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Psychomotor, respiratory and neuroendocrinological effects of nalbuphine and haloperidol, alone and in combination, in healthy subjects

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1 Actions and interactions on performance and respiration of single intramuscular doses of 0.15 mg kg^{-1} nalbuphine and oral haloperidol twice daily for 2 days were studied double-blind and cross-over in 12 healthy volunteers.

2 Objective measurements of performance (choice reaction, tracking, attention, flicker fusion, Maddox wing, digit symbol substitution) and respiratory function (minute volume, end-tidal carbon dioxide), and subjective assessments on visual analogue scales were done at baseline and 1 h, 2.5 h and 4 h after the injection of nalbuphine. Plasma concentrations of nalbuphine were estimated by radioreceptor ([^{3}H]-dihydromorphine) assay, and those of prolactin and growth hormone by radioimmunoassay.

3 Nalbuphine affected digit substitution, reaction time, extraocular muscle balance and flicker recognition, and depressed respiration most clearly 1 and 2.5 h post injection. Motor skills were impaired only briefly. Haloperidol alone proved inert on performance but enhanced the decremental effects of nalbuphine on digit substitution and exophoria at 1 h. It did not interact with nalbuphine on the ventilatory function.

4 Plasma concentrations of nalbuphine expressed as morphine equivalents ranged from 5 to 52 ng ml^{-1}, indicating considerable μ-opiate affinity. Treatment with haloperidol increased plasma prolactin moderately whilst nalbuphine raised it markedly 1 and 2.5 h post injection. Nalbuphine elevated plasma growth hormone at 1 h post injection only.

Keywords nalbuphine haloperidol interaction psychomotor performance respiration pituitary hormones radioreceptor assay

Introduction

Small doses of antipsychotics have been recommended for the management of chronic pain since they may relieve coexisting anxiety and insomnia, and counteract the hallucinogenic and emetic side-effects of opiates (Budd, 1978). Phenothiazines such as levomepromazine, chlorpromazine and promazine, have even shown analgesic activity of their own (Moore & Dundee, 1961). Neuroleptics have been suggested to potentiate the analgesic effects of opiates (Kamata *et al.*, 1985), but this has not been generally accepted due to the lack of controlled clinical trials (Twycross, 1983).

Nalbuphine is a mixed κ-agonist/μ-antagonist opioid analgesic (Schmidt *et al.*, 1985) the profile of action of which resembles that of pentazocine except that nalbuphine produces less psychotomimetic effects (Errick & Heel, 1983). It is a possible alternative to morphine in the management of chronic cancer pain (Stambaugh, 1982), and its parenteral and oral form might thus be combined with neuroleptics at least occasionally.

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The effects of nalbuphine on skilled performance have not been investigated so far.

The present study was conducted to examine the actions and interactions of nalbuphine and haloperidol on psychomotor performance and respiration. Antipsychotic drugs have previously been shown to affect psychomotor skills and their combined action with alcohol may be additive (Grübel-Mathyl, 1986). Haloperidol was chosen for the neuroleptic because it has recently been shown to interact with the opiate receptor system *in vitro* (Downes *et al.*, 1986) and to enhance opioid antinociception in animals (McGilliard & Takemori, 1979). The levels of prolactin (PRL) and growth hormone (GH) were assayed to confirm the presence of haloperidol at dopamine receptors (Müller *et al.*, 1983), and to assess neuroendocrinological responses to nalbuphine.

Methods

Subjects

Twelve healthy students (five females and seven males), 20 to 25 years of age, weighing 57 to 79 kg, volunteered for the trial and were paid for their time. None of the subjects suffered from mental or somatic illness, abused alcohol, or was on any medication (contraception excluded) during the trial. The subjects gave their informed consent and were pretrained for the tests. The study protocol was accepted by the departmental committee of ethics.

Experimental design

The subjects participated in a cross-over, double-blind fashion in four test sessions at 1 week intervals. The subacute treatment at home on days 1 and 2 consisted of either haloperidol or placebo given in identical capsules (Table 1). On day 3, the baseline tests were first administered in the laboratory. Immediately thereafter the subjects received oral haloperidol 0.5 mg or placebo and 1 h later an intramuscular injection of 0.15 mg kg^{-1} nalbuphine (maximum 10 mg) or saline. Drug administration was thus scheduled to give peak plasma concentrations simultaneously. Due to a technical error the randomized sequence of the treatments became nonorthogonal, but the mutual sequences of nalbuphine and haloperidol + nalbuphine remained balanced.

The tests were always done in the same order, starting at 09.30 h on Sundays. Each test round lasted 25 min, and the subjects began the rounds at 7 min intervals 10 min before the 'official' test time. The post-drug test times 1 h, 2.5 h and 4 h refer to the times elapsed from the nalbuphine injection. The subjects were asked to refrain from coffee, tea and cola beverages for 12 h before the experiment and to remain supine 45 min after the nalbuphine injection. A light standard meal was served after the 2.5 h test. Venous blood was drawn into heparinized vacuum tubes, and the plasma was stored at −60°C for several weeks until assayed for the drug and hormone concentrations.

Performance tests

Performance was measured objectively by a set of tests previously used in our laboratory (Saarialho-Kere *et al.*, 1986). They consisted of critical flicker fusion test watched at the distance of 100 cm. Pupillary size was kept constant with special spectacles. Maddox wing device was used to measure the tone of extraocular muscles. In the digit symbol substitution test the number of digits correctly substituted in 3 min was counted. Matched new material was provided for each test round. In the combined tracking and choice reaction test (Linnavuo *et al.*, 1987) hand-to-eye coordination was measured by a tracking task driven at fixed speed for 5 min. The first half of the track comprised 'undisturbed' driving. During the latter 'disturbed' half 60 consecutive light and/or sound stimuli were presented and the subject had to respond to them while driving, and reaction errors and cumulative reaction times were recorded. Numbers of tracking errors and error % (relative length of track driven off the road) were computed separately for both halves of the track. Tracking error severity index which refers to the sum of the products (error numbers × error duration) was computed for the whole track.

Table 1 Trial design

Day 1	*Day 2*	*Day 3*
Placebo	Placebo twice daily	Placebo + placebo
Haloperidol 0.5 mg	Haloperidol 0.5 mg twice daily	Haloperidol 0.5 mg + placebo
Placebo	Placebo twice daily	Placebo + nalbuphine 0.15 mg kg^{-1}
Haloperidol 0.5 mg	Haloperidol 0.5 mg twice daily	Haloperidol 0.5 mg + nalbuphine 0.15 mg kg^{-1}

A novel computerized version of the divided attention test (Linnoila, 1973), comprised four parallel computer screens each having a spot circling along a steeple course, at different rates on each screen. Every time the spot on any screen encountered an obstacle, the subject had to press a button for that screen. To minimize learning, the obstacles changed their position randomly at 10 s intervals. The test lasted 5 min, and it measures the information processing capacity of the subject. The numbers of stimuli, total answers and correct answers were computed for each screen separately as well as for two lateral and medial screens together.

Subjective assessments were done by using ungraded horizontal visual analogue scales (VAS). The pairs of extremes were: drowsy/alert; mentally slow/quick-witted; sad/happy; clumsy/skilful; calm/nervous; contented/discontented; strong/feeble; clear-headed/muzzy; anxious/relaxed and very bad/very good performance. The subjects also scored various psychosomatic symptoms from 0 to 3 on a 42-item questionnaire at every test time.

Measurement of ventilatory function

Drug-induced respiratory depression was assessed by using a method developed for quick and accurate psychomotor test rounds (Saarialho-Kere *et al.*, 1987).

The resting minute ventilation ($\dot{V}_E$) was measured by using a tight fitting mask (dead space 258 ml) with a Fleisch pneumotachometer (differential pressure over a grid mesh, Godart) and a strip recorder. End-tidal carbon dioxide (ET_{CO_2}) was measured with an infrared capnograph (CD-300, Datex) by sampling gas (150 ml min^{-1}) at the internal orifice of the face mask. Ventilatory response to hypercapnia ($\dot{V}_E/ET_{CO_2}$) was determined as outlined by Jordan (1982). Rebreathing was achieved (aside from the increased dead space) with a Mapleson D circuit by stepwise decreasing fresh gas flow (V_F, 9.40, 6.05 and 3.00 l min^{-1}, room air, pre-calibrated constant flow generators, R-900-90, Air Logic, USA).

The measurements were carried out at baseline, and at 1, 2.5 and 4 h after the drug intake. The subjects were lying comfortably supine and held the mask with their supported hand. Three 1 min measuring periods, one for each V_F were performed after the average minute volume (as indicated by the pneumotachograph) and ET_{CO_2} were stabilized. The rebreathing periods lasted approximately 9 min altogether at each test round.

The $\dot{V}_E/ET_{CO_2}$ response curves for corresponding mean values for each drug and test round were plotted to indicate the shifts in both $\dot{V}_E$ and ET_{CO_2} as outlined by Read (1967). Triplicate measurements revealed eventual drug effects in regard to pre-drug state and, secondly, changes in the rebreathing response line slopes.

Drug and hormone assays

Plasma concentrations of nalbuphine were estimated by radioreceptor assay (Saarialho-Kere *et al.*, 1986) after extraction with ether, evaporation and dissolution of the residue in TRIS buffer. The sample was incubated for 15 min with rat brain (cerebellum excluded) homogenate (0.5 mg protein) at 25°C in the presence of [^{3}H]-dihydromorphine (0.9 pmol) as radioligand and 2 mg ml^{-1} of 'cold' morphine for measuring non-specific binding, the amount of which was 25% or less. The receptor preparation was preincubated for 30 min at 37°C to remove endogenous ligands. Samples of plasma with 4, 20 and 80 ng ml^{-1} of morphine as hydrochloride were included as standards in each assay run and 50 ng ml^{-1} nalbuphine was used as a reference. The nalbuphine-induced displacement of the radioligand from the receptors was calculated against the baseline plasma sample. The results were read off the standard log-probit graph.

Plasma PRL and GH were assayed from the samples taken at baseline and at 1 h and 2.5 h after the nalbuphine injection using ^{125}I-immunoassay kits (Farmos Diagnostica, Turku, Finland). Undetectable GH values were assigned values corresponding to the limit of detection of the assay (1.0 mIU l^{-1}).

Statistics

Mean ± s.e. mean values were computed separately for absolute values of performance and respiratory parameters, as well as for Δ-values (changes from respective baseline). Since the experimental design was nonorthogonal with respect to drug and week effects, these effects were correlated. For this reason the drug effects had to be tested within a model adjusted for week effects. Four-way ANOVA (subject + week + drug) × time, followed by Duncan's multiple comparison between treatments was computed for the Δ-values. Five-way ANOVA (subject + week + drug 1 × drug 2) × time was also done to reveal the possible potentiation of nalbuphine effects by haloperidol. Nonparametric Friedman two-way ANOVA followed by Duncan's test applied to the within subject ranks was computed for subjective VAS-data. Side effects were analyzed with Fisher's exact probability test.

Results

Mean ± s.e. mean values computed for absolute performance values in terms of week/test time, did not reveal a significant contribution by the test week to baseline values of objective tests, when assessed with paired *t*-test *vs* week 1. However, the five-way ANOVA revealed a statistically significant contribution by test week to the baseline values of digit substitution, flicker fusion, reaction time and percentage of correct answers in the divided attention test. This might be due to practice effect or the presence of haloperidol pretreatment in the trial scheme. The responses to placebo were almost negligible: subjective alertness increased, and exophoria and tracking errors (only second half) decreased after placebo ($P < 0.05$ *vs* baseline).

Effects on performance

Nalbuphine The decremental effects of nalbuphine on performance peaked at the 1 h and 2.5 h tests. Nalbuphine reduced the number of digits correctly substituted, impaired critical flicker recognition ($P < 0.05$ *vs* Δ-placebo), caused exophoria, and prolonged cumulative reaction time without increasing the number of reaction errors (Table 2, Figure 1). Tracking errors (second half of the track), error % and tracking error severity index increased 1 h post drug (Table 2). Nalbuphine rendered the subjects drowsy, muzzy, relaxed and clumsy (Table 3), feeble, mentally slow ($P < 0.01$) and calm ($P < 0.05$ *vs* baseline). Subjective estimate of performance was affected at the 1 and 2.5 h tests (Table 3).

Haloperidol Haloperidol proved indistinguishable from placebo in most tests. It tended to impair digit substitution ($P < 0.01$) at 4 h, but the treatment sequence contributed significantly to this result. Haloperidol rendered the subjects drowsy at 2.5 h, whilst all other subjective assessments remained unchanged.

Table 2 Mean ± s.e. mean values of some objective tests in 12 healthy subjects after treatment with placebo (Plac), haloperidol (HAL), nalbuphine (NLB) and their combination (HAL-NLB). For more details see text

Test/Drug	*Baseline*	*1 h*	*2.5 h*	*4 h*
Critical flicker fusion frequency (Hz × 10)				
Plac	244 ± 8.2	248 ± 8.4	248 ± 11.1	252 ± 6.9
HAL	249 ± 9.0	259 ± 8.2	251 ± 8.7	250 ± 8.6
NLB	247 ± 7.5	233 ± 8.8	236 ± 9.1	236 ± 8.9
HAL-NLB	245 ± 7.6	235 ± 9.2	234 ± 9.4	246 ± 10.8
F values		3.19*	1.39	1.31
Tracking error % (part I)				
Plac	8.3 ± 1.6	7.7 ± 0.9	8.9 ± 1.6	9.2 ± 1.7
HAL	6.6 ± 0.8	7.6 ± 1.2	7.7 ± 1.1	7.9 ± 1.2
NLB	7.5 ± 1.0	11.0 ± 1.1[b]	9.3 ± 1.5	6.7 ± 1.1
HAL-NLB	8.0 ± 1.1	10.0 ± 1.7	9.5 ± 1.4	8.7 ± 1.8
F values		1.57	0.19	1.03
Tracking severity index				
Plac	38 ± 9.5	28 ± 4.2	31 ± 5.1	32 ± 4.9
HAL	27 ± 3.4	28 ± 4.9	28 ± 3.7	30 ± 4.1
NLB	31 ± 6.1	44 ± 6.3[b]	33 ± 5.3	28 ± 5.6
HAL-NLB	35 ± 7.6	46 ± 7.2	37 ± 6.6	36 ± 6.7
F values		6.23*	1.12	0.02
Reaction time (s)				
Plac	52.5 ± 1.9	51.7 ± 1.6	52.6 ± 1.3	52.7 ± 1.1
HAL	51.5 ± 1.4	51.3 ± 1.1	52.6 ± 1.4	53.3 ± 1.3[a]
NLB	52.2 ± 1.7	53.9 ± 1.7[a]	56.6 ± 1.5[b]	55.0 ± 1.6[a]
HAL-NLB	54.7 ± 2.1	53.4 ± 1.7	54.2 ± 1.7	55.1 ± 1.4
F values		0.19	0.66	0.26

*$P < 0.05$, four-way ANOVA between treatments.
[a]$P < 0.05$; [b]$P < 0.01$ *vs* baseline, paired *t*-test.

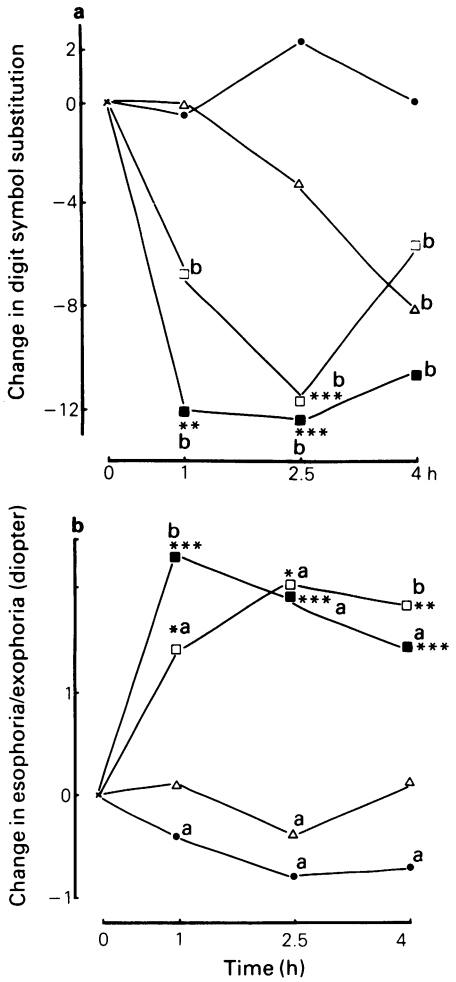

Figure 1 a) Change in digit symbol substitution test. $^{**}P < 0.01$; $^{***}P < 0.001$, four-way ANOVA *vs* placebo; $^{b}P < 0.01$ *vs* baseline, paired *t*-test. b) Change in Maddox wing. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$, four-way ANOVA *vs* placebo. $^{a}P < 0.05$; $^{b}P < 0.01$ *vs* baseline, paired *t*-test. • placebo, □ nalbuphine, △ haloperidol and ■ haloperidol-nalbuphine.

Nalbuphine combined with haloperidol The combination impaired psychomotor skills in the same tests as plain nalbuphine did (Figure 1, Table 2) except that reaction time remained unaffected. According to the five-way ANOVA, haloperidol enhanced the effects of nalbuphine on digit substitution ($P < 0.01$) and exophoria ($P < 0.05$) at 1 h. The combination of nalbuphine with haloperidol rendered the subjects drowsy, clumsy, and muzzy (Table 3), mentally slow and feeble ($P < 0.05$). The magnitude of subjective effects did not exceed that produced by nalbuphine alone and at 2.5 h haloperidol even seemed to attenuate the nalbuphine-induced increase in muzziness and impaired subjective performance (Table 3).

Table 3 Mean baseline values and mean changes of some visual analogue scale assessments (mm) by 12 healthy subjects after treatment with placebo, haloperidol (HAL), nalbuphine (NLB) and haloperidol combined with nalbuphine (HAL-NLB). The first mentioned extreme of each pair refers to zero and the latter to 100. For more details see text

Test/Drug	*Baseline*	*1 h*	*2.5 h*	*4 h*
Drowsy/alert				
Placebo	35	4.5	11.0	11.6
HAL	52	−5.0	−3.2*	−3.5
NLB	37	−14.0*	−15.6*	−4.9*
HAL-NLB	30	−12.7*	−2.3*	2.3
Clumsy/skilful				
Placebo	46	−3.2	5.5	4.5
HAL	53	0.6	3.0	1.4
NLB	48	−24.8*	−21.5*	−7.7
HAL-NLB	42	−19.2*	−12.3*	1.7
Anxious/relaxed				
Placebo	58	6.0	6.4	10.2
HAL	72	−3.7	−1.4	0.3
NLB	62	14.5*	16.2*	8.3
HAL-NLB	58	14.7	13.7	8.4
Clear-headed/muzzy				
Placebo	40	−3.9	−1.6	−4.7
HAL	29	2.3	−0.7	−0.2
NLB	29	35.0*	32.4*	17.8*
HAL-NLB	41	25.8*	16.7*•	−6.5*
Performance bad/good				
Placebo	53	−7.7	−2.2	−3.7
HAL	60	−3.9	−3.0	−9.4
NLB	52	−23.0*	−20.6*	−1.6
HAL-NLB	44	−17.2	−8.7•	1.3

$^{*}P < 0.05$ *vs* placebo, Duncan's test.
$^{\bullet}P < 0.05$ *vs* nalbuphine, Duncan's test.

Effects on respiration

The intersubject variation of the minute ventilation was fairly large; the intrasubject day-to-day variability was acceptable. Coefficients of variation for flow rates of 9.40, 6.05 and 3.00 l min^{-1} ranged 0.046–0.187, 0.026–0.220, 0.069–0.280 ($\dot{V}_E$), and 0.020–0.089, 0.018–0.032, 0.012–0.068 (ET_{CO_2}), respectively. The rebreathing slopes were comparable since the subjects served as their own controls in the trial. Supernormal ET_{CO_2} values with the highest V_F were due to added dead space and the apparent rebreathing seen in the capnograms.

Nalbuphine decreased minute ventilation and

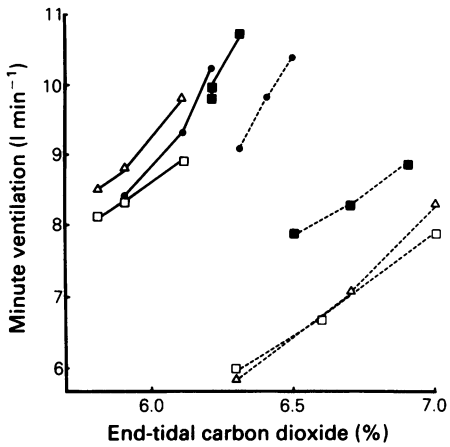

Figure 2 Respiratory patterns to placebo and nalbuphine expressed as response curves relating mean values to total ventilation to end-tidal CO_2%. — = placebo; --- = nalbuphine. ● = baseline; △ = 1 h; □ = 2.5 h; ■ = 4 h. Each curve connects the values obtained with three different flow rates (V_F = 9.4, 6.0, 3.0 l min^{-1}).

elevated ET_{CO_2} most clearly at the 1 h and 2.5 h tests (Figure 2). The combined treatment induced the same effects except that minute ventilation had almost returned to baseline at the 4 h test (Table 4). Haloperidol proved inert on respiration. According to five-way ANOVA (subject + week + drug 1 × drug 2) × time haloperidol did not enhance the nalbuphine-induced respiratory depression.

Side effects

The statistically significant side effects reported on questionnaire were dizziness (haloperidol-nalbuphine), drunkenness (nalbuphine, haloperidol-nalbuphine) and itching (nalbuphine). Dry mouth, nausea and increased perspiration were also frequently reported after nalbuphine but they did not reach statistical significance. Two of the subjects fainted when trying to stand up 45 min after the injection of nalbuphine, and two 2.5 h after having received the combined

Table 4 Mean ± s. e. mean baseline values and mean changes of minute volume and end-tidal carbon dioxide % after treatment with placebo, haloperidol (HAL), nalbuphine (NLB) and haloperidol combined with nalbuphine (HAL-NLB)

Treatment	*Baseline*	*1 h*	*2.5 h*	*4 h*
V_9				
Placebo	8.4 ± 0.6	0 ± 0.5	−0.3 ± 0.3	1.5 ± 0.5
HAL	8.3 ± 0.7	−1.0 ± 0.5	−0.7 ± 0.5	0.5 ± 0.5
NLB	9.1 ± 0.7	−3.1 ± 0.7[b]	−3.0 ± 0.5[b]	−1.1 ± 0.5[b]
HAL-NLB	9.2 ± 0.9	−3.2 ± 0.7[b]	−2.5 ± 0.8[b]	−0.9 ± 0.5[b]
F		13.6***	9.79***	7.66***
V_3				
Placebo	10.2 ± 0.6	−0.6 ± 0.4	−1.3 ± 0.4	0.5 ± 0.6
HAL	9.7 ± 0.6	−0.7 ± 0.3	−0.7 ± 0.4	0.7 ± 0.3
NLB	10.4 ± 0.6	−2.1 ± 0.5[a]	−2.5 ± 0.4	−1.5 ± 9.7
HAL-NLB	9.9 ± 0.8	−2.0 ± 0.6[a]	−1.9 ± 0.7	−0.2 ± 0.7
F		4.42*	3.32*	4.22*
ET_9				
Placebo	5.9 ± 0.2	−0.1 ± 0.1	−0.1 ± 0.1	0.2 ± 0.1
HAL	6.1 ± 0.1	−0.2 ± 0.1	−0.2 ± 0.1	0.1 ± 0.1
NLB	6.1 ± 0.1	0 ± 0.1	0 ± 0.1	0.2 ± 0.1
HAL-NLB	6.3 ± 0.1	0.1 ± 0.1	0 ± 0.1	0.1 ± 0.1
F		1.18	0.52	0.91
ET_3				
Placebo	6.2 ± 0.2	−0.1 ± 0.1	−0.1 ± 0.1	0.1 ± 0.1
HAL	6.4 ± 0.1	−0.1 ± 0.1	−0.1 ± 0.1	0 ± 0.1
NLB	6.3 ± 0.2	0.5 ± 0.1[b]	0.4 ± 0.1[b]	0.3 ± 0.1[a]
HAL-NLB	6.3 ± 0.2	0.6 ± 0.1[b]	0.4 ± 0.1[b]	0.5 ± 0.1[a]
F		41.48***	18.55***	10.55***

*$P < 0.05$; ***$P < 0.001$, four-way ANOVA between treatments.
[a]$P < 0.05$; [b]$P < 0.01$ *vs* placebo, Duncan's test.
V_9, V_3 = minute volume measured when rebreathing corresponding airflows of 9.4 and 3 l; ET_9, ET_3 = end-tidal CO_2%.

treatment. No clear-cut effects on blood pressure were recorded.

Plasma concentrations of nalbuphine and hormones

Radioreceptor assay revealed clear-cut displacements of [^{3}H]-dihydromorphine in the presence of nalbuphine, thus indicating considerable affinity to μ-opiate receptors (Table 5). However, the 'bioassayed' concentrations expressed as morphine equivalents were lower than those assayed by gas chromatography after 10 mg intramuscular dose of morphine sulphate (Berkowitz, 1976). Pretreatment with haloperidol elevated the baseline PRL levels as expected (Table 6). Nalbuphine caused an increase in PRL secretion 1 and 2.5 h after administration. Haloperidol did not modify the plasma level of GH, whereas nalbuphine elevated it 1 h post injection (Table 6).

Table 5 Plasma levels of nalbuphine (NLB) measured with radioreceptor assay in 12 subjects. Concentrations of nalbuphine refer to ng ml^{-1} of standard morphine

	Mean ± s.e. mean plasma drug levels (ng ml^{-1})		
Treatment	*1 h*	*2.5 h*	*4 h*
NLB	35 ± 2	21 ± 2	14 ± 2
HAL-NLB	35 ± 5	17 ± 1	11 ± 1*

* $n = 11$

Discussion

Narcotic analgesics may impair psychomotor performance by inducing drowsiness, changes in mood, and mental clouding. This also applies to the present study where intramuscular nalbuphine impaired sensory processing and visual functions and affected central nervous system arousal. Motor performance, reflected in the results of tracking, was also affected, yet only 1 h post injection. These results resemble those obtained with sublingual buprenorphine 0.4 mg (Saarialho-Kere *et al.*, 1987) and intramuscular pentazocine 30 mg (Saarialho-Kere, unpublished, 1987) in our previous trials except that tracking and critical flicker discrimination were then insensitive to both drugs. The transient impairment of tracking now observed, supports the suggestion that motor incoordination is uncommon with agonist/antagonist opioids (Starmer, 1986). That no clear-cut changes on attention after either opiate or haloperidol were observed, was probably due to the difficulty of the divided attention test.

Nalbuphine produced the most profound effects on respiration at the 1 h and 2.5 h tests, which tallies with the results of Gal *et al.* (1982). As in our previous studies, psychomotor decrement subsided earlier than changes in respiration, suggesting that respiratory depression is a more sensitive measure of opiate action than psychomotor changes.

Our radioreceptor assayed nalbuphine concentrations are in agreement with the gas chromatographic data of Errick & Heel (1983) and

Table 6 Mean plasma levels of prolactin and growth hormone after treatment with placebo, haloperidol (HAL), nalbuphine (NLB) and haloperidol combined with nalbuphine (HAL-NLB)

Treatment	*Mean ± s.e. mean plasma hormone concentrations (mIU l^{-1})*		
Hormone	*Baseline*	*1 h*	*2.5 h*
Placebo			
PRL	228.4 ± 35.2	160.2 ± 21.7	164.9 ± 23.4
GH	9.9 ± 3.6	4.0 ± 1.4	4.1 ± 1.5
HAL			
PRL	281.1 ± 38.7**	228.2 ± 37.2	245.9 ± 48.0
GH	3.1 ± 1.3	6.5 ± 3.0	2.6 ± 1.0
NLB			
PRL	208.7 ± 31.0	876.6 ± 250.7**$^{\bullet\bullet}$	519.2 ± 158.9**$^{\bullet}$
GH	5.5 ± 2.8	16.4 ± 5.0**	5.3 ± 1.8
HAL-NLB			
PRL	292.8 ± 50.7**	890.6 ± 141.7**$^{\bullet\bullet\bullet}$	629.0 ± 113.0**$^{\bullet\bullet\bullet}$
GH	6.2 ± 3.1	15.4 ± 4.2$^{\bullet}$	3.5 ± 1.1

**$P < 0.01$ *vs* placebo
$^{\bullet}P < 0.05$; $^{\bullet\bullet}P < 0.01$; $^{\bullet\bullet\bullet}P < 0.001$ *vs* △-placebo, four-way ANOVA.

Lo *et al.* (1987) who detected nalbuphine concentrations of 29–48 ng ml^{-1} 30 min post intramuscular injection. Although pentazocine 30 mg which produced peak 'bioassayed' concentrations of 7 ng ml^{-1} expressed as morphine equivalents (Saarialho-Kere, unpublished, 1987), may not be quite as equipotent as 10 mg of nalbuphine, it is obvious that nalbuphine produces considerably higher μ-opiate affinity than pentazocine.

The 0.5 mg oral dose of haloperidol used in this study was relevant considering the adjuvant anxiolytic medication of chronic pain patients (Kocher, 1979). In accordance with the results of Milner & Landauer (1973) it did not impair reactive or coordinative skills. This lack of impairment might be due to low dosage, since, for example, thioridazine 25 mg three times daily and chlorpromazine 50 mg three times daily have deteriorated performance still after 2 weeks' treatment (Seppälä *et al.*, 1979). Haloperidol tended to increase the decremental effects of nalbuphine on digit substitution and heterophoria. This enhancement could subside in long-term treatment since tolerance to the psychomotor effects of neuroleptics is known to develop in the first weeks of treatment (Seppälä *et al.*, 1979). Interestingly, loss in haloperidol potency in morphine-dependent animals has been reported, suggesting that pharmacodynamic tolerance to haloperidol develops simultaneously with tolerance to the narcotics (Lal, 1975).

Few studies on the respiratory interactions of neuroleptics and agonist/antagonist opioids have been done. Haloperidol 0.5 mg did not depress respiration in this trial, which confirms the results of Tandon (1976). Neither did we find any enhancement by haloperidol in nalbuphine induced respiratory depression. Droperidol together with the μ-agonist fentanyl (Harper *et al.*, 1976) or methotrimeprazine combined with morphine (Petts *et al.*, 1983) did not increase or prolong the respiratory depression seen with the opioids alone. In contrast, chlorpromazine produced stronger and longer respiratory depression than plain meperidine, and similar effects have been found with prochlorperazine and morphine, and propiomazine and meperidine (Keats, 1985). This controversy may result from the different doses, routes of administration, type of neuroleptic, or the method used.

Recent data suggest that opiates are non-uniform in their effects on PRL and GH secretion (Delitala *et al.*, 1983) and could perhaps be classified into agonists and antagonists on this basis. Our finding that nalbuphine induced a marked rise in serum PRL, reflecting decreased dopamine turnover in the hypothalamus, is consistent with agonist-antagonistic action of this opioid (Rolandi *et al.*, 1984). We cannot exclude a possibility that the increase in GH was partly due to sedation. However, our results tally with those of Duka *et al.* (1986), who observed significantly elevated GH plasma levels 45 min post nalbuphine 0.3 mg kg^{-1}. Thus, nalbuphine resembles many κ-agonists (Pfeiffer *et al.*, 1986) in its effects on GH secretion. Interestingly, roughly equipotent doses of agonist/antagonist opioid pentazocine 30 mg i.v. (Delitala *et al.*, 1983) and partial μ-agonist buprenorphine 0.4 mg sublingually (Saarialho-Kere *et al.*, 1987), have failed to modify GH secretion in man.

In conclusion, intramuscular nalbuphine clearly impairs perceptual and cognitive skills with minor effects on motor performance. Haloperidol at anxiolytic dose levels may enhance the decremental effects of nalbuphine on psychomotor skills but not on respiration. In view of the profound psychological effect of chronic pain, mood-altering drugs may be useful under special circumstances. However, our results do not support routine use of neuroleptics in patients with chronic pain, since neuroleptics may not only have serious adverse effects, but the neuroleptic-opiate interaction also proved deleterious on traffic and industrial skills.

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