A dose-response study of intravenous $m$-chlorophenylpiperazine in normal subjects

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Abstract. A placebo-controlled dose-response study of the direct serotonin receptor agonist $m$-chlorophenylpiperazine (MCPP), intravenously infused over 90 s in 0.06 and 0.08 mg/kg doses, was conducted in nine normal male subjects. Cortisol, prolactin, MCPP serum levels and behavioral responses were measured over a 210-min period. Both doses caused significant cortisol and prolactin release and were associated with significantly greater behavioral effects as compared to placebo. Though the two doses were associated with different MCPP serum levels, they did not significantly differ in their hormonal and behavioral effects.

Key words: MCPP – Serotonin – Dose-response – Intravenous

$m$-Chlorophenylpiperazine (MCPP), a selective serotonin (5-hydroxytryptamine, 5HT) agonist, has been used extensively to evaluate 5HT receptor sensitivity (Mueller et al. 1985, 1986; Charney et al. 1987, 1988; Zohar et al. 1987, 1988; Hollander et al. 1988; Kahn et al. 1988, 1990a, b, c; Lawlor et al. 1989; Murphy et al. 1989). When administered orally to normal subjects in doses of 0.25 and 0.5 mg/kg, MCPP caused a dose-dependent increase in cortisol and prolactin levels (Kahn et al. 1990a) and behavioral effects, including physical symptoms (Kahn et al. 1990a) and anxiety (Mueller et al. 1985; Murphy et al. 1989). At approximately low oral doses (0.25 mg/kg), MCPP has also been able to detect differences in 5HT receptor sensitivity between certain patient groups and controls (Kahn et al. 1988, 1990c; Zohar et al. 1987).

Oral administration causes significant inter-subject MCPP blood level variability which would be expected to be minimized by intravenous (IV) administration. However, unlike oral administration, the dose-dependent effects of intravenous MCPP, and the dose most suitable for detecting 5HT receptor differences have not been clearly established. It may be that the IV doses studied thus far were too high. For example, Charney et al. (1987) found no differences between panic disorder patients and normal subjects using 0.1 mg/kg MCPP IV infused over 20 min, in contrast to our study using oral 0.25 mg/kg MCPP (Kahn et al. 1988). The lack of a differential response with IV MCPP may have been due to overstimulation of 5HT receptors in the control group, which would explain the high rate of panic attacks (32%) (Charney et al. 1987) and significant anxiety (Murphy et al. 1989) in normal subjects on IV MCPP.

To further characterize the effects of IV MCPP, a dose-response study was conducted. Since the effects of 0.1 mg/kg were well described and 0.05 mg/kg was reported to induce minimal hormonal release (infused over 5 min) (Murphy et al. 1989), 0.06 and 0.08 mg/kg doses were selected.

Materials and methods

Subjects. Nine male normal controls (mean age = 44.0 ± 12.6 years), who met RDC criteria (Spitzer et al. 1978) for “never mentally ill” based on a SADS interview (Endicott and Spitzer 1978) and had no history of medical disorders, participated in the study. Subjects were within 25% of their ideal body weight, had normal laboratory and physical exams, were free of drug and alcohol use for at least 2 weeks and gave written informed consent prior to participation in the study.

Procedure. Subjects participated in three tests: placebo (normal saline), 0.06 and 0.08 mg/kg MCPP. The interval between tests ranged from 2 to 4 weeks. Subjects fasted (except for water intake) from 11 p.m. on the night preceding the procedure. At 9 a.m. an indwelling IV catheter was inserted. Subjects were not allowed to drink, eat, smoke or sleep during the procedure. After a 1 h adaptation period, subjects received a 20 ml bolus IV infusion over 90 s.

Blood samples were collected for plasma prolactin, cortisol and MCPP concentrations immediately before the time of infusion and at 15, 30, 45, 60, 90, 120, 150, 180, and 210 min following the infusion. All blood samples were drawn from the same IV catheter through which the infusion was administered. MCPP blood level data from the first sample (time point 15 min) were excluded from analyses because of the likely contamination of residual MCPP from the infusion (personal communication, Thomas Cooper). Behavioral effects were assessed using the 15 DSM-III-R panic attack symptoms. Each symptom was rated by the subject (using a 0–4...
point scale) at the same time points blood was drawn. Total behavioral ratings were calculated with a maximum possible score of 60 points at each time point.

Prolactin and cortisol levels were determined by a homologous double antibody radioimmunoassay using reagents purchased from Diagnostic Products Corporation (Los Angeles, CA). The lower limits of sensitivity for cortisol and prolactin were 0.3 and 2 ng/ml, respectively. The inter-assay coefficients of variance for cortisol and prolactin were 8.2% and 7.5%, respectively, and the intra-assay coefficients of variance for cortisol and prolactin were 5.5% and 5.2%, respectively.

MCPP was obtained from Aldrich Chemical Company (Milwaukee, WI) and assayed as described in Suckow et al. (1990).

Data analysis. Baseline levels (time 0, immediately prior to infusion) across the three tests were compared using repeated measures ANOVA. To assess the effects of MCPP on hormonal response, repeated measures MANOVAs were conducted with two repeated measures (test: 0.08 and 0.06 mg/kg MCPP, and placebo; and time: 0, 30, 45, 60, 90, 120, 150, 180, and 210 min). When a significant main effect for test or a test x time interaction was identified, follow-up repeated measures MANOVAs were conducted with pairwise comparisons.

Results

MCPP blood level

Mean MCPP blood levels for 0.06 mg/kg (12.6+/−2.8 ng/ml) and 0.08 mg/kg (16.5+/−5.2 ng/ml) were significantly different (t = 2.39, df = 8, P < 0.05).

Cortisol

Baseline plasma cortisol did not differ between tests. As Fig. 1 indicates, mean cortisol levels over time were different for the three tests (test x time interaction: F = 6.83, df = 18,144, P < 0.001). Follow-up analyses revealed differences between high dose and placebo (test x time interaction: F = 10.58, df = 9,72, P < 0.001), differences between low dose and placebo (test x time interaction: F = 10.87, df = 9,72, P < 0.001), and no differences between doses (test x time interaction: F = 0.67, df = 9,72, P = 0.73). Peak cortisol levels were reached at 30 minutes on high dose and at 45 min on low dose.

Prolactin

Baseline prolactin did not differ between tests. As Fig. 2 indicates, mean prolactin levels were different across time for the three tests (test x time interaction: F = 2.49, df = 18,144, P < 0.001). Follow-up analyses revealed differences between high dose and placebo (test x time interaction: F = 3.42, df = 9,72, P < 0.001), differences between low dose and placebo (test x time interaction: F = 2.90, df = 9,72, P < 0.01), and no differences between doses (test x time interaction: F = 1.05, df = 9,72, P = 0.41). Peak prolactin levels were reached at 30-45 min on high dose and at 90-120 min on low dose.

Behavioral ratings

Baseline symptomatology did not differ between tests. As Fig. 3 indicates, mean symptomatology was different across time for the three tests (test x time interaction: F = 5.09, df = 18,144, P < 0.001). Follow-up analyses revealed differences between high dose and placebo (test x time interaction: F = 8.33, df = 9,72, P < 0.001), differences between low dose and placebo (test x time interaction: F = 8.12, df = 9,72 P < 0.001) and no differences