a steady decline (Figure 3). The analysis showed that the treatment effects differed significantly ($F_{(3,720)} = 30.31$, $P < 0.001$) and that the threshold values after the four treatments had a similar development over time (time-factor, $F_{(5,720)} = 2.66$, $P < 0.025$). The effects of all of

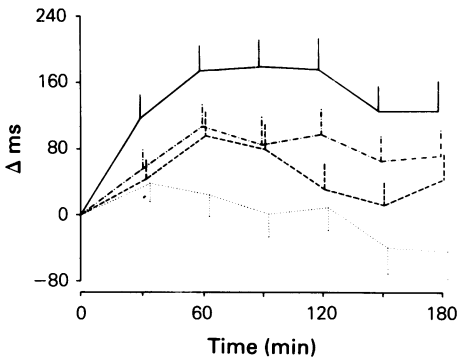

Figure 3 Threshold to thermally induced pain. Mean changes ± s.e. mean from basal values (△ms) 30, 60, 90, 120, 150, and 180 min after administration of diclofenac 150 mg (——), diclofenac 75 mg (-----), codeine 60 mg (—·—), and placebo (·····).

the active drugs differed significantly from those of placebo. Diclofenac 150 mg was significantly more potent than diclofenac 75 mg and than codeine 60 mg, while codeine 60 mg was more active than diclofenac 75 mg.

Psychomotor function

Reaction time to acoustic stimuli The four treatments had only slight and highly variable effects and there was a general trend towards an increase of reaction time over time. Diclofenac 150 mg had no more influence than placebo, whereas diclofenac 75 mg and codeine 60 mg caused but slight prolongations (Figure 4). The analysis showed differing treatment effects ($F_{(3,720)} = 6.33$, $P < 0.001$) and the effects of 75 mg diclofenac and of 60 mg codeine to differ

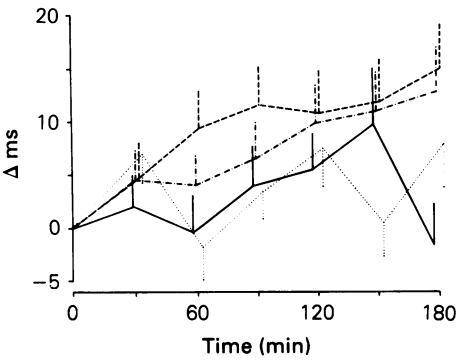

Figure 4 Reaction time to acoustic stimuli. Mean changes ± s.e. mean from basal values (△ms) 30, 60, 90, 120, 150, and 180 min after administration of diclofenac 150 mg (——), diclofenac 75 mg (-----), codeine 60 mg (—·—), and placebo (·····).

significantly from those of placebo and 150 mg diclofenac.

Fine motor control After placebo and also after diclofenac 75 mg, slight increases in fine motor control occurred, whereas there were practically no changes after codeine 60 mg. With diclofenac 150 mg, fine motor control decreased in the first hour but returned to the initial values thereafter (Figure 5). The analysis revealed significant treatment differences ($F_{(3,720)} = 4.51$, $P < 0.005$) and that the performance in the test was significantly weaker after diclofenac 150 mg than after diclofenac 75 mg and placebo.

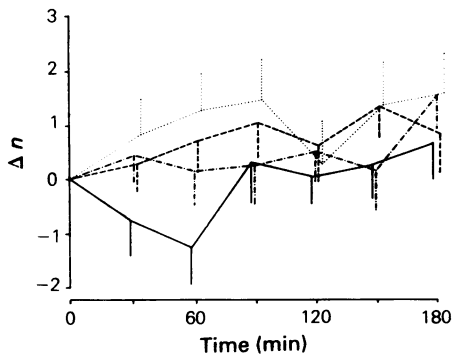

Figure 5 Fine motor control. Mean changes ± s.e. mean from basal values (Δ *n*, number of correct hits) 30, 60, 90, 120, 150, and 180 min after administration of diclofenac 150 mg (——), diclofenac 75 mg (-----), codeine 60 mg (—·—), and placebo (·····).

Subjective feelings and side effects

Wakefulness After the administration of both 75 and 150 mg diclofenac, the subjects rated themselves as only slightly less wakeful than after placebo, whereas they felt much less wakeful after codeine 60 mg (Figure 6). The analysis showed that these effects differed significantly ($F_{(3,720)} = 10.49$, $P < 0.001$) and that the effect of codeine differed significantly from those of all other treatments.

Tiredness After the two doses of diclofenac as well as after placebo, the subjects rated themselves as only slightly more tired than in the basal periods. By contrast, massive increases in reports of tiredness occurred after the administration of codeine 60 mg (Figure 7). The treatment effects differed significantly ($F_{(3,720)} = 12.00$, $P < 0.001$) and there was also a significant influence of the time-factor ($F_{(5,720)} = 4.70$, $P < 0.001$), reflecting the general increase in tiredness over time. The effects of the two doses of diclofenac did not differ from those of placebo, whereas codeine produced significantly more tiredness than each of the other treatments.

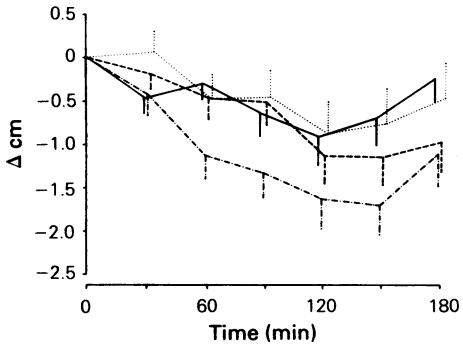

Figure 6 Self-rated wakefulness. Mean changes ± s.e. mean from basal values (Δ cm) 30, 60, 90, 120, 150, and 180 min after administration of diclofenac 150 mg (——), diclofenac 75 mg (-----), codeine 60 mg (—·—), and placebo (·····).

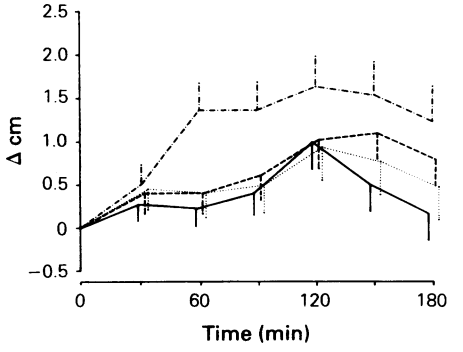

Figure 7 Self-rated tiredness. Mean changes ± s.e. mean from basal values (Δ cm) 30, 60, 60, 90, 120, 150, and 180 min after administration of diclofenac 150 mg (——), diclofenac 75 mg (-----), codeine 60 mg (—·—), and placebo (·····).

Fitness for work After all of the treatments, the subjects felt less fit for work. The decrement was small with placebo, slightly larger with the two doses of diclofenac and marked with codeine 60 mg (Figure 8). The analysis showed that the treatments were significantly different ($F_{(3,720)} = 18.66$, $P < 0.001$) and that the general decrease in fitness for work over time was significant ($F_{(5,720)} = 4.89$, $P < 0.001$). The effects of the two diclofenac doses did not differ from

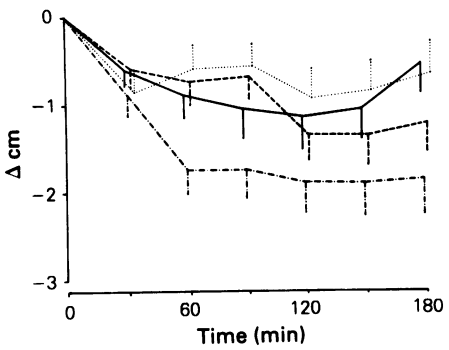

Figure 8 Self-rated fitness for work. Mean changes ± s.e. mean from basal values (Δ cm) 30, 60, 90, 120, 150, and 180 min after administration of diclofenac 150 mg (——), diclofenac 75 mg (-----), codeine 60 mg (—·—), and placebo (·····).

those of placebo, whereas codeine 60 mg caused the subjects to report significantly less fitness for work than all other treatments.

Dryness of mouth Self-reported dryness of mouth was not altered systematically by placebo and the two doses of diclofenac, while markedly more dryness was reported after codeine 60 mg. The treatment effects differed significantly ($F_{(3,720)} = 15.11$, $P < 0.001$), the codeine effects differing significantly from those of all other treatments.

Well-being and warmth In both dimensions, the reports showed no systematic changes from basal values or any treatment differences.

Side effects No severe side effects whatsoever were reported or observed after any of the treatments. Drowsiness, tiredness, giddiness, concentration difficulties, dizziness, abdominal discomfort, euphoria, and warmth were reported more often after codeine 60 mg than after any of the other treatments. The effects of the two diclofenac doses neither differed from each other nor from those of placebo. Nausea, abdominal pain, dysphoria, mood changes, headache, and trembling were reported only infrequently and not more often after any of the active drugs than after placebo (Table 1).

Plasma concentrations of diclofenac sodium

On all occasions the subjects had received diclofenac sodium, the plasma concentrations of that drug rose quickly to reach peak values 30 min after administration. Thereafter, a steady fall in concentrations occurred (Figure 9). With diclofenac 75 mg, a mean concentration of 1.90 mg l^{-1} ± 0.24 s.e. mean (range: 0.04 – 6.66 mg l^{-1}) was reached after 30 min, while the concentration was only 0.48 ± 0.07 mg l^{-1} (range: 0.09 – 3.02 mg l^{-1}) at 120 min. With diclofenac 150 mg, the 30 and 120 min concentrations were 3.20 ± 0.38 mg l^{-1} (range: 0.14 – 9.23 mg l^{-1}) and 1.01 ± 0.09 mg l^{-1} (range: 0.25 – 2.51 mg l^{-1}), respectively. There were no statistically significant correlations between plasma concentrations of diclofenac sodium and any of the pain measures.

Table 1 Side effects of diclofenac, codeine and placebo

Side effect	*Diclofenac* 75 mg	*Diclofenac* 150 mg	*Codeine* 60 mg	*Placebo*
Drowsiness	28	28	33	29
Tiredness	32	32	35	31
Giddiness	9	8	27	13
Concentration difficulties	11	14	24	16
Dizziness	5	4	10	5
Nausea	1	2	2	2
Abdominal discomfort	9	11	14	10
Abdominal pain	1	2	2	1
Euphoria	4	1	8	3
Dysphoria	3	—	1	2
Mood changes	3	1	6	5
Warmth	2	1	8	2
Headache	8	4	10	10
Trembling	2	—	1	1
Number of subjects with side effects	40	39	44	40
Number of side effects	118	108	181	130

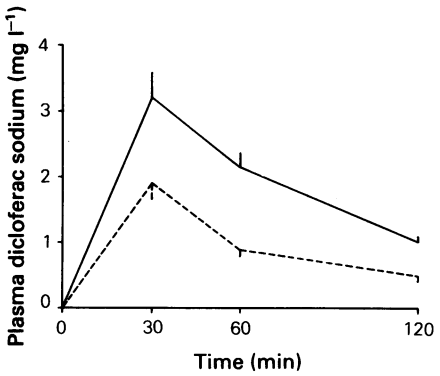

Figure 9 Plasma concentrations of diclofenac sodium. Mean concentrations ± s.e. mean (mg l^{-1}) 30, 60, and 120 min after administration of diclofenac 150 mg (——) and diclofenac 75 mg (-----).

Discussion

The results of the present study show that with both electrically and thermally induced pain not only the effects of codeine 60 mg but also those of diclofenac sodium 150 and 75 mg administered orally could be differentiated as statistically significant from the effects of placebo. The effects of diclofenac sodium, furthermore, were found to be significantly dose-related. As these clearcut results were obtained with a smaller number of subjects than usually employed in clinical pain studies, the sensitivity of the two experimental pain models can be regarded to be at least as high as that of models using clinical pain. Other advantages over clinical models are the relative speed of study — the experiments were carried out in 9 weeks — as well as the comparatively unproblematic recruitment of the subjects. Responses to painful stimuli might be influenced by drugs reducing central nervous system activation and impairing psychomotor function. However, in the present study both doses of diclofenac sodium had only slight effects on sensorimotor function as measured by the reaction time to acoustic stimuli and on fine motor control as an index of motor function and behavioural coordination and did not affect self-rated drowsiness, tiredness, and fitness for work. The fact that codeine 60 mg did not alter psychomotor function in a systematic fashion although it decreased self-rated central nervous activation significantly and also produced a high number of side effects pointing in the same direction, possibly can be attributed to an unchanged capability of the subjects to concentrate for the relative short periods of time required for their performance in the psychomotor tasks. The relatively high incidence of side effects observed in the present investigation after the administration of all of the treatments including placebo might reflect the fact that healthy subjects are more attentive to side effects than patients concentrated on the pain they suffer. The absence of a direct relationship between plasma concentrations of diclofenac sodium and any of the pain measures as well as the fact that analgesic effects lasted much longer than the elevation of plasma levels indicates that the pain relief produced by diclofenac depends, in parallel to other nonsteroidal anti-inflammatory agents, on the activity of the drug at the receptor site rather than on its plasma levels. In conclusion, both models with experimentally induced pain seem suited for an application in the screening for analgesic properties of nonsteroidal anti-inflammatory drugs. They further could help to determine doses for clinical trials, which, of course, would still be necessary and cannot be substituted for by studies on healthy subjects.

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