ELSEVIER

Psychiatry Research 79 (1998) 11–20

PSYCHIATRY RESEARCH

Acute intravenous administration of ondansetron and m-CPP, alone and in combination, in patients with obsessive–compulsive disorder (OCD): behavioral and biological results

Andreas Broocks[a,*], Teresa A. Pigott[b], James L. Hill[c], Stephanie Canter[a], Tana A. Grady[d], Francine L'Heureux[a], Dennis L. Murphy[a]

[a] *Section on Clinical Neuropharmacology, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD, USA*

[b] *Department of Psychiatry, University of Texas Medical Branch at Galveston, Galveston, TX, USA*

[c] *National Institute on Drug Abuse, Rockville, MD, USA*

[d] *Department of Psychiatry, Duke University, School of Medicine, Durham, NC, USA*

Received 23 October 1997; revised 9 March 1998; accepted 12 March 1998

Abstract

Obsessive–compulsive disorder (OCD) has been linked to abnormal function of brain serotonin (5-HT) pathways. Since ondansetron is a highly selective 5-HT_3 receptor antagonist, the present study was undertaken to investigate 5-HT_3 function in OCD. We administered m-CPP (0.08 mg/kg i.v.) and the potent 5-HT_3 antagonist, ondansetron (0.15 mg/kg i.v.), to 11 OCD patients. All of the subjects received four separate challenges (m-CPP + placebo, m-CPP + ondansetron, ondansetron + placebo and placebo + placebo). In comparison to placebo, administration of m-CPP was associated with significant behavioral effects, particularly self-rated measures of anxiety, altered self-reality, functional deficit and OCD symptoms. Pretreatment with ondansetron did not affect any of the self-rated behavioral symptoms. After administration of m-CPP relative to placebo, significant increases in plasma cortisol and prolactin were found. These changes were not affected by ondansetron. In conclusion, our results do not support the hypotheses that 5-HT_3 receptor-mediated mechanisms modulate m-CPP's behavioral and neuroendocrine effects in patients with OCD. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Obsessive–compulsive disorder; Meta-chlorophenylpiperazine hydrochloride; Ondansetron; Anxiety; Cortisol; Norepinephrine; Serotonin

* Corresponding author. Psychiatrische Klinik der Medizinischen, Universität zu Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. Tel.: +49 451 5000; fax: +49 451 5002603.

0165-1781/98/$19.00 © 1998 Elsevier Science Ireland Ltd. All rights reserved.
PII S0165-1781(98)00029-8

1. Introduction

This study continues ongoing efforts to elucidate the pathophysiology of OCD in regard to a possible dysregulation of serotonergic neurotransmitter systems. The most compelling findings suggesting a role of serotonergic pathways in the symptomatology of OCD come from well-replicated treatment studies. Most OCD patients improve during treatment with serotonin (5-HT) reuptake inhibitors including clomipramine, fluoxetine, fluovoxamine, paroxetine and sertraline, but not with non-5-HT selective antidepressants, such as desipramine, amitriptyline, and clorgyline (Insel et al., 1983; Goodman et al., 1989; Murphy et al., 1996; Zohar and Judge, 1996; Jenike et al., 1997). In a placebo-controlled design, discontinuation of clomipramine was followed by an increase of OCD symptoms in patients (Pato et al., 1991). Interestingly, coadministration of the 5-HT_2 receptor antagonist metergoline to OCD patients being treated with clomipramine was associated with higher OC symptoms in comparison to placebo coadministration (Benkelfat et al., 1989). In another study, metergoline antagonized the therapeutic action of fluoxetine (Greenberg et al., 1994). In addition, three studies have demonstrated that when the serotonergic agent, *m*-chlorophenylpiperazine hydrochloride (m-CPP), is administered orally to patients with OCD, they exhibit evidence of behavioral hyperresponsivity and some neuroendocrine hyporesponsivity in comparison to control subjects (Zohar et al., 1987; Hollander et al., 1988, 1992a). However, an exacerbation of OC symptoms after administration of m-CPP was not observed in all studies (Charney et al., 1988; Goodman et al., 1995). When oral m-CPP was re-administered during chronic treatment with clomipramine (Zohar et al., 1988) or fluoxetine (Pigott et al., 1990; Hollander et al., 1992b), OCD patients did not show an exacerbation of OC symptoms although plasma prolactin and cortisol responses to m-CPP were not attenuated. This suggests that chronic clomipramine or fluoxetine treatment in OCD patients may be associated with the development of an adaptative subsensitivity in one or more serotonergic subsystems (Murphy et al., 1996). So far, it is not known how 5-HT_3 receptors are affected after acute or chronic administration of 5-HT reuptake inhibitors.

As knowledge increases concerning the different 5-HT subsystems, basic and clinical research is now intensively trying to clarify their functional role, especially since discrete subpopulations of 5-HT receptors might have reciprocal functions. In humans, these efforts have been limited by the lack of sufficiently selective agents. Since ondansetron has highly selective affinity for 5-HT_3 sites in brain and other tissues (Butler et al., 1988), it appears to be a useful tool to further clarify these questions. The hypothesis that some of m-CPPs effects might be mediated by 5-HT_3 receptors is supported by data which indicate that m-CPP's affinity to 5-HT_3 receptor sites is in the nanomolar range and is only exceeded by its slightly higher affinity for 5-HT_{2C} receptors (Kilpatrick et al., 1987; Neijt et al., 1988; Watling et al., 1988). In an animal model of anxiety, m-CPP's anxiogenic effects were blocked by ICS 205-930 and BRL 46470 (Kennett et al., 1989; Kennett and Blackburn, 1990), which are other 5-HT_3 antagonists similar to ondansetron. Ondansetron is used clinically to attenuate the nausea and emesis associated with anti-cancer chemotherapeutic drugs (Cubeddu et al., 1990), an effect thought to be mediated via the high density of 5-HT_3 receptors localized in the area postrema and solitary tract nucleus in the brainstem (Kilpatrick et al., 1987; Barnes et al., 1989, 1990a). 5-HT_3 receptors, however, are also widely distributed in other brain areas including cortical and limbic system areas (Kilpatrick et al., 1987; Barnes et al., 1989, 1990a). Studies using selective 5-HT_3 antagonists from different chemical classes have documented that 5-HT_3 receptors play an important role in controlling the release of serotonin, dopamine, acetylcholine and other neuromodulators in the brain and the periphery (Barnes et al., 1989b, 1990b; Martin et al., 1992). In addition, agents acting at 5-HT_3 receptors alter the effects of drugs of psychopharmacologic interest, including cocaine, morphine, nicotine and alcohol via mod-

ulatory effects on other neurotransmitters including dopamine, norepinephrine and acetylcholine (Costall et al., 1990; Hamon, 1992; Apud, 1993; Grant, 1995)

This is, to our knowledge, the first study in patients with OCD examining the behavioral and neuroendocrinological effects of ondansetron alone and in combination with m-CPP.

2. Methods

2.1. Study design

Every subject received four different challenges in a randomized double-blind design. m-CPP was given after pretreatment with ondansetron or placebo. In order to examine possible behavioral or hormonal effects of ondansetron alone, we included two other challenges consisting of an ondansetron/placebo and a double placebo condition. The interval between two neuroendocrine challenges was at least 48 h.

2.2. Subjects

Eleven OCD patients participated in the study. All patients were referred by local psychiatrists to the National Institute of Mental Health (NIMH) OCD outpatient program and were screened by at least two clinicians. All patients were given a structured interview by a research psychiatrist and diagnosed as having OCD by DSM-III-R criteria. Additional inclusion criteria were duration of illness for at least 1 year and a minimum age of 18 years. Patients with mild to moderate depression, which was defined by a score between 12 and 26 on the Beck Depression Inventory, were included in this study.

All patients were free from psychotropic drugs for at least 4 weeks prior to the test sessions. Before this, most patients had been on different treatments, some patients had also received fluoxetine in the past. All patients had normal physical examinations, normal routine laboratory tests (renal, hepatic, pancreatic, hematologic and thyroid function) and normal electrocardiograms prior to inclusion in the study. All patients gave voluntary written informed consent for their participation in the study.

2.3. Procedures

On the day of each challenge session, subjects arrived at the outpatient clinic of the National Institute of Mental Health (Bethesda, MD) at approximately 08:30 h. Prior to each challenge session, subjects had fasted overnight starting at 22:00 h. During the challenge sessions, subjects abstained from eating or sleeping and remained in bed with the head elevated. At 09:00 h, an intravenous catheter was placed in an antecubital vein for repeated blood sampling and a second catheter was placed in a forearm vein on the opposite side for drug or placebo administration. Starting at 10:00 h, a pretreatment infusion of either ondansetron (0.15 mg/kg) or a first placebo (50 ml in total) was administered over a 15-min period using procedures established previously for ondansetron chemotherapy protocols (Cubeddu et al., 1990). This was followed by a 30-min equilibration period. At 10:45 h, m-CPP (0.08 mg/kg) or a second saline placebo, given in a total volume of 20 ml, was administered by intravenous infusion over a 90-s period. Both m-CPP hydrochloride and ondansetron were purchased from commercial sources. The identity and purity of the m-CPP was verified by the NIH Clinical Center Pharmaceutical Development Service, Bethesda, MD.

A baseline blood draw was made at 10:00 h (immediately prior to the pretreatment infusion) and serial blood draws were subsequently made at 10:30, 11:15, 11:45 and 12:15 h. Samples of blood were immediately placed on ice, centrifuged within 2 h of collection and the plasma stored at −70°C until time of assay. Plasma samples were assayed for prolactin, cortisol, growth hormone, and norepinephrine, using previously described assays (Murphy et al., 1989; Benjamin et al., 1996). Throughout each challenge session, oral temperature, blood pressure and heart rate were measured at 15-min intervals using an automated Dinamapp monitor. Behavioral data from all 11 patients were included in the analyses; due to technical problems, neuroendocrine data from

only nine patients could be evaluated. Baseline growth hormone values were substantially elevated in two out of 11 subjects (> 2 pg/ml); data from these subjects were excluded from this analysis.

2.4. Assessment

The behavioral rating scales used for all subjects included a modified version of the NIMH Self-Rating Scale that comprises 24 questions, each rated 0 ('not present') to 6 ('very marked') and defines six subscales of behavioral change: anxiety, activation, euphoria, altered self-reality, depressive affect, dysphoria and functional deficit (Murphy et al., 1989). In addition, each OCD patient completed, with the aid of an experienced rater, specific ratings aimed at assessing changes in obsessions and compulsions. The scales that were used included: (1) a modified form of the Comprehensive Psychiatric Rating Scale [Obsessive–Compulsive subscale, CPRS-OC (Thorén et al., 1980)]; (2) the NIMH Obsessive–Compulsive Rating Scale, NOC (Insel et al., 1983), which is an eight-item observer rating scale that rates OCD symptoms from 0 to 7 in terms of frequency, intensity, interference and ability to resist OCD symptoms. Behavioral ratings were performed at the following time points: 10:00, 10:30, 11:00, 11:30, 12:00 and 12:30 h.

2.5. Statistical analysis

All results were evaluated by analysis of variance (ANOVA) with repeated measures procedures. The analyses including all four treatments were performed in a sequential fashion: first, an overall ANOVA tested for significant main effects plus all interactions. Second, and only if the overall ANOVA revealed significant main effects and/or interactions, a subsequent ANOVA was done to compare the three active medication conditions (ondansetron alone, m-CPP alone, m-CPP + ondansetron) with the results under placebo condition and with each other. In addition, drug conditions were also compared within time points across the challenges by ANOVA. All calculation procedures were those of the SAS Institute. Data are reported as means ± S.E.M.s.

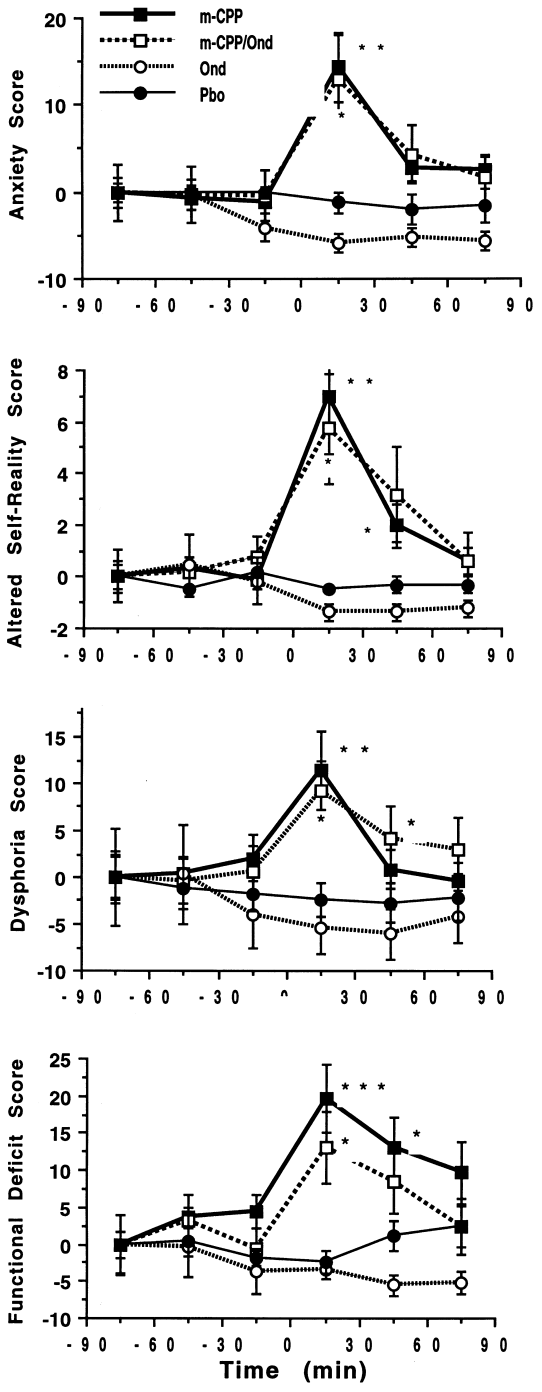
3. Results

Six male and five female patients with OCD fulfilled the inclusion criteria for our study. The mean age was 39.1 years (S.D. = 14.4 years, range 22–58), and the mean duration of illness was 15.7 years (S.D. = 8.1 years, range 8–33). The severity of obsessive–compulsive symptoms, as estimated by the Maudsley Obsessive–Compulsive Inventory (MOCI), was 12.6 (S.D. = 5.2, range 6–22), and the mean depression score on the Beck Depression Inventory (BDI) was 11.3 (S.D. = 6.9, range 1–26). Six out of 11 patients fulfilled the criteria of mild to moderate depression, which were defined by a score between 12 and 26 on the BDI.

At baseline, there were no significant differences between the four challenge conditions in any of the behavioral or the hormonal data.

3.1. Psychobehavioral effects

Fig. 1 depicts changes from baseline in regard to self-rated anxiety, altered self-reality, dysphoria and functional deficits for the four challenge conditions across time. Overall ANOVA revealed significant interactions (drugs × time) for anxiety ($F_{15,50} = 4.86$; $P = 0.0004$), altered self-reality ($F_{15,50} = 5.76$; $P = 0.0001$), dysphoria ($F_{15,50} = 4.75$, $P = 0.0004$), functional deficit ($F_{15,50} = 4.41$, $P = 0.0015$), and depression ($F_{15,50} = 3.29$, $P = 0.0063$). Only the activation/euphoria subscale did not show significant main effects. When the three active challenge conditions were compared to placebo, the self-rating scores after m-CPP administration alone differed significantly from placebo ratings for anxiety ($F_{1,10} = 9.51$; $P = 0.012$), altered self-reality ($F_{1,10} = 7.15$; $P = 0.02$), and dysphoria ($F_{1,10} = 8.69$; $P = 0.014$), but not for depression and activation. There was a trend for increased functional deficit ($F_{1,10} = 3.6$; $P = 0.087$) associated with administration of m-CPP alone. After pretreatment with ondansetron, self-rated symptoms were significantly different



from placebo only for anxiety ($F_{1,10} = 8.43$; $P = 0.02$), and there were statistical trends for differences in altered self-reality ($F_{1,10} = 4.77$; $P = 0.054$), dysphoria ($F_{1,10} = 4.53$; $P = 0.06$), and functional deficit ($F_{1,10} = 3.6$; $P = 0.07$). A direct comparison of self-ratings after m-CPP alone vs. the ondansetron/m-CPP condition revealed no significant effects.

On the basis of significant interactions, univariate testing for the different time points was performed. In comparison to placebo, significant increases within 15 min after infusion of m-CPP were observed for anxiety, altered self-reality, dysphoria and functional deficit. This peak response was followed by a gradual decline of self-rated symptoms (Fig. 1) which were not different from placebo ratings at the end of the procedure (75 min after m-CPP administration). Pretreatment with ondansetron did not attenuate peak responses to m-CPP. It also did not modulate the decrease of symptoms during the following 75 min. Ondansetron alone did not elicit any psychobehavioral changes in comparison to the placebo condition (Fig. 1).

3.2. Obsessive–compulsive (OCD) symptoms

Fig. 2 shows the respective changes in obsessive–compulsive (OCD) symptoms. Overall ANOVA revealed highly significant main effects for drug condition ($F_{3,30} = 4.77$, $P = 0.0078$), time ($F_{5,50} = 4.58$, $P = 0.0075$) and drug condition × time interaction ($F_{15,150} = 3.29$, $P = 0.0003$) for OCD symptoms as measured by the NOC scale. When the CPRS-OC scale was used, significant main effects were noted for drug condition ($F_{3,30} = 3.55$, $P = 0.0261$) and time ($F_{5,50} = 3.59$, $P = 0.0187$), but only a statistical trend for the interaction of drug condition and time ($F_{15,50} = 1.95$, $P = 0.0518$). Administration of m-CPP was followed by a significant increase of OCD symptoms

Fig. 1 Self-rated behavioral symptoms in 11 OCD patients during challenge sessions with m-CPP alone, m-CPP + ondansetron, placebo, and ondansetron alone. Data are presented as changes from baseline. Mean baseline values (±S.D.) across the 4 challenge days were as follows: anxiety, 6.5 ± 1.3; altered self-reality, 0.8 ± 0.4; dysphoria, 5.7 ± 3.1; functional deficit, 5.7 ± 2.7; * m-CPP alone or m-CPP + ondansetron vs. placebo; $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$.

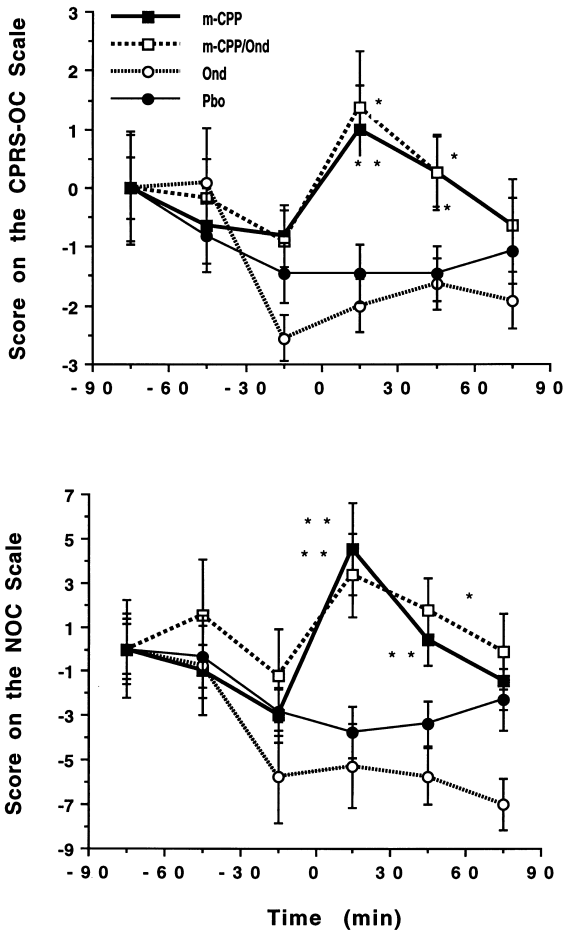


Fig. 2. Obsessive–compulsive symptoms in 11 OCD patients during challenge sessions with m-CPP alone, m-CPP + ondansetron, placebo, and ondansetron alone. Data are presented as changes from baseline. Mean baseline values (±S.D.) across the 4 challenge days were as follows: Obsessive–Compulsive subscale of the Comprehensive Psychiatric Rating Scale (CPRS), 3.1 ± 0.3; NIMH Obsessive–Compulsive Rating Scale (NOC), 9.2 ± 1.5; *m-CPP alone or m-CPP + ondansetron vs. placebo, $P < 0.05$; **$P < 0.01$.

within 15 min relative to placebo conditions (Fig. 2). CPRS and NOC scores were still significantly increased 45 min after infusion of m-CPP and returned to baseline levels within 75 min. Pretreatment with ondansetron did not change the m-CPP-induced exacerbation of symptoms. Also, administration of ondansetron alone or placebo had no significant effect on OC symptoms (Fig. 2).

3.3. Neuroendocrine responses

For plasma cortisol, overall ANOVA revealed a significant main effects for drug condition ($F_{3,24} = 7.16$, $P = 0.0013$), time ($F_{4,32} = 5.77$, $P = 0.0131$) and the interaction of drug condition by time ($F_{12,96} = 4.32$, $P = 0.0034$). In comparison to placebo, cortisol levels were significantly higher 30 and 60 min after administration of m-CPP. This response was not altered by pretreatment with ondansetron (Fig. 3). For plasma prolactin, overall ANOVA revealed a significant main effects for drug condition ($F_{3,24} = 7.16$, $P = 0.0013$), time ($F_{4,32} = 5.77$, $P = 0.0131$) and the interaction of drug condition by time ($F_{12,96} = 4.32$, $P = 0.0034$). The administration of m-CPP in combination with ondansetron was followed by a significant increase of plasma prolactin concentrations. The increase after administration of m-CPP alone was of the same magnitude, but did not reach significance in comparison to placebo conditions (Fig. 3). For plasma norepinephrine (NE), main effects for drug condition and time were not significant with an interaction close to statistical significance ($F_{12,96} = 2.1$, $P = 0.056$). NE levels were elevated 30 min after administration of m-CPP. No increase was observed after pretreatment with ondansetron (Fig. 3). Since the overall interaction was not significant, a further statistical analysis was not performed. Main effects for growth hormone were not significant. Plasma concentrations of m-CPP measured in 10 of the 11 subjects did not differ between the m-CPP only and the m-CPP/ondansetron condition (data not shown).

3.4. Physiological findings

The ANOVA did not reveal any significant main effects for oral temperature, blood pressure and heart rate across the different challenge conditions. Therefore, we have not reported these measures.

3.5. Side effects

Overall, the procedure was well tolerated by all patients. The most unpleasant side effect was the sudden increase of anxiety feelings after the in-

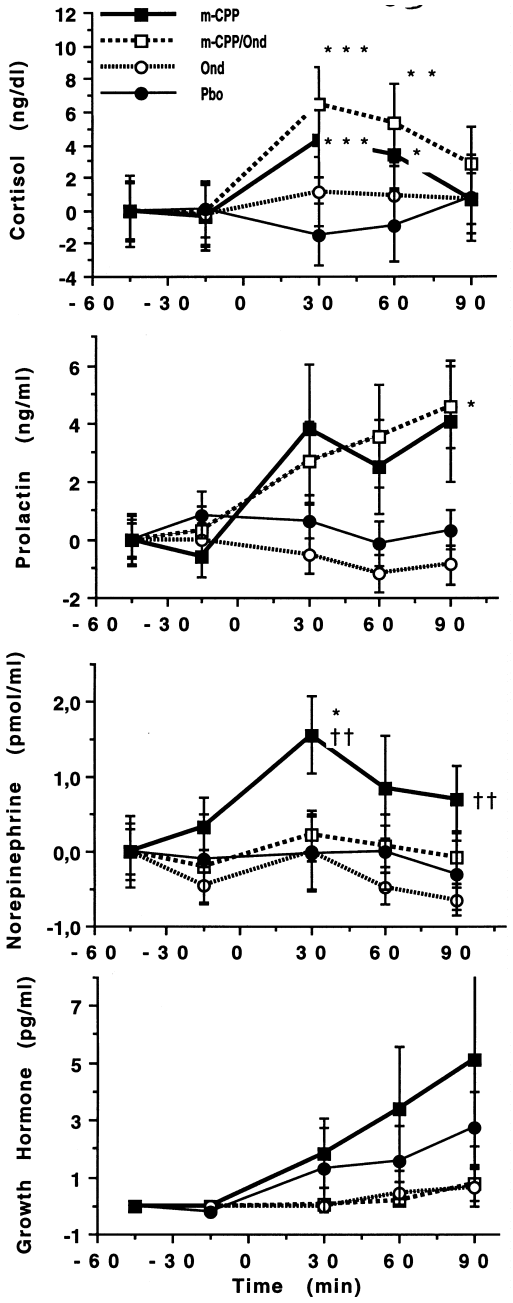


Fig. 3. Plasma concentrations of cortisol, norepinephrine, prolactin, and growth hormone in nine OCD patients during challenge sessions with m-CPP alone, m-CPP + ondansetron, placebo, and ondansetron alone. Data are presented as changes from baseline. Mean baseline values (±S.D.) across the 4 challenge days were as follows: cortisol, 12 + 1.8 ng/dl; norepinephrine, 6.6 + 0.1 pmol/ml; prolactin, 6.5 + 1.1 ng/ml; growth hormone, 1.1 + 0.5 ng/ml. * m-CPP alone or m-CPP + ondansetron vs. placebo, $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. ††m-CPP alone vs. m-CPP + ondansetron, $P < 0.01$.

travenous injection of m-CPP. Other physical symptoms which were commonly reported during m-CPP challenge sessions were sweating, nausea, drowsiness, tremor, yawning and a warm skin sensation. These symptoms were generally of equal frequency following m-CPP alone or m-CPP plus ondansetron. Overall, the intensity of these symptoms peaked after 5–15 min followed by a slow, continuous decline.

4. Discussion

The intravenous administration of m-CPP in 11 patients with OCD was followed by significant increases of self-rated anxiety, feelings of altered self, dysphoria and an exacerbation of OCD symptoms. However, when the CPRS-OC scale was used, only a statistical trend was observed for the interaction of drug condition with time. Regarding functional deficits, there was also only a statistical trend towards increased ratings after administration of m-CPP. Although the m-CPP dose was 20% lower in comparison to our former dose (Pigott et al., 1993), the psychobehavioral response was very similar.

An exacerbation of OCD symptoms was observed after oral (Zohar et al., 1987; Hollander et al., 1988; Pigott et al., 1991; Hollander et al., 1992a) and intravenous administration of m-CPP (Pigott et al., 1993). In contrast, two studies of OCD patients using oral and/or intravenous infusions of m-CPP (0.5 mg/kg and 0.1 mg/kg, respectively) did not report any increase of OCD symptoms (Charney et al., 1988; Goodman et al., 1995). Two major differences in methodology may have contributed to the discrepancy in results. M-CPP was administered in a 20-min infusion in the latter two studies, whereas it was delivered in a 90-s bolus in the current study and in the other positive intravenous study (Pigott et al., 1993). Also, the small sample size, interrater variability, differences in the assessment procedures or the characteristics of the patient samples could have been involved. In the two studies which showed no worsening of OCD symptoms, the first behavioral rating was done not earlier than 60 min (Goodman et al., 1995) or 90 min after infusion of m-CPP (Charney et al., 1988). Chronic treatment

with clomipramine (Zohar et al., 1988) and fluoxetine (Hollander et al., 1992b) abolished m-CPP's ability to stimulate OCD symptoms.

Pretreatment with ondansetron did not affect any of the self-rated behavioral symptoms in the current study. In contrast, both the peak and total anxiogenic effects of oral or intravenous m-CPP were antagonized by the non-selective serotonin antagonist, metergoline (Pigott et al., 1991, 1993) and were also attenuated after pretreatment with the 5-HT_{2A}/5-HT_{2C} antagonist, ritanserin (Seibyl et al., 1991). Metergoline also antagonized the m-CPP-induced increase in OCD symptomatology (Pigott et al., 1993). Since ritanserin and metergoline both have high affinity for 5-HT_{2A}/5-HT_{2C} receptor sites, and m-CPP is a partial agonist at 5-HT_{2C} sites, but an antagonist at 5-HT_{2A} sites, it has generally been concluded that most of m-CPP's anxiety-related effects in humans are mediated by 5-HT_{2C} agonist actions (Murphy, 1990; Kahn and Wetzler, 1991; Pigott et al., 1991, 1993; Benjamin et al., 1996).

In healthy control subjects, ondansetron pretreatment appeared to attenuate some behavioral effects and the cortisol response induced by the administration of m-CPP (Broocks et al., 1997). Specifically, behavioral ratings obtained 45 min after m-CPP administration demonstrated an earlier return to baseline after ondansetron pretreatment. This effect was most pronounced for the anxiety and functional deficit subscales, as well as the summary measure of overall behavioral effect. There was also some attenuation of m-CPP-induced cortisol secretion after pretreatment with ondansetron (Broocks et al., 1997). In contrast, ondansetron did not affect any of the behavioral or neuroendocrine responses to m-CPP in OCD patients examined in the current study. One possible explanation for these discrepant findings in OCD patients and control subjects is that a higher ondansetron dose might have been necessary to antagonize m-CPP's effects, because patients with OCD are characterized by a behavioral hyperresponsiveness to serotonergic agonists. Another important difference between OCD patients and healthy control subjects is the fact that the patients had much higher baseline scores of all behavioral subscales, particularly anxiety. The modest effect of ondansetron observed in control subjects might have been masked by this high background effect. We do not think that pharmacological aspects account for the different findings. Plasma concentrations of m-CPP in OCD patients were in the same range as in the healthy control subjects in our earlier studies. We found no differences in plasma concentrations of m-CPP when the m-CPP alone and the ondansetron/m-CPP conditions were compared. Also, in both studies, ondansetron was administered in the same dose that has proved to be effective against chemotherapy-induced emesis when given 30 min prior to chemotherapy (Blackwell and Harding, 1989). There appear to be no other studies examining the effects of ondansetron on anxiogenic or other m-CPP-induced behavioral changes in humans, but pretreatment with another 5-HT_3 antagonist, BRL 46470, had no apparent effect on behavioral or neuroendocrine effects induced by m-CPP (Silverstone and Cowen, 1994). However, there were several important differences in the study design. BRL 46470 was administered orally whereas we gave ondansetron intravenously. The time of administration of the 5-HT_3 antagonist relative to m-CPP administration was also different and the dose of BRL 46470 was tenfold lower than the equivalent ondansetron dose in the current study.

The elevation of plasma NE after administration of m-CPP was not observed after pretreatment with ondansetron. In healthy control subjects, a significant increase of NE was noted both after m-CPP alone and in combination with ondansetron (Broocks et al., 1997). Combined administration of metergoline and m-CPP was also associated by a significant elevation of NE in OCD patients (Pigott et al., 1993). In animal experiments, contradictory findings were reported concerning the modification of m-CPP-induced NE secretion by 5-HT_3-receptor antagonists (Bagdy et al., 1989; Aulakh et al., 1992).

In summary, in this study acute administration of m-CPP was associated with an exacerbation of OCD symptoms and other psychobehavioral symptoms. In contrast to healthy volunteers (Broocks et al., 1997), ondansetron pretreatment did not attenuate any of these changes in this group of patients with OCD. Since our study is limited by the lack of a control group, this obser-

vation alone would not justify speculations about involvement of 5-HT_3 receptors in the pathophysiology of OCD. Selective 5-HT_3 agonists would be a valuable tool in order to directly compare 5-HT_3 receptor-related responsiveness in OCD patients and healthy control subjects.

Acknowledgements

We thank Dr. John Bartko for statistical consultation, Mrs. Suzanne Bernstein for assistance during the study, and Mrs. Wilma Davis for editorial assistance.

References

Apud, J.A., 1993. The 5-HT3 receptor in mammalian brain: a new target for the development of psychotropic drugs? Neuropsychopharmacology 8, 117–130.

Aulakh, C.S., Hill, J.L., Murphy, D.L., 1992. Effects of various serotonin receptor subtype-selective antagonists alone and on m-chlorophenylpiperazine-induced neuroendocrine changes in rats. Journal of Pharmacology and Experimental Therapeutics 263, 588–595.

Bagdy, G., Szemeredi, K., Kanyicska, B., Murphy, D.L., 1989. Different serotonin receptors mediate blood pressure, heart rate, plasma catecholamine and prolactin responses to m-chlorophenylpiperazine in conscious rats. Journal of Pharmacology and Experimental Therapeutics 250, 72–78.

Barnes, J.M., Barnes, N.M., Costall, B., Ironside, J.W., Naylor, R.J., 1989a. Identification and characterisation of 5-hydroxytryptamine 3 recognition sites in human brain tissue. Journal of Neurochemistry 53, 1787–1793.

Barnes, J.M., Barnes, N.M., Costall, B., Naylor, I.L., Naylor, R.J., Rudd, J.A., 1990a. Topographical distribution of 5-HT3 receptor recognition sites in the ferret brain stem. Naunyn Schmiedebergs Archives of Pharmacology 342, 17–21.

Barnes, J.M., Barnes, N.M., Costall, B., Naylor, R.J., Tyers, M.B., 1989b. 5-HT3 receptors mediate inhibition of acetylcholine release in cortical tissue. Nature 338, 762–763.

Barnes, J.M., Costall, B., Coughlan, J., Domeney, A.M., Gerrard, P.A., Kelly, M.E., Naylor, R.J., Onaivi, E.S., Tomkins, D.M., Tyers, M.B., 1990b. The effects of ondansetron, a 5-HT3 receptor antagonist, on cognition in rodents and primates. Pharmacology, Biochemistry and Behaviour 35, 955–962.

Benjamin, J., Greenberg, B.D., Murphy, D.L., 1996. Daily administration of m-CPP to healthy human volunteers rapidly attenuates many of its behavioral, hormonal, cardiovascular and temperature effects. Psychopharmacology 127, 140–149.

Benkelfat, C., Murphy, D.L., Zohar, J., Hill, J.L., Grover, G., Insel, T.R., 1989. Clomipramine in obsessive-compulsive disorder. Further evidence for a serotonergic mechanism of action. Archives of General Psychiatry 46, 23–28.

Blackwell, C.P., Harding, S.M., 1989. The clinical pharmacology of ondansetron. European Journal of Cancer and Clinical Oncology 25, S21–S27.

Broocks, A., Briggs, N.C., Pigott, T.A., Hill, J.L., Canter, S.K., Tolliver, T.J., Baldemore, D., Murphy, D.L., 1997. Behavioral, physiological and neuroendocrine responses in healthy volunteers to m-chlorophenylpiperazine (m-CPP) with and without ondansetron pretreatment. Psychopharmacology (Berlin) 130, 91–103.

Butler, A., Hill, J.M., Ireland, S.J., Jordan, C.C., Tyers, M.B., 1988. Pharmacological properties of GR38032F, a novel antagonist at 5-HT3 receptors. British Journal of Pharmacology 94, 397–412.

Charney, D.S., Goodman, W.K., Price, L.H., Woods, S.W., Rasmussen, S.A., Heninger, G.R., 1988. Serotonin function in obsessive-compulsive disorder. A comparison of the effects of tryptophan and m-chlorophenylpiperazine in patients and healthy subjects. Archives of General Psychiatry 45, 177–185.

Costall, B., Jones, B.J., Kelly, M.E., Naylor, R.J., Onaivi, E.S., Tyers, M.B., 1990. Ondansetron inhibits a behavioural consequence of withdrawing from drugs of abuse. Pharmacology, Biochemistry and Behaviour 36, 339–344.

Cubeddu, L.X., Hoffmann, I.S., Fuenmayor, N.T., Finn, A.L., 1990. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting [see comments]. New England Journal of Medicine 322, 810–816.

Goodman, W.K., McDougle, C.J., Price, L.H., Barr, L.C., Hills, O.F., Caplik, J.F., Charney, D.S., Heninger, G.R., 1995. *m*-Chlorphenylpiperazine in patients with obsessive-compulsive disorder: absence of symptom exacerbation. Biological Psychiatry 38, 138–149.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Delgado, P.L., Heninger, G.R., Charney, D.S., 1989. Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo. Archives of General Psychiatry, 46(1):36–44.

Grant, K.A., 1995. The role of 5-HT3 receptors in drug dependence. Drug and Alcohol Dependence 38, 155–171.

Greenberg, B.D., Benjamin, J., Murphy, D.L., 1994. Biphasic effects of metergoline in fluoxetine-treated OCD patients. Biological Psychiatry 35, 738.

Hamon, M., 1992. Central and Peripheral 5-HT3 Receptors. Academic Press, London.

Hollander, E., DeCaria, C.M., Nitescu, A., Gully, R., Suckow, R.F., Cooper, T.B., Gorman, J.M., Klein, D.F., Liebowitz, M.R., 1992a. Serotonergic function in obsessive-compulsive disorder. Behavioral and neuroendocrine responses to oral m-chlorophenylpiperazine and fenfluramine in patients and healthy volunteers. Archives of General Psychiatry 49, 21–28.

Hollander, E., DeCaria, C., Nitescu, A., 1992b. Effects of chronic fluoxetine treatment on behavioral and neuroendocrine responses to m-CPP in obsessive-compulsive disorder. Psychiatry Research 36, 1–17.

Hollander, E., Fay, M., Cohen, B., Campeas, R., Gorman,

J.M., Liebowitz, M.R., 1988. Serotonergic and noradrenergic sensitivity in obsessive-compulsive disorder: behavioral findings. American Journal of Psychiatry 145, 1015–1017.

Insel, T.R., Murphy, D.L., Cohen, R.C., Altermann, I., Kilts, C., Linnoila, M., 1983. OCD: a double-blind trial of clomipramine and clorgyline. Archives of General Psychiatry 40, 605–612.

Jenike, M.A., Baer, L., Minichiello, W.E., Rauch, S.L., Buttolph, M.L., 1997. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. American Journal of Psychiatry 154, 1261–1264.

Kahn, R.S., Wetzler, S., 1991. m-Chlorophenylpiperazine as a probe of serotonergic function. Biological Psychiatry 30, 1139–1166.

Kennett, G.A., Blackburn, T.P., 1990. Anxiolytic-like actions of BRL 46470 — a novel 5-HT3 antagonist. Journal of Psychopharmacology 94, 8–13.

Kennett, G.A., Whitton, P., Shah, K., Curzon, G., 1989. Anxiogenic-like effects of mCPP and TFMPP in animal models are opposed by 5-HT1C receptor antagonists. European Journal of Pharmacology 164, 445–454.

Kilpatrick, G.J., Jones, B.J., Tyers, M.B., 1987. Identification and distribution of 5-HT3 receptors in rat brain using radioligand binding. Nature 330, 746–748.

Martin, K.F., Hannon, S., Phillips, I., Heal, D.J., 1992. Opposing roles for 5-HT1B and 5-HT3 receptors in the control of 5-HT release in rat hippocampus in vivo. British Journal of Pharmacology 106, 139–142.

Murphy, D.L., 1990. Neuropsychiatric disorders and the multiple human brain serotonin receptor subtypes and subsystems. Neuropsychopharmacology 3, 457–471.

Murphy, D.L., Greenberg, B., Altemus, M., Benjamin, J., Grady, T., Pigott, T., 1996. The neuropharmacology and neurobiology of obsessive-compulsive disorder. In: Westenberg, H.G.M. (Ed.), Advances in the Neurobiology of Anxiety Disorders. John Wiley Ltd., New York, pp. 279–297.

Murphy, D.L., Mueller, E.A., Hill, J.L., Tolliver, T.J., Jacobsen, F.M., 1989. Comparative anxiogenic, neuroendocrine, and other physiologic effects of m-chlorophenylpiperazine given intravenously or orally to healthy volunteers. Psychopharmacology (Berlin) 98, 275–282.

Neijt, H.C., Karpf, A., Schoeffter, P., Engel, G., Hoyer, D., 1988. Characterisation of 5-HT3 recognition sites in membranes of NG 108-15 neuroblastoma-glioma cells with [^{3}H]ICS 205-930. Naunyn Schmiedebergs Archives of Pharmacology 337, 493–499.

Pato, M.T., Zohar-Kadouch, R., Zohar, J., Murphy, D.L., 1991. Return of symptoms after discontinuation of clomipramine in patients with obsessive-compulsive disorder. American Journal of Psychiatry 145, 1521–1525.

Pigott, T.A., Hill, J.L., Grady, T.A., L'Heureux, F., Bernstein, S., Rubenstein, C.S., Murphy, D.L., 1993. A comparison of the behavioral effects of oral versus intravenous mCPP administration in OCD patients and the effect of metergoline prior to i.v. mCPP. Biological Psychiatry 33, 3–14.

Pigott, T.A., Pato, M.T., Bernstein, S.E., Grover, G.N., Hill, J.L., Tolliver, T.J., Murphy, D.L., 1990. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Behavioral and biological results [see comments]. Archives of General Psychiatry 47, 926–932.

Pigott, T.A., Zohar, J., Hill, J.L., Bernstein, S.E., Grover, G.N., Zohar Kadouch, R.C., Murphy, D.L., 1991. Metergoline blocks the behavioral and neuroendocrine effects of orally administered m-chlorophenylpiperazine in patients with obsessive-compulsive disorder. Biological Psychiatry 29, 418–426.

Seibyl, J.P., Krystal, J.H., Price, L.H., 1991. Effects of ritanserin on the behavioral, neuroendocrine and cardiovascular responses to m-CPP in human healthy subjects. Psychiatry Research 38, 227–236.

Silverstone, P.H., Cowen, P.J., 1994. The 5-HT3 antagonist BRL 46470 does not attenuate m-CPP-induced changes in human volunteers. Biological Psychiatry 36, 309–316.

Thorén, P., Åsberg, M., Cronholm, B., 1980. Clomipramine treatment of obsessive-compulsive disorder. Archives of General Psychiatry 37, 1281–1285.

Watling, K.J., Aspley, S., Swain, C.J., Saunders, J., 1988. [^{3}H]quaternised ICS 205-930 labels 5-HT3 receptor binding sites in rat brain. European Journal of Pharmacology 149, 397–398.

Zohar, J., Insel, T.R., Zohar Kadouch, R.C., Hill, J.L., Murphy, D.L., 1988. Serotonergic responsivity in obsessive-compulsive disorder. Effects of chronic clomipramine treatment. Archives of General Psychiatry 45, 167–172.

Zohar, J., Judge, R., 1996. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. OCD paroxetine study investigators. British Journal of Psychiatry 169, 468–474.

Zohar, J., Mueller, E.A., Insel, T.R., Zohar Kadouch, R.C., Murphy, D.L., 1987. Serotonergic responsivity in obsessive-compulsive disorder. Comparison of patients and healthy controls. Archives of General Psychiatry 44, 946–951.