Psychomotor, Respiratory and Neuroendocrinological Effects of Buprenorphine and Amitriptyline in Healthy Volunteers

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Summary. Actions and interactions of buprenorphine (BUP) and amitriptyline (AMI) on performance and respiration were studied double-blind and cross-over in 12 healthy volunteers. After one-week pretreatments with AMI or placebo, the subjects received on Day 8 placebo, BUP or AMI so that the final treatments were 1) placebo, 2) acute AMI 50 mg, 3) acute BUP, 4) subchronic AMI±acute BUP and 5) subchronic AMI. The subacute treatments were started at two-week intervals.

A Mapleson D rebreathing circuit including a pneumotachograph and an infrared capnograph was employed to study drug effects on respiration. Minute volume and end-tidal carbon dioxide as well as psychomotor performance were measured and the blood samples taken on Day 8 before the drug intake and 2 and 4 h thereafter. The performance tests included tracking, choice reaction, flicker fusion, exophoria, nystagmus, digit symbol substitution and the subjective assessment of mood.

BUP depressed respiration, and subchronic AMI increased this depression. Both BUP and acute AMI 50 mg each alone impaired various measures of performance and rendered the subjects drowsy, feeble, mentally slow and muzzy but subchronic AMI did not enhance BUP effects. BUP increased plasma prolactin levels similarly after both pretreatments.

The results suggest that both BUP and AMI moderately affect psychomotor performance but the interaction between these agents is mild and restricted mainly to respiration.

Key words: buprenorphine, amitriptyline; interaction, psychomotor performance, respiration, pituitary hormones, healthy volunteers

Antidepressants are widely used as adjuvant medication to enhance the pain relief from various addictive analgesics. This seems reasonable because long-lasting pain often gives rise to depression, and because chronic pain is a common symptom in depressive disorders [1]. Animal experiments have demonstrated that sedative [2] as well as 5HT-selective antidepressants [3] increase the antinociceptive effect of opiates. Controlled and uncontrolled clinical trials in man, have further suggested the beneficial effects of antidepressants in chronic pain [4]. Whether these result from the interaction of antidepressants with opiate receptors [5] or simply from their mood-altering and sedative properties [6], is still an open issue.

The purpose of the present study was to investigate the interactions of buprenorphine, a long-acting partial μ-opiod agonist [7] and amitriptyline with a broad spectrum of tests measuring different central nervous system functions. Administration of such combinations to outpatients raises the question of their effects on human skilled performance needed in safe traffic and occupational life, since at least acute doses of amitriptyline have been found to impair skilled performance [8]. Respiratory depression is another important measure of safety which also confirms the presence of adequate amounts of opiate in the brain. Both antidepressants and opioids may have an effect on the release of prolactin (PRL) and growth hormone (GH) [9, 10]. Therefore, the plasma levels of these hormones were also assayed.

Material and Methods

Subjects

Twelve healthy students aged 21–28 years, and weighing 50–85 kg, volunteered for the trial. They
were physically and mentally healthy and were not taking any medications apart from oral contraceptives. All subjects gave their written informed consent, and were paid for their time. The study protocol was approved by the departmental Ethics Committee. The subjects were trained on the tests before entering the trial.

**Trial Design**

The trial comprised five randomized double-blind and crossover treatment periods started at two-week intervals. Treatment at home on Days 1 to 7 was either amitriptyline (AMI; 10 mg t.i.d. on Days 1-3, and 25 mg t.i.d. on Days 4-7) or placebo given in identical gelatine capsules. On Day 8, the subjects received in the laboratory oral AMI (25 or 50 mg) or placebo together with sublingual buprenorphine (BUP) 0.4 mg or matched placebo. Thus, the following drug combinations were given: 1) placebo-placebo; 2) placebo-AMI 50 mg; 3) placebo-BUP; 4) AMI 25 mg-BUP and 5) AMI 25 mg-placebo. Both drugs were administered simultaneously after the baseline tests.

The tests (day 8) were done on Sunday, the baseline tests being started at 10 a.m. The subjects began the test round at 6-rain intervals and the whole test round took about 25 rain from the beginning of first test to blood sampling. The post-drug test times, 2 h and 4 h, refer to the time when tests were completed. Food, coffee, tea or cola were not allowed for 2 h before or during the test sessions. Venous blood was taken into heparinized vacume tubes, once before the intake of drugs and 1, 2 and 4 h after it. Plasma was stored at $-60^\circ$ C for several weeks until assayed.

**Performance Tests**

**Objective tests.** Psychomotor skills were repeatedly tested by the following set of tests also previously used in our laboratory [11]: *Digit symbol substitution* test measures the number of correct symbols substituted for digits in 3 min. *Flicker fusion* test measures the flickering frequency of a red light distinguished at a distance of 100 cm. Pupil diameter was standardized artificially. Heterophoria expressed in dipters was measured by the Maddox wing test, which reveals the coordination of extraocular muscles. The angle at which horizontal nystagmus appeared was assessed with finger perimetry along a plastic scale. Reflex rate was measured by a finger tapping task (taps/1 min) [12].

**Hand-to-eye coordination and reactive skills** were measured by a novel computerized driving simulator [13]. The test took 5 min altogether and consisted of two reaction tests while tracking along an easy route, separated by a more difficult tracking task which lasted for 2 min. 12 auditive and 18 visual signals were presented during both attention tests, which lasted 1.5 min each. The subjects had to respond to the signals by pushing hand or foot pedals. The number of deviations from the track, the cumulative length of the deviations in per cent of total track length (error %), reaction errors, and cumulative reaction times were separately recorded for the three sections of the test.

**Subjective Assessments.** The subjects rated their feelings on 100 mm long horizontal ungraded visual analogue scales (VAS) for the following dimensions: drowsy-alert, calm-nervous, mentally slow-quick-witted, hostile-friendly, sad-happy, bored-interested, clumsy-skilful, lazy-energetic, withdrawn-social, satiated-hungry, contented-discontented, silent-talkative, active-passive, strong-feeble, clear-headed-muzzy and very bad-very good performance. A 42-item questionnaire (VIGFIN) for various psychosomatic symptoms was employed to check side-effects at the end of each test round.

**Respiratory Measurements**

Evaluation of the drug-induced respiratory depression was done as follows:

a) The resting minute ventilation ($V_e$) 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.

b) End-tidal carbon dioxide ($ETCO_2$) was measured with an infrared capnograph (CD-300, Datex) by sampling gas (150 ml/min) at the internal orifice of the face mask.

c) Ventilatory response to hypercapnia ($V_e/ETCO_2$) was determined as outlined by Jordan [14]. Rebreathing was achieved (aside from the increased dead space) with a Mapleson D circuit by stepwise decreasing fresh gas flow ($V_f$, 9.5, 6, and 3 l/min, room air, pre-calibrated constant flow generators, R-900-90, Air Logic, USA).

The capnometer was calibrated with a known gas mixture (CO$_2$ in air) and control recordings for the pneumotachograph were obtained with 3 and 6 l gas flows. Appropriate $ETCO_2$ concentrations were measured from the capnographs. Minute ventilations for each $V_f$ were measured from the recordings and calculated according to the calibration curves.

The measurements were carried out at baseline, and at 2 and 4 h after the drug intake. The subjects