Br. J. clin. Pharmac. (1987), **24**, 689–697

Meptazinol and pentazocine: plasma catecholamines and other effects in healthy volunteers

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1 This double-blind, random-order study was designed to compare the clinical effects and the plasma catecholamine responses after i.v. administration of meptazinol at doses 0.7 and 1.4 mg kg^{-1}, pentazocine at doses 0.3 and 0.6 mg kg^{-1} and saline placebo to six healthy volunteers.

2 Mean arterial pressure was not affected by either drug. Heart rate showed slight drug-related changes. Respiratory rate fell slightly with both drugs, but independently of dose.

3 The critical flicker fusion threshold-test and Maddox wing readings could both clearly differentiate active drugs from placebo. Meptazinol caused more nausea and dysphoria as expressed with visual analogue scales. Both analgesics caused short-lived feelings of euphoria.

4 After pentazocine plasma noradrenaline increased almost two-fold in 10–20 min. The effect of meptazinol was slightly smaller, whereas meptazinol caused a pronounced increase in plasma adrenaline concentrations in two of six subjects. Pentazocine had a smaller, but significant effect on plasma adrenaline.

5 We conclude that the effects of meptazinol in healthy volunteers do not differ markedly from those of pentazocine, although it may cause more nausea and dysphoria. The pronounced increase in plasma adrenaline concentrations in two of six subjects calls for caution in its use in patients with cardiac diseases.

Keywords meptazinol pentazocine healthy volunteers plasma catecholamines clinical effects

Introduction

Meptazinol is a new centrally acting analgesic drug. Its analgesic efficacy is comparable with typical opiates and mixed agonist-antagonists (Holmes & Ward, 1985; Paymaster, 1977; Robson, 1983). However, its negligible effects on respiration (Jones, 1983; Jordan *et al.*, 1979) and the cardiovascular system (Paymaster, 1977) differ from both morphine and partial agonists such as pentazocine. Also fewer central nervous system (CNS) side-effects (e.g. euphoria, dysphoria, hallucinations and effects on psychomotor performance) have been reported. Nausea and vomiting are the most often reported side-effects of meptazinol (Chestnutt & Dundee, 1986; Kaiko *et al.*, 1985; Spiegel & Pasternak, 1984).

The mode of action of meptazinol has been suggested to be related to its selectivity at μ_1-(high affinity) opioid binding sites, where it acts as a partial agonist (Spiegel & Pasternak, 1984; Green, 1983). In addition, a cholinergic mechanism has been implicated in its antinociceptive activity in some animal species (Bill *et al.*, 1983).

Pentazocine is a classical mixed agonist-antagonist analgesic with a slightly longer duration of

action when compared with meptazinol (Holmes & Ward, 1985). In previous studies pentazocine has increased plasma catecholamine concentrations about 70% above control values (Tammisto *et al.*, 1971). This increase comprised both adrenaline (A) and noradrenaline (NA) and was associated with elevations in systolic blood pressure and heart rate, and unpleasant subjective sensations. The purpose of this study was to compare the effects of meptazinol and pentazocine in healthy volunteers. The focus was on cardiovascular effects and rate of respiration, CNS side-effects, and plasma catecholamine concentrations.

Methods

Six healthy volunteers (three males and three females), mean age 29.5 years (range 22–41 years), mean weight 67.7 kg (range 55–80 kg) and mean height 172. 7 cm (range 160–184 cm), gave their informed consent to participate. The study was approved by the local ethics committee. The subjects had no history or signs of any significant illness and were not on drug treatment. Five were non-smokers. The study was performed in five separate sessions for each subject, with at least 1 week intervals between the sessions. After abstaining from alcohol for 36 h and from caffeinated beverages for 16 h, and having a light lunch 3 h before the sessions, the subjects had a polypropylene cannula inserted into an antecubital vein. They stayed recumbent and were allowed to rest for 30 min. After blood sampling and the baseline tests every subject received in a double-blind, random-order fashion meptazinol (Meptid®, Wyeth) at doses 0.7 and 1.4 mg kg^{-1}, pentazocine (Fortralin®, Medipolar) at doses 0.3 and 0.6 mg kg^{-1}, or saline placebo in a volume of 2 ml as a slow (60 s) i.v. injection. The higher dosages are maximal recommended i.v. doses for both drugs. We considered them to have equipotent analgesic effects. Venous blood samples for measurement of catecholamines in plasma were collected from the cannula just before and 5, 10, 20, 30, 45 and 60 min after the drug injections. The effects on CNS integrative functions were assessed with the Maddox wing apparatus (MW), which measures the centrally co-ordinated extraocular muscle balance expressed in diopters (Hannington-Kiff, 1970 a, b; Manner *et al.*, 1987 a, b) and with the critical flicker fusion threshold-test (c.f.f.), which reflects overall CNS arousal. The subjects were instructed to detect the fusion of a flickering red light (diameter 3 mm) at 1 m distance; expressed in Hz, mean of three observations for each time point (Simonson & Brozek, 1952; Smith & Misiak, 1976).

The subjective sensations of nausea, dysphoria, euphoria and sedation were measured with visual analogue scales (VAS). A 10 cm long line was used with numbers from 0 to 10 between the following extremes: nausea: none/vomiting; sedation; quite alert/ extremely tired; euphoria: none/extremely elevated mood; dysphoria: none/extremely dysphoric mood. The CNS function tests and subjective ratings were performed just before and 5, 10, 20, 30, 45, 60, 90, 120 and 180 min after drug administration. The respiratory rate (breaths min^{-1}), heart rate and systolic and diastolic blood pressure were also recorded at the same intervals. An automated indirect method was used for the cardiovascular measurements, averaging the value from two recordings (Nippon Colin 203 Y). All experiments were performed in a quiet laboratory, with stable artificial light and other environmental conditions. Catecholamines in plasma were determined using h.p.l.c. with electrochemical detection (Goldstein *et al.*, 1981). The method had a detection limit of 0.10 nM, and its intra-assay coefficient of variation was about 5% for noradrenaline and 10% for adrenaline in the physiological concentration range.

The statistical analysis was performed by analysis of variance for repeated measurements using BMDP programmes (factors were drug and time, Table 1). Mean ± s.d. values were computed from the raw data and for convenience expressed in tables for all results, although the VAS-scores are non-parametric in nature. In addition at every time point the changes from baseline (= predrug values) were compared by Student's *t*-test (paired data; Tables 2–5).

Results

Circulatory variables and respiration

Both study drugs caused a slight but insignificant increase in systolic blood pressure, i.e. + 12 mm Hg with meptazinol and + 11 mm Hg with pentazocine (means). This effect lasted longer after pentazocine than after meptazinol. Diastolic blood pressure was increased (also insignificantly) only after pentazocine. Mean arterial pressure was not significantly affected by either drug, whereas heart rate showed slight drug-related changes (drug-time interaction, $P < 0.01$; Tables 1 and 2). Respiratory rate fell slightly with both drugs, but independently of dosage (Tables 1 and 2).

Table 1 *F*-values and probability levels. Analysis of variance with repeated measurements

	Factor 1 = drug	*Factor 2 = time*	*Interaction*
Heart rate	0.31	6.95	1.77
P	NS	< 0.001	< 0.01
Respiratory rate	3.16	5.24	1.04
P	< 0.05	< 0.001	NS
Mean arterial pressure	1.61	4.08	1.31
P	NS	< 0.001	NS
Systolic blood pressure	1.22	4.98	1.52
P	NS	< 0.001	< 0.05
Diastolic blood pressure	1.70	2.97	1.22
P	NS	< 0.01	NS
Critical flicker fusion	1.69	17.04	5.15
P	NS	< 0.001	< 0.001
Δ Critical flicker fusion	27.49	12.63	3.46
P	< 0.001	< 0.001	< 0.001
Maddox wing	6.96	13.35	3.60
P	< 0.01	< 0.001	< 0.001
Adrenaline	2.68	2.53	2.32
P	NS	< 0.05	< 0.01
Noradrenaline	3.94	9.02	2.06
P	< 0.05	< 0.001	< 0.01
Visual analogue scales for:			
Nausea	5.99	3.53	1.97
P	< 0.01	< 0.01	< 0.01
Sedation	1.94	14.66	2.33
P	NS	< 0.001	< 0.001
Euphoria	6.90	22.76	4.76
P	< 0.01	< 0.001	< 0.001
Dysphoria	1.44	1.32	1.70
P	NS	NS	< 0.05

Psychophysiological measures

In the c.f.f.-threshold-test the subjects showed large interindividual variation already in the predrug values, and in absolute values the drug effect did not reach statistical significance; whereas the drug-time interaction was highly significant (Tables 1 and 3). When expressed as changes from baseline (Δ c.f.f.) the drug responses were clearly different from placebo (Tables 1 and 3) and further, meptazinol was found to produce a more marked, dose-dependent effect (max. -4.1 ± 1.1 Hz at 5 min after meptazinol 1.4 mg kg^{-1} i.v.; Table 3) compared with pentazocine 0.6 mg kg^{-1} i.v. (max -3.1 ± 0.9 Hz). The Maddox wing readings showed statistically significant responses (Table 1) for both drugs, but no marked differences between drugs or dosages were found (max. values $+7.8 \pm 4.7$ diopters and $+6.4 \pm 2.6$ diopters for meptazinol 1.4 mg kg^{-1} and pentazocine 0.6 mg kg^{-1} respectively).

Subjective estimates of nausea, sedation, euphoria and dysphoria are summarized in Table 4. The nausea scores reached statistical significance. This effect was marked with meptazinol at the higher dose 1.4 mg kg^{-1} in four of the six subjects and lasted about 90 min. No vomiting occurred, however. Pentazocine had only a minimal emetic effect. In sedation scores both study drugs caused dose-related increases with maximum values of 3.8 ± 1.5 at 10 min and 3.0 ± 1.5 at 5 min for pentazocine and meptazinol, respectively, both with higher doses. Only meptazinol produced dysphoria (marked in two

Table 2 Changes in heart rate, mean arterial pressure (MAP) and respiratory rate after administration of placebo, meptazinol and pentazocine to healthy volunteers

	Basal value	*Time (min)* 5	10	20	30	45	60	90	120	180
Heart rate (beats min^{-1})										
Placebo	64 ± 11	63 ± 9	62 ± 9	62 ± 9	59 ± 8	60 ± 7	61 ± 8	58 ± 7*	59 ± 8*	58 ± 8*
Meptazinol 0.7 mg	61 ± 9	61 ± 12	61 ± 12	58 ± 7	58 ± 7	58 ± 5	59 ± 8	57 ± 9	56 ± 7*	57 ± 8*
Meptazinol 1.4 mg	62 ± 12	62 ± 15	60 ± 13	61 ± 13	63 ± 18	64 ± 15	55 ± 10***	57 ± 10**	58 ± 9	58 ± 9
Pentazocine 0.3 mg	64 ± 11	66 ± 11	63 ± 14	61 ± 12	61 ± 10	60 ± 13	60 ± 11	58 ± 9	59 ± 11	58 ± 12
Pentazocine 0.6 mg	60 ± 9	66 ± 8	70 ± 13*	61 ± 9	65 ± 11	60 ± 8	59 ± 9	56 ± 8*	55 ± 8**	57 ± 4
MAP (mm Hg)										
Placebo	88 ± 16	88 ± 17	88 ± 17	86 ± 18	85 ± 16	87 ± 15	85 ± 16	84 ± 13	87 ± 16	88 ± 15
Meptazinol 0.7 mg	87 ± 16	92 ± 14	91 ± 15	90 ± 14	90 ± 15	88 ± 14	88 ± 15	89 ± 12	89 ± 13	87 ± 12
Meptazinol 1.4 mg	80 ± 11	88 ± 15*	86 ± 12**	85 ± 13*	86 ± 11*	82 ± 10	79 ± 13	81 ± 12	80 ± 9	81 ± 9
Pentazocine 0.3 mg	88 ± 9	93 ± 13	92 ± 10*	90 ± 10	92 ± 13	92 ± 13	90 ± 11	89 ± 12	90 ± 13	90 ± 11
Pentazocine 0.6 mg	80 ± 12	89 ± 13*	88 ± 16	87 ± 14	87 ± 11	85 ± 9	84 ± 9	84 ± 14	82 ± 14	79 ± 9
Respiratory rate (breaths min^{-1})										
Placebo	15.3 ± 0.8	14.8 ± 0.8	14.8 ± 1.2	14.3 ± 0.5*	14.0 ± 1.1*	14.3 ± 1.4	15.3 ± 0.8	14.8 ± 1.2	15.2 ± 0.8	15.2 ± 0.8
Meptazinol 0.7 mg	15.2 ± 1.0	14.0 ± 1.3	13.3 ± 1.2	13.2 ± 0.8*	13.8 ± 1.3*	13.8 ± 0.4*	14.7 ± 1.5	14.3 ± 1.5	14.3 ± 1.9	14.5 ± 1.8
Meptazinol 1.4 mg	14.0 ± 2.1	13.8 ± 3.6	13.0 ± 2.4	12.7 ± 1.8	13.5 ± 1.8	13.3 ± 1.8	13.0 ± 1.8	13.0 ± 1.3	12.8 ± 1.3*	13.0 ± 1.7*
Pentazocine 0.3 mg	14.5 ± 1.0	12.8 ± 2.0	12.7 ± 1.0*	12.5 ± 1.9	13.8 ± 1.3	13.5 ± 1.0	14.3 ± 1.6	14.2 ± 0.4	14.5 ± 0.8	14.7 ± 1.0
Pentazocine 0.6 mg	14.8 ± 1.2	12.3 ± 2.3**	12.7 ± 2.3*	13.2 ± 2.9	13.3 ± 1.5	13.5 ± 1.0*	13.8 ± 1.2*	13.8 ± 1.2	13.3 ± 1.4*	13.8 ± 1.2

Mean ± s.d., asterisks = Student's *t*-test, paired data (*vs* basal value), * = $P < 0.05$, ** = $P < 0.01$ and *** = $P < 0.001$.

Table 3 The effects of placebo, meptazinol and pentazocine on critical flicker fusion (c.f.f.) threshold and Maddox wing readings

	Basal value	*Time (min)* 5	10	20	30	45	60	90	120	180
C.f.f. (Hz)										
Placebo	31.3 ± 1.9	31.5 ±2.3	31.6 ± 1.8	31.8 ± 2.2	31.7 ± 2.2	31.7 ± 2.3	31.8 ± 2.2	31.6 ± 2.4	31.8 ± 2.3	31.6 ± 2.3
Meptazinol 0.7 mg	32.3 ± 2.5	29.7 ± 2.8***	29.4 ± 2.6***	29.3 ±1.3**	30.1 ±2.1**	30.8 ± 2.5**	31.3 ± 2.7**	32.0 ± 2.8	32.2 ± 2.6	32.4 ± 2.4
Meptazinol 1.4 mg	33.4 ± 2.2	29.3 ± 1.4***	30.3 ± 2.1***	30.1 ± 2.5**	29.7 ± 2.5**	30.4 ± 2.9***	30.6 ± 3.2**	30.8 ± 3.3*	30.6 ± 3.1**	31.3 ± 2.9**
Pentazocine 0.3 mg	30.9 ± 1.4	28.4 ± 0.9**	28.1 ± 1.3**	28.3 ± 1.4**	28.9 ± 1.4**	30.0 ± 2.2	29.9 ± 1.9*	30.5 ± 1.3	30.7 ± 1.3	30.8 ± 1.0
Pentazocine 0.6 mg	32.8 ± 2.2	29.8 ± 2.2***	29.9 ± 2.4**	30.6 ± 2.6**	30.8 ± 2.6**	31.3 ± 2.9**	31.3 ± 2.9*	31.6 ± 3.5	31.7 ± 3.2*	32.1 ± 3.0
Δ *C.f.f. (Hz)*										
Placebo		0.2 ± 0.5	0.3 ± 0.5	0.4 ± 0.7	0.3 ± 0.8	0.3 ± 0.7	0.4 ± 0.6	0.3 ± 1.1	0.5 ± 1.1	0.3 ± 0.7
Meptazinol 0.7 mg		−2.7 ± 0.7	−2.9 ± 0.9	−3.0 ± 1.5	−2.3 ± 1.1	−1.5 ± 0.6	−1.0 ± 0.5	−0.3 ± 0.6	−0.2 ± 0.7	0.1 ± 0.7
Meptazinol 1.4 mg		−4.1 ± 1.1	−3.1 ± 0.7	−3.3 ±1.4	−3.8 ± 1.5	−3.0 ± 1.0	−2.8 ± 1.4	−2.6 ± 1.6	−2.8 ± 1.6	−2.2 ± 1.2
Pentazocine 0.3 mg		−2.5 ± 1.0	−2.8 ± 1.3	−2.6 ± 1.5	−2.0 ± 0.8	−0.9 ± 1.1	−1.0 ± 0.9	−0.4 ± 0.9	−0.3 ± 0.8	−0.2 ± 0.5
Pentazocine 0.6 mg		−3.1 ± 0.9	−2.9 ± 1.1	−2.3 ± 0.9	−2.1 ± 0.8	−1.5 ± 0.9	−1.5 ± 1.0	−1.3 ± 1.7	−1.2 ± 1.1	−0.8 ± 1.0
Maddox wing (diopters)										
Placebo	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.6 ± 0.9	1.6 ± 0.9
Meptazinol 0.7 mg	1.6 ± 0.9	6.6 ± 4.2	6.6 ± 4.2*	5.0 ± 2.8*	4.4 ± 2.7	4.0 ± 2.3	4.0 ± 2.3	3.6 ± 2.1	3.0 ± 1.4	2.6 ± 1.3
Meptazinol 1.4 mg	2.0 ± 1.4	7.8 ± 4.7*	7.2 ± 3.4**	5.8 ± 2.3**	5.6 ± 2.3**	4.6 ± 1.9**	4.2 ± 1.9**	3.6 ± 2.1*	3.2 ± 1.8	2.6 ± 1.3
Pentazocine 0.3 mg	1.6 ± 0.9	6.0 ± 3.7*	5.8 ±3.2*	5.2 ± 3.4*	4.4 ± 3.0	3.8 ± 2.4	3.4 ± 1.9	2.8 ± 1.6	2.6 ± 1.3	1.8 ± 1.1
Pentazocine 0.6 mg	1.6 ± 1.7	6.4 ± 2.6***	6.0 ± 2.7***	5.6 ± 2.6*	6.0 ± 3.1**	4.4 ± 2.6*	4.2 ± 2.4*	3.8 ± 1.9*	3.0 ± 2.4	2.2 ± 1.1

Mean ± s.d., asterisks = Student's *t*-test, paired data (*vs* basal value), * = $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$.

Table 4 The subjective effects (VAS: nausea, sedation, euphoria and dysphoria) measured after administration of placebo, meptazinol and pentazocine to healthy volunteers

	Basal value	*Time (min)* 5	10	20	30	45	60	90	120	180
Nausea										
Placebo	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Meptazinol 0.7 mg	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.2 ± 0.4*	0.3 ± 0.8	0.3 ± 0.8	0 ± 0
Meptazinol 1.4 mg	0 ± 0	0.3 ± 0.8	1.2 ± 2.0	1.7 ± 1.9	1.5 ± 1.6	1.3 ± 1.2*	1.3 ± 1.2*	1.2 ± 1.2	0.3 ± 0.5	0.3 ± 0.5
Pentazocine 0.3 mg	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.2 ± 0.4	0 ± 0	0 ± 0	0 ± 0
Pentazocine 0.6 mg	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.2 ±0.4	0.3 ± 0.8	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0 ± 0
Sedation										
Placebo	0.8 ± 1.3	0.8 ± 1.3	0.8 ± 1.3	1.2 ± 1.8	1.2 ± 1.8	1.0 ± 1.5	0.8 ± 1.3	0.8 ± 1.3	0.5 ± 0.8	0.5 ± 0.8
Meptazinol 0.7 mg	0.6 ± 1.2	2.3 ± 1.6*	2.7 ± 1.4*	2.5 ± 1.5*	2.0 ± 1.5*	1.5 ± 1.4**	1.0 ± 1.3	1.0 ± 1.3	0.7 ± 1.2	0.7 ± 1.2
Meptazinol 1.4 mg	0.2 ± 0.4	3.0 ± 1.5**	2.5 ± 1.5*	2.2 ± 1.8*	1.5 ± 1.5	1.3 ± 1.2	1.0 ± 1.1	0.8 ± 1.0	0.7 ± 0.8	0.3 ± 0.5
Pentazocine 0.3 mg	0.5 ± 1.2	3.0 ± 2.1*	2.8 ± 1.9*	2.5 ± 1.8	2.3 ± 1.8	1.8 ± 1.6	1.5 ± 1.4	1.0 ± 1.3	0.5 ± 1.2	0.5 ± 1.2
Pentazocine 0.6 mg	0.7 ± 0.5	3.2 ± 2.5	3.8 ± 1.5**	3.3 ± 1.4**	2.8 ± 1.9	2.5 ± 1.6	2.2 ± 1.2*	1.5 ± 1.0	0.8 ± 0.8	0.7 ± 0.5
Euphoria										
Placebo	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Meptazinol 0.7 mg	0 ± 0	2.7 ± 2.1*	2.3 ± 2.2*	2.2 ± 1.7*	1.3 ± 1.5	0.7 ± 1.2	0.2 ± 0.4	0 ± 0	0 ± 0	0 ± 0
Meptazinol 1.4 mg	0 ± 0	4.0 ± 1.8**	2.0 ± 1.9*	1.2 ± 1.8	0.8 ± 1.3	0.3 ± 0.8	0.3 ± 0.8	0.2 ± 0.4	0 ± 0	0 ± 0
Pentazocine 0.3 mg	0 ± 0	2.7 ± 1.5**	2.5 ± 1.6*	2.0 ± 1.7*	1.2 ± 1.2	0.5 ± 0.8	0.3 ± 0.8	0 ± 0	0 ± 0	0 ± 0
Pentazocine 0.6 mg	0 ± 0	4.2 ± 1.5***	4.2 ± 1.5***	3.3 ± 1.4**	1.7 ± 1.6	1.2 ± 1.6	0.7 ± 1.2	0.2 ± 0.4	0 ± 0	0 ± 0
Dysphoria										
Placebo	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4
Meptazinol 0.7 mg	0.3 ± 0.8	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.3 ± 0.5	0.8 ± 1.3	0.5 ± 0.8
Meptazinol 1.4 mg	0 ± 0	0.2 ± 0.4	1.2 ± 2.0	1.5 ± 2.5	1.3 ± 2.2	0.8 ± 1.3	0.7 ± 1.0	0.5 ± 0.8	0.2 ± 0.4	0.2 ± 0.4
Pentazocine 0.3 mg	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Pentazocine 0.6 mg	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.3 ± 0.8	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0 ± 0

Mean ± s.d., asterisks = Student's *t*-test, paired data (*vs* basal value); * = $P < 0.05$, ** = $P < 0.01$ and *** = 0.001.

of the six subjects) with a wide variation between subjects. Both analgesics had equal maximal euphoric effects (4.0 ± 1.8 with meptazinol and 4.2 ± 1.5 with pentazocine, both with higher doses) 5 min after drug administration. After meptazinol this effect disappeared quickly, in 20 min. Interestingly, with the lower dose of meptazinol the mood-elevating effect lasted somewhat longer.

Plasma catecholamines

Both catecholamines showed relatively stable venous plasma levels after placebo (Table 5). After pentazocine 0.6 mg kg^{-1} i.v. plasma NA increased almost two-fold (max. 2.2 ± 0.6 nmol l^{-1}) at 10–20 min ($P < 0.01$, Student's *t*-test). Meptazinol caused also a dose-dependent increase in NA, but of smaller magnitude (max. 1.7 ± 0.8 nmol l^{-1}). A prominent increase in plasma A (up to 5.7 nmol l^{-1}) was seen in some, but not all of the subjects after meptazinol 1.4 mg kg^{-1}. In three of the six subjects the response was only slight, with plasma concentrations remaining below 1 nmol l^{-1}. Pentazocine had a smaller, but still significant ($P < 0.01$, Student's *t*-test) effect on plasma A.

Discussion

According to Hindmarch (1980) c.f.f. is the instrument of choice for investigating changes in the overall integrative activity of the CNS produced by psychoactive agents. Richens and coworkers (1983) have compared meptazinol and papaveretum in some tests of psychomotor performance; they found the c.f.f. threshold unaffected by either drug. Our own previous studies (Manner *et al.*, 1987 a, b) with analgesics (fentanyl and buprenorphine) in healthy volunteers and post-operative patients failed to prove c.f.f.'s sensitivity. In the present work, however, the c.f.f. test was shown to be able to differentiate meptazinol and pentazocine from placebo, particularly when the results were computed as changes from baseline. Meptazinol had a greater and longer lasting effect on the c.f.f. threshold than pentazocine. Maddox wing readings reacted also significantly to both study drugs. The peak effect after meptazinol was slightly stronger, but in all, there were no significant differences between meptazinol and pentazocine or the two dose levels.

Visual analogue scales are widely used for assessing subjective drug effects (Revill *et al.*, 1976). Meptazinol has been reported to have fewer side-effects of central origin than other agonist-antagonists or pure agonist opiates (Holmes & Ward, 1985; Robson, 1983), but nausea and vomiting are still relatively common complaints (incidences 8% and 9%) (Spiegel & Pasternak, 1984). Kaiko *et al.* (1985) compared i.m. meptazinol with morphine in postoperative pain, and they found, in addition to nausea, also sedative and mood-depressing effects after meptazinol. In the present study, meptazinol produced significantly more nausea than pentazocine, although none of the subjects vomited. Both analgesics caused a subjective feeling of euphoria lasting about 30 min. The highest dysphoria-scores (6 at 20 min) were expressed by the subject having the highest plasma A levels, but in average, the dysphoric effect seen after

Table 5 The plasma catecholamine concentrations after administration of placebo, meptazinol and pentazocine to healthy volunteers

	Basal value	*Time (min)* 5	10	20	30	45	60
Noradrenaline (nmol l^{-1})							
Placebo	0.9 ± 0.3	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.6	1.1 ± 0.4	1.1 ± 0.5	1.0 ± 0.4
Meptazinol 0.7 mg	1.1 ± 0.4	1.2 ± 0.3*	1.3 ± 0.3	1.3 ± 0.5	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.6
Meptazinol 1.4 mg	1.1 ± 0.4	1.5 ± 0.5*	1.6 ± 0.5**	1.7 ± 0.8	1.5 ± 0.7	1.3 ± 0.4	1.1 ± 0.4
Pentazocine 0.3 mg	1.1 ± 0.2	1.2 ± 0.3	1.5 ± 0.5*	1.3 ± 0.3	1.3 ± 0.4	1.2 ± 0.4	1.3 ± 0.4
Pentazocine 0.6 mg	1.2 ± 0.6	1.6 ± 0.6*	1.9 ± 0.7**	2.2 ± 0.6**	1.8 ± 0.6	1.7 ± 0.5	1.6 ± 0.5
Adrenaline (nmol l^{-1})							
Placebo	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.2	0.2 ± 0.1
Meptazinol 0.7 mg	0.2 ± 0.1	0.4 ± 0.2*	0.4 ± 0.2	0.4 ± 0.3	0.3 ± 0.2	0.3 ± 0.1*	0.3 ± 0.2
Meptazinol 1.4 mg	0.2 ± 0.1	0.5 ± 0.3	0.6 ± 0.7	1.3 ± 1.7	1.7 ± 2.1	1.3 ± 1.0*	0.8 ± 0.7
Pentazocine 0.3 mg	0.2 ± 0.1	0.3 ± 0.2	0.3 ± 0.1*	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2
Pentazocine 0.6 mg	0.3 ± 0.1	0.5 ± 0.3*	0.6 ± 0.4*	0.6 ± 0.4*	0.5 ± 0.4	0.5 ± 0.3	0.4 ± 0.2

Mean ± s.d., asterisks = Student's *t*-test, paired data (*vs* basal value); * = $P < 0.05$ and ** = $P < 0.01$.

meptazinol was only slight. Our results support the general opinion that measuring performance after psychoactive drugs requires a battery of tests (Mattila *et al.*, 1984).

Respiratory depression is a serious side-effect of opioid analgesics. Most reports have claimed that meptazinol is relatively free from respiratory side-effects (Paymaster, 1977; Jones, 1983), even if measured with more sensitive indicators than respiratory rate, such as tidal volume, end-tidal pCO_2, and ventilatory response to hypercapnia (Jordan *et al.*, 1979). However, when used as premedicant or during anaesthesia meptazinol has been found to have a depressant effect on respiration (Wilkinson *et al.*, 1985). Our simple parameter, respiratory rate, showed approximately similar, but very slight changes after administration of meptazinol and pentazocine.

The lack of significant cardiovascular effects after meptazinol has been reported in many previous investigations (Holmes & Ward, 1985; Paymaster, 1977; Robson, 1983) and our present results support these findings. Pentazocine also failed to cause any major effects on heart rate or blood pressure, although there was a slight increase in systolic and diastolic blood pressure and heart rate after the higher dose, 0.6 mg kg^{-1}. Interestingly, the increase in the catecholamine concentrations in venous plasma did not have any clear counterparts in the cardiovascular parameters, even as the measured peak plasma A values reached levels shown to be associated with marked effects on heart rate and blood pressure after adrenaline infusions in human volunteers (Hjemdahl *et al.*, 1983).

Tammisto *et al.* (1971) have previously studied the effects of pentazocine 1.2 mg kg^{-1} i.v. on plasma catecholamine levels in patients scheduled for surgery. They found 70–80% increases in both A and NA concentrations following the injection of pentazocine, with concomitant increases in heart rate (+ 12 ± 1 beats min^{-1}) and systolic blood pressure (+ 22.7 ± 9.4 mm Hg). The patients with the largest increases in catecholamines expressed unpleasant sensations (vertigo, nausea, restlessness).

Our results concerning both catecholamines after pentazocine administration are in accordance with the results of Tammisto *et al.* (1971). The prominent elevation of plasma A values following the higher dose of meptazinol was surprising, in particular the very high concentrations in two of the six subjects (max. values 5.7 and 3.0 nmol l^{-1} at 30 and 45 min, respectively). Such A levels are usually attained only in severe stress situations, e.g. surgical stress and myocardial infarction (Hjemdahl *et al.*, 1983). Therefore the use of meptazinol in patients with cardiac diseases or with a risk of arrhythmias seems at least doubtful and demands further investigations.

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(Received 25 June 1987, accepted 11 August 1987)