Effects of graded oral doses of a new 5-hydroxytryptamine/noradrenaline uptake inhibitor (Ro 15-8081) in comparison with 60 mg codeine and placebo on experimentally induced pain and side effect profile in healthy men

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1 Ro 15-8081 (Hoffmann-La Roche, Basle, Switzerland) is a novel mixed 5-HT/noradrenaline uptake inhibitor producing potent antinociceptive effects in animal pain models.

2 In healthy man, two models with electrically and thermally induced pain, respectively, have been shown to reliably discriminate between the effects of opioid as well as of antipyretic analgesics and placebo.

3 This study investigated the effects of single oral doses of 10, 25, and 50 mg Ro 15-8081 in comparison with 60 mg codeine and placebo on threshold and tolerance to electrically induced pain and on threshold to thermally induced pain. Furthermore, the effects on psychomotor function, self-rated subjective feelings, and side effect profile were studied.

4 Twenty healthy males participated each in five experiments in which they received, in random double-blind fashion, each of the treatments. Every experiment comprised two series of measurements before and twelve after drug administration, carried out at 30 min intervals.

5 Ro 15-8081 produced marked elevations of threshold and tolerance to electrically and of threshold to thermally induced pain. The effects of all doses of Ro 15-8081 were significantly superior to those of placebo. Threshold and tolerance to electrically induced pain were not affected differently by the three doses of Ro 15-8081, whereas the threshold to thermally induced pain was elevated significantly more by 50 mg than by 10 and 25 mg Ro 15-8081.

6 Codeine 60 mg had a more rapid onset of action and greater maximal effects than Ro 15-8081.

7 Psychomotor function, as measured by a reaction time and a fine motor control task, was not altered by any dose of Ro 15-8081, whereas 60 mg codeine produced a significant prolongation of reaction time.

8 Subjective feelings indicative of altered central nervous system arousal, well-being and mood were not influenced by Ro 15-8081.

9 Ro 15-8081 produced an only slightly higher number of side effects such as abdominal discomfort, headache, and nausea than did placebo.

Keywords Ro 15-8081 codeine pain 5-HT noradrenaline uptake

Introduction

Ro 15-8081 (F. Hoffmann-La Roche & Co. Ltd, Basle, Switzerland) is a novel compound which inhibits neuronal reuptake of noradrenaline and 5-hydroxytryptamine (serotonin, 5-HT) to the same extent as does the tricyclic antidepressant, amitriptyline (Hoffmann-La Roche, 1986). In various animal models, Ro 15-8081 has been shown to produce potent and long-lasting antinociceptive effects. In the hot plate test, Ro 15-8081 is more potent than opioids but somewhat less potent than amitriptyline after oral, subcutaneous, and intraperitoneal administration; following intravenous and intracerebroventricular injection, antinociceptive effects can be observed already after 5 min. By contrast, Ro 15-8081 has no detectable antinociceptive action in the tail flick test, where opioids, but not amitriptyline, exert marked effects. Since the tail flick response is a spinal reflex (Irwin *et al.*, 1951), while the hot plate response is integrated at higher supraspinal levels (Hayes *et al.*, 1978) and includes escape behaviours requiring a high degree of sensorimotor integration, these findings suggest that the antinociceptive effects of Ro 15-8081 are mediated by mechanisms involving the central nervous system. This has to be expected also in the light of studies showing that increased levels of 5-HT (Messing & Lytle, 1977) and/or noradrenaline in the brain and in the spinal cord, as occurring after the administration of drugs inhibiting 5-HT and noradrenaline reuptake, potentiate activity in descending serotonergic and noradrenergic bulbo-spinal neurons which control spinal processing of nociceptive information and thus lead to hypoalgesia (Duggan, 1985). Ro 15-8081 is structurally unrelated to opioids, acts neither agonistic nor antagonistic at opioid receptor sites and its antinociceptive effects are not antagonized consistently by naloxone. The compound does not interfere with arachidonic acid metabolism and prostaglandin synthesis and has no antipyretic effects, but does counteract inflammation in kaoline-induced paw oedema in rats. Although it selectively suppresses feline REM-sleep in a dose-dependent and long-lasting manner, an effect which is highly predictive for antidepressant activity (Scherschlicht *et al.*, 1982), Ro 15-8081 produces neither overt stimulation nor depression of central nervous functions. Ro 15-8081 is rapidly absorbed from the gastrointestinal tract and doses of up to 30 mg kg⁻¹ day⁻¹ were systematically well tolerated by dogs during a 4-week oral toxicity study (Hoffmann-La Roche, 1986). The present investigation was aimed at assessing, in healthy man, the analgesic activity of Ro 15-8081 using two models with

electrically and thermally induced cutaneous pain, which previously have been shown to discriminate reliably between the effects of opioid (Stacher *et al.*, 1979, 1982, 1983, 1986) as well as of antipyretic-antiinflammatory analgesics (Stacher *et al.*, 1986) and placebo. In addition, the study assessed the compound's effects on psychomotor function, subjective feelings and side effect profile.

Methods

Subjects

Twenty healthy males ranging in age from 23 to 35 years were studied. None of them took any drugs during the course of the study. Only such subjects were included, in whom haematological, blood chemical, and urine examinations, and further the extraversion- and neuroticism-scores in the Eysenck Personality Inventory (Eysenck & Eysenck, 1971) were within the normal range. 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 foreseeable 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.*, 1979, 1982, 1983, 1986). The stimuli were administered by means of a pair of silver ball electrodes attached to the earlobe 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 intervals between the chains ranged randomly from 15 to 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.*, 1982, 1983, 1986). 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 was recorded as a measure of sensorimotor performance (Hindmarch, 1980). Ten 800 Hz tones of an intensity of 65 dBA and a duration of 0.2 s were presented via a loudspeaker positioned 1 m from the subjects right ear with random intervals ranging from 2 to 10 s. The subjects were instructed to press the key of a Morse telegraph as soon as they perceived the tone. The response latencies were measured automatically and stored by computer on magnetic disc.

Fine motor control as an index of motor function and behavioural co-ordination (Hindmarch, 1980) 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 on round spots measuring 5 mm in diameter contained in a grid system within 15 s. When the subjects hit the 'correct' spots with their pen, an electric circuit was closed and the hit counted. Their performance was recorded and stored on-line on magnetic disc.

Assessment of subjective feelings and side effects

Subjective feelings of drowsiness, tiredness, fitness for work, well-being, mood, cheerfulness, vigourousness, warmth (i.e., the feeling of being warm in temperature), hunger, dryness of mouth, and burning of eyes were assessed using visual analogue self-rating scales. Eleven 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.

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 together with its severity, i.e., whether they considered the side effect as mild, disturbing, or unbearable.

Experimental design and procedure

Each subject participated in five experimental sessions separated by intervals of 2 or 3 days. The sequence in which the subjects received the treatments on the different days was randomised according to a plan with four 5×5 Latin squares. On each of the experimental days, three subjects were tested alternately. Thus, with 4 experimental days per week, the entire experiment could be carried out in 9 weeks. The subjects were instructed to come fasting to the laboratory at 08.00 h. On their arrival, the electrodes were attached to the right earlobe and eight spots on the right forearm were marked for application of the thermal stimuli. Fourteen series of measurements, each lasting 8 min, were carried out: 40 min and 10 min before, as well as 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 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 solutions of identical colour, and, to correct for differences in taste and concentration, together with 100 ml of grapefruit juice. Three hours after drug administration, the subjects were given two slices of buttered bread together with 200 ml of mallow tea, i.e., herbal tea prepared of the petals of marsh mallows (family *Malvaceae*). 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

The comparability of the data recorded in the

two periods before drug administration was investigated by means of an analysis of variance for repeated measures (Games, 1975). A factorial model accounting for the influences of the factors 'day' (fixed; experimental days 1 to 5), 'time' (fixed; the two periods before drug administration), and 'subjects' (random; subjects 1 to 20) was used. The data recorded after drug administration were analysed according to the Latin square design using an analysis of variance model for repeated measures (Games, 1975). These analyses were performed on the differences between the data measured in the twelve periods after and the mean values of the data measured in the two periods before drug administration. The analyses investigated the influences of the fixed within-subjects factors 'treatment' (treatments 1 to 5), 'day' (experimental days 1 to 5), 'time' (twelve periods after drug administration), as well as of the random factor 'subject' (subjects 1 to 20). To evaluate differences between the overall mean effects of the five treatments as well as between the mean effects in each period of time, 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 analysis of the data recorded before drug administration did not reveal systematic variation in any of the variables. No significant influences of the day- and of the time-factor were found. The analyses of the data recorded after drug administration showed that the sequence in which the subjects received the treatments on the five experimental days had no significant influence on their responses to the administered treatments.

Analgesic efficacy

Threshold to electrically induced pain Threshold values increased markedly after 60 mg codeine as well as after the three doses of Ro 15-8081, whereas there were slight decreases in threshold after the administration of placebo (Figure 1). Codeine (60 mg) had the most prominent effect and peak values were reached 120–210 min after administration. After Ro 15-8081, the highest threshold values were attained between 150 and 240 min, the effects of the three doses of the drug differing only little. The analysis revealed that the treatments acted significantly differently ($F(4,864) = 93.47$, $P < 0.001$). The sequentially rejective multiple test procedure (Holme, 1979) to compare the overall mean changes from basal values (Table 1) showed that all of the active drugs yielded significantly more analgesia than placebo, that 60 mg codeine produced significantly higher elevations of threshold than did each of the three doses of Ro 15-8081 and that the effects of these doses did not differ significantly from each other. The multiple test procedure to compare the treatment effects in each period of time revealed that at 60 min after drug administration, only the effects of 60 mg codeine and at 120 min only the effects of 60 mg codeine, and of 50 mg Ro 15-8081, differed significantly from those of placebo, whereas from 180 min onward until the end of the experimental time, the effects of all of the active drugs were significantly superior to placebo. The differing effects of the treatments over time were also reflected, in the analysis of variance, by a significant F -ratio for the interaction between the factors treatment and time ($F(44,836) = 3.08$, $P < 0.001$). However, the magnitude of this F -ratio seemingly resulted mainly from the difference between the effects over time after the admini-

Figure 1 Threshold to electrically induced pain. Mean changes $\pm$ s.e. mean from basal values (Δ mA) 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 min after administration of 50 mg Ro 15-8081 (—), 25 mg Ro 15-8081 (— — —), 10 mg Ro 15-8081 (---), 60 mg codeine (— · — · —), and placebo (·····).

Table 1 Threshold and tolerance to electrically induced pain, threshold to thermally induced pain, reaction time to acoustic stimuli, and fine motor control: mean changes $\pm$ s.e. mean from basal values after administration of 10 mg, 25 mg and 50 mg Ro 15-8081, 60 mg codeine and placebo

Variable	10 mg	Ro 15-8081 25 mg	50 mg	Codeine 60 mg	Placebo
Threshold to electrically induced pain (Δ mA)	0.22 $\pm$ 0.02 ^{a,b}	0.25 $\pm$ 0.02 ^{a,b}	0.23 $\pm$ 0.01 ^{a,b}	0.33 $\pm$ 0.02 ^a	-0.06 $\pm$ 0.01
Tolerance to electrically induced pain (Δ mA)	0.31 $\pm$ 0.03 ^{a,b}	0.36 $\pm$ 0.03 ^{a,b}	0.30 $\pm$ 0.02 ^{a,b}	0.46 $\pm$ 0.02 ^a	-0.18 $\pm$ 0.01
Threshold to thermally induced pain (Δ ms)	47.90 $\pm$ 14.30 ^{a,b,c}	23.70 $\pm$ 16.50 ^{a,b,c}	94.70 $\pm$ 18.80 ^{a,b}	167.90 $\pm$ 14.50 ^a	-143.10 $\pm$ 12.60
Reaction time to acoustic stimuli (Δ ms)	9.56 $\pm$ 1.63	4.05 $\pm$ 1.61 ^b	7.99 $\pm$ 1.70 ^b	13.20 $\pm$ 1.45 ^a	6.83 $\pm$ 1.48
Fine motor control (Δ correct hits)	0.13 $\pm$ 0.36	0.46 $\pm$ 0.36	0.77 $\pm$ 0.34	-0.53 $\pm$ 0.32	-1.69 $\pm$ 0.30

^aSignificantly different from placebo values; ^bsignificantly different from 60 mg codeine values; ^csignificantly different from 50 mg Ro 15-8081 values.

stration of the four active drugs on the one hand and of placebo on the other. The general increase of threshold values after administration of the active drugs was reflected by a significant *F*-ratio for the time-factor ($F(11,864) = 8.63, P < 0.001$).

Tolerance to electrically induced pain Tolerance increased markedly after all of the active treatments but decreased after placebo (Figure 2). Codeine had the most prominent effect and peak values were reached 120 to 150 min after administration. After the three doses of Ro 15-8081, maximal activities were observed after 150 to 240 min; in the following periods their effects differed neither from those of codeine nor from each other. The analysis revealed that the treatments yielded significantly different effects ($F(4,864) = 117.23, P < 0.001$). The significant *F*-

ratio for the interaction treatment $\times$ time ($F(44,836) = 2.94, P < 0.001$) has to be attributed to the fact that the tolerance values increased over time in a similar fashion after all of the active treatments but decreased after placebo. The general increases in tolerance at least after the active treatments were reflected by a significant *F*-ratio for the time-factor ($F(11,864) = 4.84, P < 0.001$). The sequential test procedures showed that the mean effects of all of the active treatments (Table 1) differed significantly from those of placebo. Codeine (60 mg) produced significantly more analgesia than each of the three doses of Ro 15-8081, whose effects did not differ from each other. The comparisons of the treatment effects at each time point revealed that at 60 min after drug administration, the effects of 60 mg codeine as well as of 50 and 25 mg Ro 15-8081 differed significantly from those

Figure 2 Tolerance to electrically induced pain. Mean changes $\pm$ s.e. mean from basal values (Δ mA) 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 min after administration of 50 mg Ro 15-8081 (—), 25 mg Ro 15-8081 (— — —), 10 mg Ro 15-8081 (— · — · —), 60 mg codeine (— · —), and placebo (·····).

of placebo, whereas in the periods thereafter all active drugs were significantly superior to placebo.

Threshold to thermally induced pain Threshold increased rapidly after 60 mg codeine to reach peak values between 30 and 150 min after administration. After the three doses of Ro 15-8081, maxima were attained 90 to 120 min after administration, whereas placebo administration resulted in a decrease of threshold values (Figure 3). The analysis showed that the treatment effects differed significantly ($F(4,864) = 62.94, P < 0.001$). There was no indication for a significant interaction between the factors treatment and time. The similar development of threshold values over time resulted in a significant F -value for the time-factor ($F(11,864) = 3.24, P < 0.001$). The sequentially rejective tests to compare the mean treatment effects showed that all of the active treatments produced mean threshold elevations significantly greater than those after placebo (Table 1). The mean effect of 60 mg codeine was significantly stronger than that of each of the three doses of Ro 15-8081, and 50 mg Ro 15-8081 was significantly more analgetic than 10 and 25 mg Ro 15-8081. The sequential tests to compare the mean effects in each period of time showed that at 60 min after administration, the effects of 60 mg codeine and of 50 mg Ro 15-8081 were significantly superior to those of placebo, whereas from 120 min after administration onwards all of the active treatments were superior to placebo.

Psychomotor function

Reaction time to acoustic stimuli All treatments had only slight and highly variable effects and

there was a general trend towards an increase of reaction time over time. The treatment effects differed significantly ($F(4,864) = 4.56, P < 0.005$) and mean reaction times were significantly longer after 60 mg codeine than after placebo as well as after 25 and 50 mg Ro 15-8081 (Table 1). The effects of the three doses of Ro 15-8081 differed neither from each other nor from those of placebo.

Fine motor control Fine motor control decreased slightly after placebo, remained virtually unchanged after 10 mg Ro 15-8081, and increased slightly after 25 and 50 mg Ro 15-8081 as well as after 60 mg codeine. The treatment effects did not differ statistically and the mean effects over time were very similar (Table 1).

Subjective feelings and side effects

Subjective feelings The self-ratings in the dimensions drowsiness, tiredness, fitness for work, mood, cheerfulness, vigorousness, and burning of eyes were not influenced by any of the treatments in a systematic fashion (Table 2). However, after the administration of 60 mg codeine, the subjects rated themselves as 'warmer' than after placebo and after 10 and 50 mg Ro 15-8081. After 25 and 50 mg Ro 15-8081 the subjects rated themselves as warmer than after placebo. All of these differences were statistically significant. With all of the active treatments, the subjects rated themselves as significantly less hungry than with placebo; the most prominent effect was noted after 50 mg Ro 15-8081. After 60 mg codeine, significantly more mouth dryness was indicated than after all of the other treatments.

Side effects The responses of the subjects in the side effect questionnaires showed that

Figure 3 Threshold to thermally induced pain. Mean changes $\pm$ s.e. mean from basal values (Δ ms) 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 min after administration of 50 mg Ro 15-8081 (—), 25 mg Ro 15-8081 (---), 10 mg Ro 15-8081 (----), 60 mg codeine (-.-.), and placebo (.....).

Table 2 Self-rated subjective feelings. Mean changes, in cm, $\pm$ s.e. mean from basal ratings after administration of 10 mg, 25 mg and 50 mg Ro 15-8081, 60 mg codeine and placebo

Self-ratings	10 mg	Ro 15-8081 25 mg	50 mg	Codeine 60 mg	Placebo
Drowsiness	1.5 $\pm$ 0.2	1.4 $\pm$ 0.2	1.0 $\pm$ 0.2	1.3 $\pm$ 0.2	1.4 $\pm$ 0.2
Tiredness	1.4 $\pm$ 0.2	1.2 $\pm$ 0.2	0.7 $\pm$ 0.2	0.7 $\pm$ 0.2	1.5 $\pm$ 0.2
Fitness for work	-1.2 $\pm$ 0.2	-1.3 $\pm$ 0.2	-1.0 $\pm$ 0.2	-0.7 $\pm$ 0.2	-0.7 $\pm$ 0.2
Well-being	-0.5 $\pm$ 0.1	-0.6 $\pm$ 0.1	-0.8 $\pm$ 0.1	-0.5 $\pm$ 0.1	-1.0 $\pm$ 0.1
Mood	-0.2 $\pm$ 0.1	0.1 $\pm$ 0.1	-0.2 $\pm$ 1.2	0.1 $\pm$ 0.1	-0.4 $\pm$ 0.1
Cheerfulness	-0.4 $\pm$ 0.1	-0.1 $\pm$ 0.1	-0.6 $\pm$ 0.1	-0.2 $\pm$ 0.1	-0.8 $\pm$ 0.1
Vigorousness	0.0 $\pm$ 0.1	-0.6 $\pm$ 0.1	-0.8 $\pm$ 0.2	-0.6 $\pm$ 0.1	-1.0 $\pm$ 0.2
Warmth	-0.1 $\pm$ 0.1 ^b	0.4 $\pm$ 0.2 ^a	0.2 $\pm$ 0.1 ^{a,b}	0.7 $\pm$ 0.1 ^a	-0.3 $\pm$ 0.1
Hunger	0.0 $\pm$ 0.2 ^{a,c}	-0.5 $\pm$ 0.2 ^a	-0.6 $\pm$ 0.2 ^a	-0.2 $\pm$ 0.2 ^a	0.8 $\pm$ 0.2
Dryness of mouth	-0.1 $\pm$ 0.2 ^b	-0.4 $\pm$ 0.2 ^b	0.3 $\pm$ 0.2 ^b	1.2 $\pm$ 0.2 ^a	0.0 $\pm$ 0.2
Burning of eyes	-0.9 $\pm$ 0.2	-0.7 $\pm$ 0.1	-0.2 $\pm$ 0.1	-0.5 $\pm$ 0.1	-0.7 $\pm$ 0.1

^aSignificantly different from placebo values; ^bsignificantly different from 60 mg codeine values;

^csignificantly different from 50 mg Ro 15-8081 values.

drowsiness, tiredness, concentration difficulties, lightheadedness, dizziness, abdominal pain, and mood changes were experienced no more often after the three doses of Ro 15-8081 than after placebo (Table 3). Nausea, abdominal discomfort, and headache were reported slightly more frequently after 10, 25, and 50 mg Ro 15-8081 than after placebo. After 60 mg codeine there were more reports of lightheadedness and dizziness than after all of the other treatments.

Discussion

The results of the present study show that Ro 15-

8081 produces marked and long-lasting elevations of threshold and tolerance to electrically and of threshold to thermally induced cutaneous pain in healthy man. The effects of all doses were significantly superior in attenuating pain than those of placebo, but did not differ systematically from each other except for threshold to thermally induced pain, where 50 mg Ro 15-8081 were significantly more active than 10 and 25 mg of the compound. The absence of a clear dose-response relationship on threshold and tolerance to electrically induced pain may indicate that maximal analgesic effects were reached with all of the employed doses of Ro 15-8081 and that

Table 3 Side effects. Symptom-scores* after administration of single oral doses of 10 mg, 25 mg, and 50 mg Ro 15-8081, 60 mg codeine and placebo

Side effect	10 mg	Ro 15-8081 25 mg	50 mg	Codeine 60 mg	Placebo
Sleepiness	5.3	4.8	2.3	1.3	4.4
Tiredness	2.9	3.6	0.1	-0.2	4.4
Concentration difficulties	2.0	1.6	2.2	2.9	1.1
Lightheadedness	2.9	0.8	0.2	5.8	1.6
Dizziness	0.8	0.8	0.5	2.8	0.6
Nausea	1.0	0.7	1.4	0.3	0.1
Abdominal discomfort	2.3	3.0	2.7	0.6	1.3
Abdominal pain	-0.5	-0.6	1.0	0.1	0.3
Headache	0.8	0.8	1.9	0.4	0.4
Mood changes	1.7	0.5	0.3	0.7	0.7
Euphoria	0.3	0.8	1.0	0.8	-1.4
Dysphoria	1.5	0.3	0.2	0.1	0.7
Sum	21.0	17.1	13.8	15.6	14.2

*Symptom scores are derived from the mean number of subjects reporting a side effect in the twelve 30 min periods after drug administration minus the mean number of subjects reporting this side effect in the two 30 min periods before drug administration. All reported side effects are weighted by their severity (1, mild; 2, disturbing; 3, unbearable).

lower doses may already be active. The fast onset of the analgesic action of Ro 15-8081 suggests that the mechanism by which this effect is brought about involves the blockade of 5-HT and noradrenaline reuptake, effects which occur shortly after administration, rather than a down-regulation of the sensitivity of monoaminergic receptor sites, which is held responsible for the antidepressant action of the drugs and requires prolonged contact of such receptors with their neurotransmitters. There is a wide variety of reports on the actions of monoamine uptake inhibiting antidepressant agents on chronic pain: disorders in which treatment with such drugs has produced good results include chronic headaches, facial, cervical, and low-back pain as well as post-herpetic neuralgia (for review see Rosenblatt *et al.*, 1984). It has been proposed that the analgesic effect of antidepressant drugs has to be attributed mainly to a heightened serotonergic activity in the central nervous system (Messing & Lytle, 1977). However, mixed 5-HT/noradrenaline uptake inhibitors seem to be superior in analgesic activity to selective 5-HT uptake inhibitors. Zimelidine, which inhibits the neuronal reuptake of 5-HT to a much greater extent than that of noradrenaline (Ross *et al.*, 1981), has been shown to alleviate chronic pain as assessed by the investigators' ratings significantly better than placebo (Gourlay *et al.*, 1986), but to yield significantly less pain relief in patients with post-herpetic neuralgia than the mixed 5-HT/noradrenaline reuptake inhibitor, amitriptyline (Watson & Evans, 1985). In contrast to their effects on chronic pain states, there is only scarce information on the effects of antidepressant drugs of the 5-HT and/or noradrenaline reuptake inhibitor class on acute and on experimentally induced pain in humans. Using electrical stimulation of the dental pulp and the sensory decision method, Chapman & Butler (1978) were not able to discriminate between the effects of the tricyclic antidepressant, doxepin, and placebo, whereas in a study using intracutaneous electrical shocks as pain stimuli, imipramine 100 mg was found to be superior to placebo and about equipotent to

meperidine 150 mg in its action on pain estimates and somatosensory evoked potentials (Bromm *et al.*, 1986). In the present study, the onset of analgesic activity of Ro 15-8081 was clearly slower than after codeine, whereas the attained peak activity was only slightly inferior to that of codeine. In combination, these facts led to the significantly lower overall analgesic activity of Ro 15-8081 in comparison with codeine. A somewhat weaker analgesic activity of Ro 15-8081 than of codeine has also been observed in a study on the responses of Rhesus monkeys to pain induced by electrical stimulation of the dental pulp (Hoffmann-La Roche, 1986). Together with data from animal studies, the results of the present study suggest that 5-HT and/or noradrenaline play not only a role in the regulation of chronic pain, but also in the perception and the processing of acute pain. Ro 15-8081 had no effects on psychomotor function as measured by a reaction time and a fine motor control task, respectively, and also did not affect self-rated subjective feelings indicative of altered central nervous system arousal, well-being, and mood. These findings are consonant with observations made in animal studies, in which neither stimulatory nor depressant effects of Ro 15-8081 on central nervous functions were found (Hoffmann-La Roche, 1986). Similarly, the low incidence of side effects after administration of Ro 15-8081, which exceeded the incidence after placebo only slightly, confirms findings obtained in studies on dogs: Ro 15-8081 in doses of 5, 15, and 30 mg kg⁻¹ day⁻¹, i.e., in daily doses 30 to 40 times higher than the single doses used in the present study, were well tolerated during a 4-week period of regular administration (Hoffmann-La Roche, 1986). In conclusion, 10, 25, and 50 mg Ro 15-8081 elevate threshold and tolerance to electrically and threshold to thermally induced cutaneous pain to about the same degree than does 60 mg codeine, although the onset of action is somewhat slower than after codeine. Further studies will be necessary to evaluate whether Ro 15-8081 is also effective in clinical pain states.

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