

Behavioural effects of rapid intravenous administration of *meta*-chlorophenylpiperazine in patients with panic disorder and controls

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Abstract

Oral and intravenous challenge paradigms with the direct 5-HT agonist *meta*-chlorophenylpiperazine (*m*-CPP) in panic disorder (PD) have shown only moderate sensitivity or selectivity of the panicogenic effects in PD. However, the results of a study examining the effects of rapid intravenous administration of 0.1 mg/kg of *m*-CPP in healthy volunteers suggested that this approach may be a more selective and sensitive panicogenic paradigm in PD. We therefore compared the behavioural, neuroendocrine and physiological effects of rapid intravenous administration of 0.1 mg/kg of *m*-CPP in 10 patients with PD and 10 healthy controls. Panic attacks were significantly more provoked in patients with PD (90%) compared to healthy controls (0%). Effects on the behavioural, but not on the neuroendocrine and physiological parameters, were significantly greater in patients. Our data suggests that the behavioural effects of rapid intravenous administration of 0.1 mg/kg of *m*-CPP in patients with PD indeed show a unique combination of high sensitivity and selectivity.

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1. Introduction

There is substantial evidence to support a role for serotonin (5-HT) in the pathophysiology of panic disorder (PD). Early evidence came from treatment studies showing that selective serotonin reuptake inhibitors are more efficacious than selective noradrenergic reuptake inhibitors (den Boer and Westenberg, 1988). Studies that examined the behavioural and neuroendocrine consequences of acute administration of 5-HT receptor agonists have further supported the putative role of 5-HT in the pathogenesis of PD. Thus, 5-HT challenge probes such as fenfluramine or *meta*-chlorophenylpiperazine (*m*-CPP) may increase anxiety and result in augmented cortisol, prolactin and growth hormone responses in patients with PD (Kahn et al., 1988a; Kahn et al., 1988b; Targum, 1991).

The anxiogenic properties of non-selective 5-HT receptor agonists have led to the hypothesis that some 5-HT

receptor antagonists may possess anxiolytic and panicolytic properties. One approach to examine the potential panicolytic properties of 5-HT receptor antagonists is to evaluate their ability to reduce the panicogenic effects of a direct 5-HT receptor agonist in patients with PD. *m*-CPP, a (partial) 5-HT_{2c} receptor agonist that also possesses moderate to low affinity for other 5-HT receptors, as well as for (alpha₂) adrenergic and dopamine receptors, is currently available for this approach. Studies using *m*-CPP as a challenge agent reveal that this substance possesses moderate sensitivity and selectivity for patients with PD with regard to its panicogenic effects. *m*-CPP has been administered either orally or slowly and rapidly intravenously. Oral administration in doses ranging from 0.25 to 0.5 mg/kg of *m*-CPP resulted in panic attack rates between 55% and 70% in PD patients and in virtually no effect in the control subjects (Broocks et al., 2000; Kahn et al., 1988a; Klein et al., 1991). Panic attacks occurred typically at 60 min after administration. Both slow (0.05 and 0.1 mg/kg) and rapid intravenous administration (0.06 and 0.08 mg/kg) of *m*-CPP resulted in lower panic rates in PD varying between 9% and 52%, occurring within 30 min after administration (Benjamin et al., 1997; Charney et al., 1987; Germine et al., 1994;

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Wetzler et al., 1996). Thus, sensitivity and selectivity of the behavioural effects following *m*-CPP administration seem to depend in part on the route and speed of administration.

Murphy et al. (1989) performed a direct comparison of the effects of intravenous and oral *m*-CPP administration in healthy controls. They studied the effects of rapid intravenous administration of 0.1 mg/kg of *m*-CPP in 90 s and oral administration of 0.5 mg/kg of *m*-CPP. Increases in measures of anxiety were seen following the intravenous approach only, but panic attacks were not observed following either route of administration. In addition, both oral and intravenous administration resulted in similar increases in cortisol, prolactin and growth hormone. The mean plasma levels of *m*-CPP did not differ between the two routes of administration, but there was a twofold higher plasma peak level following the intravenous approach. These findings suggest a relationship between the peak plasma levels of *m*-CPP and the occurrence of behavioural responses in healthy subjects.

Although previous intravenous *m*-CPP challenge paradigms in general show a low sensitivity and selectivity with regard to the panicogenic properties in PD, the findings of Murphy et al. (1989) in healthy controls suggest that a possible stronger and more selective behavioural effect may be obtained after rapid intravenous administration of 0.1 mg/kg of *m*-CPP. We decided to further explore the characteristics of intravenous administration of 0.1 mg/kg of *m*-CPP in 90 s as a possible model to evaluate the panicolytic properties of a novel 5-HT receptor antagonist in patients with PD.

2. Experimental procedures

Ten patients (eight males, two females, age 41 ± 8 years) with PD with or without agoraphobia according to DSM-IV criteria and with no other psychopathology and 10 age- and sex-matched healthy controls (36 ± 8 years) participated in this study. Diagnoses were established by experienced psychiatrists (N.W., H.M.) using standard clinical interviews. Subjects had no history of medical disorders, were drug free for minimal 2 weeks (60 days for fluoxetine, 6 months for corticosteroids), had not donated blood during the 60 days preceding the test day, female subjects were not pregnant or breast-feeding and all subjects had normal physical and laboratory examinations. There were no subjects with a history or suspicion of substance abuse. As previous placebo-controlled challenge studies in patients with PD at our center, using the same type of experimental procedure, showed a placebo response of 0%, we choose to administer only *m*-CPP and no placebo (van Meegen et al., 1994, 1996). Subjects were informed that they would receive either *m*-CPP or a saline-based solution mimicking possible initial effects of *m*-CPP like hot flushes or light-headedness. The study was approved by the medical ethical committee of the University Medical Center Utrecht. All

subjects gave written informed consent prior to inclusion in the study.

Subjects took a light breakfast at least 1 h before the test. Coffee, smoking and alcoholic beverages were not allowed from 9 p.m. on the evening before. Immediately after baseline assessments, an indwelling intravenous catheter was placed in a forearm vein in each arm at 9 a.m. At 10 a.m., *m*-CPP (0.1 mg/kg diluted in 20 ml of normal saline) was administered in 90 s by means of an automatic pump (Becton Dickinson). Behavioural, physiological and neuroendocrine responses as well as *m*-CPP plasma levels were measured immediately before infusion and regularly at 30-min intervals until 150 min after the infusion. Behavioural responses were measured prior to the measurement of physiological and neuroendocrine responses. When subjects experienced behavioural effects immediately after the intravenous administration, onset and duration were recorded by one of the investigators. When these effects abated within the first 30-min interval, peak values were assessed retrospectively.

Behavioural responses were assessed by using a Visual Analogue Scale (VAS) for anxiety and the Panic Symptom Scale (PSS) (van Meegen et al., 1994, 1996; Bradwejn et al., 1992). The PSS is a self-rating instrument derived from DSM-III-R criteria for panic attack. Both the symptom severity and the fear of the symptom are rated on a five-point scale (0 = *not at all* to 4 = *severe*). The PSS can be divided into a somatic (PSS-somatic, 18 items) and a cognitive subscale (PSS-cognitive, 6 items) and into subscales for the presence of symptoms (PSS-A) and the fear provoked by symptoms (PSS-B). For each subscale, the mean total score was calculated. For the somatic and cognitive subscales, we also calculated a mean score per item to allow for a comparison with the subscale profiles found with some other challenge paradigms.

After the challenge, the eventual occurrence of a panic attack was assessed. A panic attack had to fulfil the following criteria (Charney et al., 1987): an increase in anxiety as measured with the VAS of at least 25 mm, the occurrence of at least four DSM-IV symptoms of a panic attack and also a rating of at least 2 on an item of fear or apprehension of the PSS-A, and patients had to report that the panic attack was similar to their spontaneous ones.

Neuroendocrine measurements consisted of assessment of cortisol and growth hormone levels. Cortisol was measured using a competitive, chemiluminescent assay (ACS: Centaur Cortisol, Chiron Diagnostics, East Walpole, MA, USA). The intraassay and interassay coefficients of variation at 4 $\mu\text{g/ml}$ were 4% and 6%, respectively. Growth hormone was assayed using a commercially available radioimmunoassay kit (Oris Industry, Gif-sur-Yveth, France), with a lower limit of detection of 0.5 mU/l and an intra- and interassay coefficient of variation of 8% and 11%, respectively. Physiological measurements consisted of blood pressure supine and standing, pulse rate supine and standing and orally measured temperature.

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