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EFFECTS OF GRADED ORAL DOSES OF MEPTAZINOL AND PENTAZOCINE IN COMPARISON WITH PLACEBO ON EXPERIMENTALLY INDUCED PAIN IN HEALTHY HUMANS

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1 The opioid agonist/antagonist meptazinol has proven to exert significant analgesia in a series of painful conditions.

2 This study investigated the effects of single oral doses of meptazinol 100, 200, and 400 mg in comparison with pentazocine 50 and 100 mg and with placebo on experimentally induced pain. In addition, the side effect profiles were assessed.

3 Twenty-four healthy subjects participated each in six experiments in which they received, in random double-blind fashion, each of the treatments. Every experiment comprised 10 series of measurements, two before and eight after drug administration, carried out at 30 min intervals.

4 Meptazinol produced significant dose-related increases of threshold and tolerance to electrically and thermally induced pain.

5 Meptazinol 400 mg was significantly superior to placebo in all pain measures and proved as effective as pentazocine 50 and 100 mg, which yielded about equal effects.

6 Meptazinol 200 mg was significantly weaker than pentazocine 50 mg and differed significantly from placebo only in its effects on pain tolerance.

7 Meptazinol did not cause any severe side effects or systematic alterations of respiration, blood pressure, heart rate and central nervous functions. Pentazocine caused a higher number and more severe side effects, one subject reporting severe dysphoria after pentazocine 100 mg.

8 The results give further evidence that meptazinol is well suited to replace other opioid analgesics compromised by a high incidence of adverse effects.

Keywords meptazinol pentazocine experimentally induced pain

Introduction

Meptazinol (Wyeth, Maidenhead, England) is a potent opioid analgesic of the mixed agonist/antagonist type. It exerts reliable analgesic effects after parenteral, oral, and rectal administration, and the duration and the degree of analgesia was found to be dose-dependent over a range of 50–400 mg (Stephens *et al.*, 1978). An intramuscular (i.m.) dose of 75 mg meptazinol was reported to be as effective in relieving pain in cancer patients as 60 mg pentazocine (Staquet, 1978), and in post-operative patients, doses of 60–100 mg produced as much analgesia as 100 mg pethidine (Hedges *et al.*, 1980). About five times the parenterally effective dose of meptazinol is required for effective analgesia via the oral route (Stephens *et al.*, 1978). This is not due to poor absorption, as meptazinol is absorbed from the gut almost completely (Franklin *et al.*, 1975), but to an extensive metabolism of the drug on its first passage through the liver. In post-operative pain, oral doses of 400 mg meptazinol were found to be significantly superior to placebo (Hedges *et al.*, 1977; Paymaster, 1976). In elderly patients suffering moderate to severe pain from a variety of chronic conditions, meptazinol 100 mg orally provided not only better analgesia than placebo, but also, during the first hours after administration, than pentazocine 25 mg (Pearce & Robson, 1980). In patients with chronic rheumatoid and osteoarthritis (Flavell-Matts & Ward, 1980) and in patients with chronic backache (Ward, 1981), 200 mg meptazinol was as effective as 50 mg pentazocine. In patients suffering from chronic painful musculoskeletal conditions, meptazinol 200 mg, administered 3–6 hourly, was significantly superior to placebo and produced pain relief equivalent to paracetamol 1000 mg (Wade

& Ward, 1982). In a study with experimentally induced tooth pulp pain in healthy volunteers, doses of 50, 100, 150, and 200 mg meptazinol produced linear dose-related effects, only the dose of 200 mg, however, providing significantly better analgesia than placebo (Gabka & Price, 1982). These reports, together with the fact that meptazinol has no effects on respiratory function (Paymaster, 1976; Stephens *et al.*, 1978; Jordan, 1982; Pearce & Robson, 1980), blood pressure, electrocardiogram, and pulse rate (Budd, 1976; Stephens *et al.*, 1978; Pearce & Robson, 1980; Gabka & Price, 1982), is characterised by a low order of dependence liability (Stephens *et al.*, 1978), and has not been reported to cause nalorphine-like psychotomimetic effects suggest that the drug is well suited for therapeutic application in a wide spectrum of painful conditions. The present study was aimed to investigate, in healthy human subjects and under double-blind conditions, the effects of oral doses of 100, 200, and 400 mg meptazinol in comparison to 50 and 100 mg pentazocine as well as to placebo on experimentally induced pain. In addition, the study assessed the drugs' effects on central nervous system arousal, psychomotor function, subjective feelings, as well as on cardiovascular and respiratory functions.

Methods

Subjects

Twelve female and twelve male healthy subjects ranging in age from 20 to 39 years were studied. None of them took any drugs during the course of the study, with the exception of nine 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 millisecond (ms) duration and a pulse frequency of 30 per second (s) were used to induce pain (Lahoda *et al.*, 1977; Stacher *et al.*, 1979, 1982a, 1982b). The stimuli were administered by means of a pair of silver ball electrodes attached to the earlobule of the subjects' non-dominant side. In a first run, the stimuli were triggered by an experimenter. Their intensity increased, in steps of 0.05 milliampère (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. Six chains of electrical stimuli were presented. The interval between the chains ranged randomly from 15 to 25 s. In a second run, the subjects administered the stimuli on their own. They were instructed to turn a wheel fitted with a handle and thereby to increase stimulus intensity until they felt unable to tolerate any further increase and to turn the wheel back at this very moment. The stimulation was stopped on the reversal of direction and the attained value was recorded, in mA, as tolerance to self-administered painful stimuli. In each series of measurement, this procedure was repeated four times at 30 s intervals.

Thermal stimulation Radiant heat of a constant intensity was used to induce pain (Stacher *et al.*, 1982a, 1982b). On the volar surface of the subjects' dominant forearm, six spots were marked and numbered from one to six. 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. The intervals between the application of the radiant heat stimuli ranged randomly between 15 and 25 s.

Assessment of central nervous system arousal, psychomotor function, and of subjective feelings

Electroencephalogram The EEG as an index of arousal was recorded with the subjects lying with closed eyes for 2 min. The active electrodes were placed at a parietal (P_3, 10–20 International System) and at an occipital (O_1) site and were referenced to the mastoid (A_1). EEG signals were digitised on-line by a Hewlett-Packard 21MX E-series computer at 100 Hz, band-pass filtered, and subjected to a Fast Fourier Transform. The relative spectral power densities of the θ- (4–7 Hz), slower α- (8–9 Hz), faster α- (10–13 Hz), slower β- (14–20 Hz), and faster β- (21–30 Hz) range of frequencies were analysed. In addition, the θ-to-α ratio was computed as an index of drowsiness (Gevins *et al.*, 1977).

Reaction time to acoustic stimuli as a measure of sensorimotor performance was recorded in response to six tones presented with random intervals ranging from 10 to 20 s and the mean reaction time was scored.

Critical flicker fusion threshold as an index for change in overall integrative activity of the central nervous system (Hindmarch, 1980) was measured using the method of limits. The intensity of the light source was kept constant, while the frequency was progressively decreased or increased, respectively. The subjects were instructed to press a key as soon as, with increasing frequency, they perceived the flickering light as a steady light or, with decreasing frequency, the steady light as flickering. Four trains of stimuli with increasing and four trains with decreasing frequency were presented in alternating order.

Fine motor control as an index of motor function and behavioural coordination 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.

Subjective feelings of activation, well-being, mood, and warmth were assessed using visual analogue scales containing 18 pairs of polar adjectives, written on the right and the left edge of a sheet of paper. Between the two words there was a 10 cm line and the subjects were instructed to make a check mark at that point of the line, which they considered to indicate most correctly their feelings in the given moment. Each three pairs of adjectives were aimed to obtain information on activation ('awake – drowsy', 'quick – slow', 'enterprising – inert'), on well-being ('happy – unhappy', 'sultry – clear', 'oppressed – free'), and on mood ('merry – sad', 'euphoric – dysphoric', 'pleasant – qualmish'), while the pairs 'warm – cold' and 'sweating – shivering' were aimed to quantitate feelings of warmth. The remaining pairs were non-relevant to the above dimensions. The mean ratings in each dimension were analysed.

Measurement of cardiovascular and respiratory functions

Systolic and diastolic blood pressure were measured by means of an automatic device using an inflatable cuff around the non-dominant arm.

Heart rate was recorded on the basis of an electrocardiogram derived from two chestwall electrodes.

Respiratory rate was monitored using a strain gauge transducer mounted around the subjects' abdomen and recorded as cycles/min.

Assessment of side effects

Side effects reported spontaneously by the subjects were recorded together with the experimenters' observations.

Experimental design

Each subject took part in six experimental sessions separated by intervals of 3 or 4 days. Before they entered the experiments, the subjects were given all necessary instructions and had one training session to become familiar with the experimental procedure and to preclude learning effects. The subjects were instructed to come fasting to the laboratory at 08.00 h in the morning. On arrival, they were given a cup of mallow tea and half a slice of buttered bread. The experiment started 30 min after the end of this meal. In each session, ten series of measurements were carried out: 30 min and immediately before, as well as 30, 60, 90, 120, 150, 180, 210 and 240 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, critical flicker fusion threshold, fine motor control, tolerance to self-administered painful electrical stimuli, as well as EEG, systolic and diastolic blood pressure, heart rate, respiratory rate, and the subjective feelings of activation, well-being, mood and of warmth were recorded sequentially.

On each experimental day, the subjects received, according to a randomisation plan with four 6×6 Latin squares and under double-blind conditions, one of the following treatments: (1) meptazinol 100 mg, (2) meptazinol 200 mg, (3) meptazinol 400 mg, (4) pentazocine 50 mg, (5) pentazocine 100 mg and (6) placebo. All drugs were administered as tablets of identical shape and colour together with 50 ml water. 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 eight 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 factor 'sex' and the fixed within-subjects factors 'treatment' (1 to 6), 'day' (experimental days 1 to 6), 'time' (eight periods after drug administration), as well as of the random factor 'subject' (1 to 24). To investigate dose-response relationships, linear con-

trasts over the treatment means of the three doses of meptazinol and of the two doses of pentazocine were calculated on the basis of the analysis of variance. In addition, a comparison was made between the mean effect of the active drugs on the one hand and the effect of placebo on the other. To evaluate differences between the mean effects of all of the six treatments, a sequentially rejective multiple test procedure (Holme, 1979) was used. In this procedure, which was also 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 neither the sex of the subjects, nor the sequence in which they received the treatments on the six experimental days had a significant influence on their responses to the administered treatments.

Threshold to electrically induced pain

Threshold values increased with all treatments, all of the active substances causing higher elevations than placebo (Figure 1). The analysis showed that the treatments produced significantly differing effects (F (5,800) = 8.93, $P < 0.0005$) and that the mean effect of the active treatments was significantly larger than that of placebo (F (1,800) = 18.60, $P < 0.0005$). With meptazinol, threshold increased linearly with increasing dose (F (1,800) = 13.64, $P < 0.0005$), whereas the effects of the two doses of pentazocine did not differ statistically. Meptazinol 400 mg and the two pentazocine doses produced analgesic effects which lasted for the entire experimental time. By contrast, meptazinol 100 and 200 mg were active only in the first 2 h after administration. The sequential test procedure revealed that meptazinol 400 mg and the two doses of pentazocine were not only significantly superior to placebo, but also to the effects of 100 mg meptazinol. Meptazinol 400 mg and pentazocine 50 mg were significantly more active than meptazinol 200 mg.

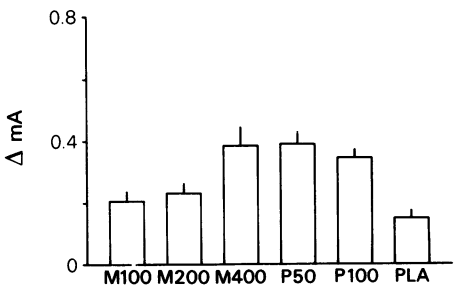

Figure 1 Threshold to electrically induced pain. Overall mean changes ± s.e. mean (Δ mA) from basal values in the 240 min after administration of meptazinol 100 mg (M100), meptazinol 200 mg (M200), meptazinol 400 mg (M400), pentazocine 50 mg (P50), pentazocine 100 mg (P100), and placebo (PLA).

Tolerance to electrically induced pain

Tolerance increased markedly after the administration of the active drugs, but only slightly after placebo. While the effects of meptazinol 400 mg and of pentazocine 50 and 100 mg lasted until the end of the experimental time, the effects of the two lower doses of meptazinol tended to subside after the first 2 h (Figure 2). The analysis revealed that the treatments acted significantly different (F (5,800) = 12.96, $P < 0.0005$) and that the mean effect of the active drugs differed significantly from placebo (F (1,800) = 36.34, $P < 0.0005$). Meptazinol increased the tolerance values dose-dependently in a linear fashion (F (1,800) = 18.58, $P < 0.0005$). By contrast, the effects of the two doses of pentazocine were virtually undistinguishable, 50 mg producing a slightly higher peak effect than 100 mg. The sequential test procedure showed that all active drugs, except of meptazinol 100 mg, were significantly more active than placebo. Meptazinol 400 mg and the two doses of pentazocine were significantly superior to meptazinol 100 mg, meptazinol 400 mg and pentazocine 50 mg were significantly more active than meptazinol 200 mg.

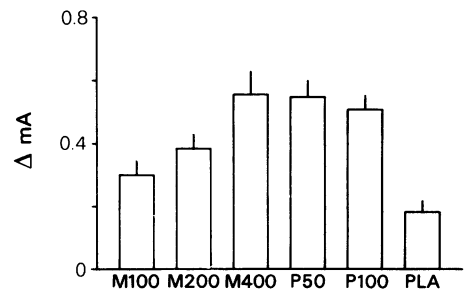

Figure 2 Tolerance to electrically induced pain. Overall mean changes ± s.e. mean (Δ mA) from basal values in the 240 min after administration of meptazinol 100 mg (M100), meptazinol 200 mg (M200), meptazinol 400 mg (M400), pentazocine 50 mg (P50), pentazocine 100 mg (P100), and placebo (PLA).

Tolerance to self-administered painful electrical stimuli

Tolerance to self-administered painful stimuli was influenced in the same fashion by the various treatments as the tolerance to painful stimuli inflicted by an experimenter: while there were only minor changes after placebo, marked increases occurred after all of

the active substances (Figure 3). The effects of the two doses of pentazocine increased during the entire experimental time, whereas the effects of meptazinol reached their maximum during the first 2 h after administration and tended to decrease thereafter. The analysis showed that the treatment effects differed significantly (F (5,800) = 5.71, $P < 0.0005$) and that the mean effect of the active drugs was significantly stronger than the effect of placebo (F(1,800) = 10.20, $P < 0.001$). With increasing dose of meptazinol, tolerance levels increased in a linear fashion (F (1,800) = 11.09, $P < 0.0005$). The two doses of pentazocine produced similar analgesic effects, the overall effect of 50 mg pentazocine being slightly larger than that of 100 mg. The sequential tests showed that meptazinol 400 mg as well as pentazocine 50 and 100 mg differed significantly from placebo, and that meptazinol 400 mg and pentazocine 50 mg acted significantly stronger than both meptazinol 100 and 200 mg.

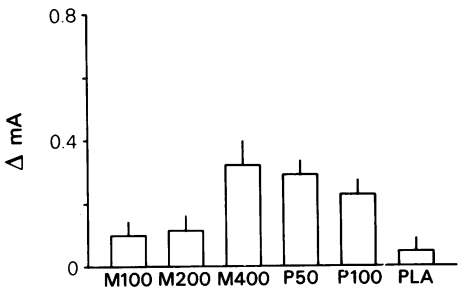

Figure 3 Tolerance to self-administered painful electrical stimuli. Overall mean changes ± s.e. mean (Δ mA) from basal values in the 240 min after administration of meptazinol 100 mg (M100), meptazinol 200 mg (M200), meptazinol 400 mg (M400), pentazocine 50 mg (P50), pentazocine 100 mg (P100), and placebo (PLA).

Threshold to thermally induced pain

Threshold increased with all treatments, meptazinol 100 mg causing smaller increments than placebo. All drug effects peaked at 2 h after administration, whereas the highest responses to placebo occurred already after 1 h (Figure 4). The analysis revealed that the treatments acted significantly different (F (5,800) = 3.43, $P < 0.005$). Meptazinol produced dose-related linear elevations of threshold (F (1,800) = 5.54, $P < 0.01$), whereas pentazocine 100 mg caused only slightly larger changes than did pentazocine 50 mg. The sequential comparisons showed that both doses of pentazocine were significantly more active than meptazinol 100 mg.

Electroencephalogram

With the exception of the faster β-range of frequencies,

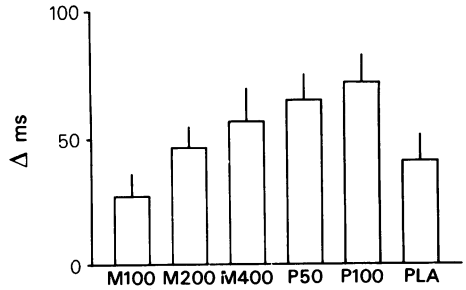

Figure 4 Threshold to thermally induced pain. Overall mean changes ± s.e. mean (Δ ms) from basal values in the 240 min after administration of meptazinol 100 mg (M100), meptazinol 200 mg (M200), meptazinol 400 mg (M400), pentazocine 50 mg (P50), pentazocine 100 mg (P100), and placebo (PLA).

the EEG was not systematically influenced by any of the treatments. The relative spectral power density in the faster β-range decreased by 0.48% after placebo, by 0.34, 0.24, and 0.06% after meptazinol 100, 200, and 400 mg, respectively, and by 0.10% after pentazocine 50 mg. After pentazocine 100 mg, by contrast, there was an increase of 0.58%. The treatment effects differed significantly (F (5,800) = 11.59, $P < 0.0005$) and the mean effect of the active treatments was significantly larger than the effect of placebo (F (1,800) = 14.02, $P < 0.0005$). There were linear dose-response relationships for both meptazinol (F(1,800) = 3.29, $P < 0.04$) and pentazocine (F (1,800) = 19.39, $P < 0.0005$). The sequential tests showed that the effects of meptazinol 400 mg and of pentazocine 100 mg differed significantly from placebo.

Reaction time to acoustic stimuli

Slight increases of reaction time in the magnitude of 10–15 ms occurred with all of the six treatments. The increments were most pronounced with the two doses of pentazocine, whereas all doses of meptazinol caused smaller increases than did placebo (Figure 5). The analysis revealed no significant differences between the treatments and no significant dose-response relationships.

Critical flicker fusion threshold

Decreases of threshold occurred with all treatments, but only the decrements caused by pentazocine 100 mg and by meptazinol 400 mg were larger than those with placebo (Figure 6). The analysis showed that the effects differed significantly (F (5,800) = 5.01, $P < 0.0005$) and that the mean effect of the active drugs was significantly larger than that of placebo (F(1,800) = 2.99, $P < 0.05$). There were significant linear dose-response relationships for both meptazinol (F(1,800) = 10.69, $P < 0.001$) and pentazocine (F (1,800) =

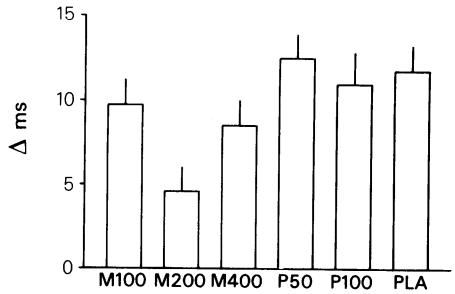

Figure 5 Reaction time to acoustic stimuli. Overall mean changes ± s.e. mean (Δ ms) from basal values in the 240 min after administration of meptazinol 100 mg (M100), meptazinol 200 mg (M200), meptazinol 400 mg (M400), pentazocine 50 mg (P50), pentazocine 100 mg (P100), and placebo (PLA).

6.40, $P < 0.006$). The sequential tests revealed that only the effect of pentazocine 100 mg differed significantly from placebo and that meptazinol 400 mg and pentazocine 100 mg were more active than the two lower meptazinol doses.

Fine motor control

Fine motor control remained virtually unchanged after the administration of placebo and increased with 100 and 400 mg meptazinol, whereas it decreased with meptazinol 200 mg, pentazocine 50 mg and, markedly, with pentazocine 100 mg (Figure 7). The analysis revealed significantly differing treatment effects (F (5,800) = 6.41, $P < 0.0005$) and a significant linear dose-response relationship for pentazocine (F (1,800) = 3.39, $P < 0.04$). The effect of pentazocine 100 mg but not those of other treatments differed significantly from placebo.

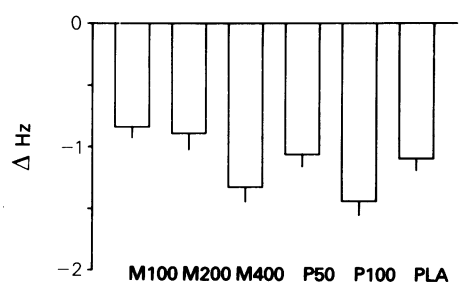

Figure 6 Critical flicker fusion threshold. Overall mean changes ± s.e. mean (Δ Hz) from basal values in the 240 min after administration of meptazinol 100 mg (M100), meptazinol 200 mg (M200), meptazinol 400 mg (M400), pentazocine 50 mg (P50), pentazocine 100 mg (P100), and placebo (PLA).

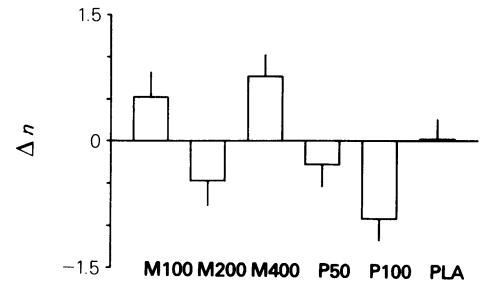

Figure 7 Fine motor control. Overall mean changes ± s.e. mean (Δ n, number of correct hits) from basal values in the 240 min after administration of meptazinol 100 mg (M100), meptazinol 200 mg (M200), meptazinol 400 mg (M400), pentazocine 50 mg (P50), pentazocine 100 mg (P100), and placebo (PLA).

Subjective feelings

The self-ratings in the dimensions activation and well-being as well as of mood were not influenced systematically by any of the treatments. On the self-ratings of warmth, however, the six treatments had significantly differing effects (F (5,800) = 5.88, $P < 0.005$): whereas placebo caused no changes from basal values and the three doses of meptazinol produced slight and about equal increases, the increases were more pronounced and dose-dependent (F (1,800) = 11.04, $P < 0.0005$) with pentazocine. The mean effect of the active drugs was significantly stronger than that of placebo (F (1,800) = 9.18, $P < 0.0015$) and the sequential tests showed that pentazocine 100 mg prompted the subjects not only to indicate more warmth than did placebo but also than the three doses of meptazinol.

Blood pressure

Systolic pressure decreased with all of the treatments, meptazinol 400 mg and placebo producing the same decrement of 5.1 millimetres of mercury (mm Hg). Pentazocine 100 mg caused the smallest pressure decrease, i.e., 0.9 mm Hg. The analysis showed that the treatments differed significantly (F (5,800) = 9.77, $P < 0.0005$) and that there was a significant linear dose-response relationship for pentazocine (F (1,800) = 27.19, $P < 0.0005$).

Diastolic pressure increased slightly under the influence of all treatments. The increments ranged between 3.9 mm Hg after placebo and 6.5 mm Hg after pentazocine 100 mg. The analysis revealed that there were no significant differences between the treatment effects.

Heart rate

Heart rate was not changed systematically by any of the treatments.

Table 1 Side effects of meptazinol, pentazocine and placebo

	Meptazinol			*Pentazocine*		*Placebo*
Side effect	*100 mg*	*200 mg*	*400 mg*	*50 mg*	*100 mg*	
Drowsiness	–	1	–	–	4	–
Tiredness	6	8	6	5	12	3
Lethargy	–	1	1	1	–	–
Lightheadedness	–	3	3	4	5	–
Concentration difficulties	–	1	2	2	2	1
Euphoria	1	2	2	–	3	1
Dysphoria	–	–	1	–	1	–
Mood changes	–	1	–	–	–	–
Oppression	–	–	1	–	–	–
Dizziness	1	1	3	2	5	–
Nausea	–	1	4	–	2	–
Abdominal discomfort	–	1	3	–	2	–
Warmth	–	1	3	3	3	–
Headache	1	–	1	–	1	1
Trembling	–	–	–	–	1	–
Palpitation	–	–	–	–	1	–
Number of subjects with side effects	8	12	12	11	18	5
Number of side effects	9	21	30	17	42	6

Respiratory rate

With placebo, the respiratory rate averaged over the entire experimental time accelerated by 1.1 cycles/min, while the rate remained virtually unchanged after administration of meptazinol. After pentazocine 50 mg there was a deceleration of 1.5 cycles/min, which contrasted to an acceleration of 0.4 cycles/min after pentazocine 100 mg. The analysis revealed significantly differing treatment effects ($F(5,800) = 5.78$, $P < 0.0005$) and a significant difference between the mean effect of the active treatments and placebo ($F(1,800) = 10.17$, $P < 0.001$). The deceleratory effect of pentazocine 50 mg differed significantly from the effect of all of the other treatments.

Side effects

The number of subjects reporting side effects as well as the total number of side effects were lowest with placebo and increased with increasing dose of both meptazinol and pentazocine. Pentazocine 100 mg caused the highest number of side effects. The quality of side effects was similar for meptazinol and pentazocine. Tiredness, lightheadedness, and dizziness were reported most frequently (Table 1). Mild euphoria was reported once after meptazinol 100 mg and twice after each of the two higher meptazinol doses, as compared to three times after pentazocine 100 mg. Mild dysphoria was reported by one subject after meptazinol 400 mg, whereas after pentazocine 100 mg one subject complained of severe dysphoria. The latter reaction was the only severe adverse effect reported or observed in the entire study.

Discussion

The results of the present study show that meptazinol produced dose-related effects on threshold and tolerance to electrically and on threshold to thermally induced pain. Meptazinol 400 mg was significantly more active than placebo and equally effective as both 50 and 100 mg pentazocine. The two doses of pentazocine yielded significantly more analgesia than placebo, while their effects did not differ statistically from each other. 200 mg meptazinol proved to be significantly inferior to pentazocine 50 mg but was clearly more active than placebo, although this difference reached a significant level only for tolerance to electrically induced pain and not for the other pain measures. This inferiority of meptazinol 200 mg to pentazocine 50 mg contrasts to earlier studies, in which it was reported that the two dosages were equally effective (Ward, 1981) or that meptazinol 200 mg acted only insignificantly weaker than pentazocine 50 mg (Flavell-Matts & Ward, 1980). Meptazinol had only slight effects on central nervous system arousal and psychomotor function. Sensorimotor performance as measured by the reaction time task, overall integrative activity as assessed by the critical flicker fusion threshold, and fine motor control were impaired markedly more by pentazocine than by meptazinol. However, only the effects of pentazocine 100 mg on these functions differed significantly from placebo. The minor extent to which meptazinol influenced the objective measures of central nervous function is in concordance with the lack of subjectively perceived effects in the activation-, well-being-, and mood-dimensions as quantitated by the visual analogue

scales. The incidence of side effects increased dose-dependently with both drugs, the number as well as the intensity being higher with pentazocine than with meptazinol. However, with the exception of severe dysphoria after pentazocine 100 mg in one subject, all reported side effects were only mild. Blood pressure was not affected by meptazinol, and but slight pressor effects occurred with pentazocine 100 mg. Meptazinol was also devoid of respiratory depressant effects, while there was a distinct slowing of respiratory rate with pentazocine 50 mg. In conclusion, oral meptazinol produces dose-dependent effects on experimentally induced pain, 400 mg being equianalgesic to 50 and 100 mg pentazocine while inducing less undesirable effects. Meptazinol seems well suited to replace other opioid analgesics compromised by a high incidence of adverse effects.

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