Chapter 4
Sumatriptan (5-HT$_{1D}$ Receptor Agonist) does not Exacerbate Symptoms in Obsessive-compulsive Disorder

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Abstract

The non-selective serotonin (5-HT) receptor agonist meta-chlorophenylpiperazine (mCPP) has been reported to elicit symptoms in patients with obsessive-compulsive disorder (OCD). MK-212, another non-selective 5-HT receptor agonist, does not seem to induce obsessive-compulsive symptoms in OCD patients. The major pharmacological difference between mCPP and MK-212 is their affinity for the 5-HT_{1D} receptor. The aim of this study was to explore the role of the 5-HT_{1D} receptor in the pathophysiology of OCD, by using a challenge paradigm with the selective 5-HT_{1D} receptor agonist sumatriptan (Imigran®). A randomized, double-blind, placebo-controlled cross-over challenge with sumatriptan (100 mg p.o.) was performed in 15 OCD patients. Neither the obsessive-compulsive symptoms nor mood or anxiety symptoms changed significantly following sumatriptan administration as compared to placebo. Sumatriptan did induce a significant increase in plasma growth hormone (GH) levels. In the present study, no indication was found for the role of the 5-HT_{1D} receptor in the pathophysiology of OCD. It should be noted, however, that sumatriptan does not readily pass the blood-brain barrier. Selective 5-HT_{1D} receptors with better brain penetrating properties may shed more light on the role of this 5-HT receptor subtype in OCD.
Introduction

Symptom provocation through a pharmacological challenge with serotonin (5-HT) receptor agents is a commonly used means to characterize serotonergic function in obsessive-compulsive disorder (OCD). The 5-HT receptor agonist meta-chlorophenylpiperazine (mCPP) has been extensively used for this purpose. Some investigators have found mCPP to induce obsessive-compulsive symptoms\(^1\)-\(^4\), hinting at a possible role for 5-HT in OCD, but others could not replicate these findings\(^3\),\(^5\)-\(^7\).

mCPP is a non-selective 5-HT receptor agonist with high affinity for the 5-HT\(_{2C}\) receptor, but it also binds to 5-HT\(_{1A}\), 5-HT\(_{1D}\), 5-HT\(_1\) and α\(_2\)-adrenergic receptors. To dissect the mechanism of action underlying the OCD symptoms inducing properties of mCPP, studies with more selective agents are warranted. Several agents have already been tested, including ipsapirone and buspirone (5-HT\(_{1A}\) receptor agonists)\(^8\)-\(^10\), ondansetron (5-HT\(_3\) antagonist)\(^11\) and MK-212 (5-HT\(_{1A}\), 5-HT\(_{1B}\) and 5-HT\(_{2C}\) receptor agonist)\(^12\). All were found to be ineffective in inducing obsessive-compulsive symptoms. The major difference between MK-212 and mCPP is the affinity for the 5-HT\(_{1D}\) receptor of the latter compound. The data may suggest, therefore, that the effects of mCPP on obsessive-compulsive symptoms could be due to its affinity for the 5-HT\(_{1D}\) receptor subtype, although other mechanisms cannot be excluded as yet.

A high density of the 5-HT\(_{1D}\) receptor is found in the basal ganglia and frontal cortex\(^13\). These brain areas have also been reported to be involved in the pathophysiology of OCD\(^14\). It is therefore of interest to investigate the role of the 5-HT\(_{1D}\) receptor in OCD. Sumatriptan (Imigran\(^\text{\textregistered}\)) is a selective 5-HT\(_{1D}\) receptor agonist, clinically used for the treatment of migraine. Preliminary results of a challenge study with sumatriptan in OCD have revealed an exacerbation of obsessive-compulsive symptoms\(^15\). In order to assess the role of the 5-HT\(_{1D}\) receptor in OCD, behavioral effects were investigated during a placebo-controlled challenge with sumatriptan. Neuroendocrine effects were determined as a measure of central cerebral activity of sumatriptan.

Patients and Methods

Patients

Patients aged 18-60 years, referred to the outpatient clinic of the University Hospital Utrecht and suffering from OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)\(^16\) were recruited for this study. Patients with concomitant
anxiety disorders, major depressive disorder, a score of more than 15 on the 17-item Hamilton depression scale\textsuperscript{17} and alcohol or drug abuse were excluded. Patients suffering from migraine or those who had previously used sumatriptan were also excluded. Subjects were in good physical health as determined by physical examination, routine laboratory tests and an electrocardiogram. Female patients who were pregnant, lactating women and women not using reliable methods of contraception were excluded.

Table 1. Patient Characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Duration symptoms (yrs)</th>
<th>YBOCS total score</th>
<th>YBOCS obsessions</th>
<th>YBOCS compulsions</th>
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<td>3</td>
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mean ± SD 39.4 ± 11.4 17.6 ± 9.7 27.3 ± 4.9 13.5 ± 2.9 13.8 ± 2.5

F = female, M = male, YBOCS = Yale-Brown Obsessive-compulsive Scale

The clinical characteristics of patients are summarized in Table 1. Fifteen patients (12 women, three men) were included in this study. Four patients were drug-naïve. The washout period for patients using antidepressants other than fluoxetine was at
least 2 weeks. The washout period was 8 weeks for one patient who had been taking fluoxetine. Mean ± SD length and weight were 170.9 ± 8.2 cm and 68.2 ± 11.5 kg, respectively. All patients had OCD symptoms of at least moderate severity as determined by the Yale-Brown Obsessive-Compulsive scale (YBOCS) score at entry (mean ± SD score 27 ± 5; maximal score 40)\(^{18,19}\). Patients suffered most from checking and washing compulsions accompanied by counting, but also ordering compulsions and rituals were present. Less often, excessive listmaking, need to touch and tell and hoarding compulsions were reported. The mean ± SD score on the Hamilton Anxiety Rating Scale\(^{20}\) was 9.8 ± 5.0 and the score on the Hamilton Depression Rating Scale was 7.5 ± 4.0. The study was approved by the Ethics Committee of the University Hospital Utrecht. Written informed consent was obtained from all patients.

**Methods**

Patients were subjected to a challenge procedure with sumatriptan 100 mg p.o. or placebo on two separate occasions, 1 week apart. The study was conducted according to a randomized, placebo-controlled, double-blind and cross-over design. Patients fasted for 12 hours before the procedure. They were asked to refrain from extensive use of alcohol, coffee and chocolate during the study period. Patients remained in a semi-recumbent position for the duration of the challenge and were not allowed to sleep or eat.

On arrival at 8.45 AM an indwelling IV catheter was inserted in an antecubital vein and kept patent with 1 ml heparin 100 units, following each blood-sample drawing. After 30 min. of adaptation, subjects received a capsule with sumatriptan or placebo (t = 0 min). Blood pressure and pulse rate were measured at baseline (t = 0) and at 30 min intervals for the remainder of the test, with the last measurement at 240 min. Blood samples for sumatriptan and growth hormone (GH) plasma level determination were drawn at the same time points. Sumatriptan was analyzed using high performance liquid chromatography\(^{21}\). GH was assayed using a commercially available radio-immunnoassay (RIA) kit (Oris Industry Company Gif-sur Yvette, France), which had a lower limit of detection of 0.5 mU/L. The intra- and inter-assay coefficients of variation for the GH determination were 8 and 11 %, respectively.

Behavioral measurements were completed every 60 min from baseline by means of two psychometric scales; the Dutch translation of the Profile of Mood Scale (POMS)\(^{22}\), a 21-item self-rating scale from which six subscales (anxiety, depression, vigor, somatic symptoms, hostility and fatigue) can be derived and the Yale-Brown Obsessive-compulsive challenge scale (YBOCCS)\(^{23}\), an abbreviated and modified version of the
YBOCS developed for challenge studies. The YBOCCS is a ten item analog patient-rating scale with a maximal score of 100. The YBOCCS was administered twice at each time point. Firstly, the YBOCCS was administered to assess the “actual” obsessive-compulsive symptoms experienced during the test. This is the primary measure for this study. Because OCD patients are frequently bothered by their symptoms in specific situations only (e.g. performing household tasks, driving the car, working at the office), it was also attempted to mimic these situations by asking patients to picture themselves in these situations. The specific aversive situation was “talked through” for 5 minutes with the patients, until they could clearly imagine themselves in that situation. Subsequently, the YBOCCS was administered again, asking the patients to take the imaginary situations into account while rating their symptoms. At all time points, the “actual” and “imagining” YBOCCS scores were assessed in this fixed order.

**Statistical analysis**

Statistical analyses were performed by means of the Statistical Package for the Social Sciences (SPSS for WINDOWS software, Chicago, 1999). Baseline differences for behavioral, physiological and GH measurements were analyzed with paired Student’s t-tests. The YBOCCS was analyzed in three statistical ways. The “actual” and “imagining” YBOCCS scores were analyzed using multivariate analysis of variance with repeated measures. Secondly, change scores during sumatriptan and placebo were calculated by subtracting the baseline score from the maximal score reached during the challenge. Differences in change scores for “actual” and “imagining” YBOCCS scores were analyzed using paired Student’s t-tests. And finally, a $2 \times 2 \chi^2$ analysis was used for determination of responders and non-responders in both groups. Patients were defined as responders when the YBOCCS showed an increase of $\geq 20\%$ calculated from the baseline measurement for each patient. Physiological measurements, GH measurements and the subscales of the POMS were analyzed using multivariate analysis of variance with repeated measures.

All results were reported as significant when $p < 0.05$ with two-tailed test. Huyn-Feldt adjustment for data that depart from the sphericity assumption was used for the analysis of variance.
Results

Biochemical and neuroendocrine effects of sumatriptan

The mean peak sumatriptan plasma level was 69.9 ng/ml (range 31-123 ng/ml). The peak level was reached at 60 minutes after administration of sumatriptan. From 60 minutes sumatriptan plasma levels gradually declined (Figure 1).

For the statistical analysis of the GH data, two patients with high baseline GH levels (more than 2 SD deviating from baseline) were excluded. Thus, GH data were evaluated for the remaining 13 patients. The baseline GH levels were not different on both test days; the mean ± SD baseline levels on the sumatriptan and placebo test day were 5.7 ± 6.8 mU/l and 4.3 ± 4.6 mU/l, respectively. Administration of sumatriptan caused a significant rise in plasma GH levels as compared to placebo (Figure 2). Multivariate analysis of variance with repeated measures on time revealed a significant drug by time interaction ($F = 4.35$, df = 2.31, $p = 0.019$).
Behavioral effects

The challenge procedure was well tolerated by all patients. Sumatriptan did not cause a significant change in obsessive-compulsive symptoms, mood or anxiety, as measured by the YBOCCS and POMS. Sumatriptan did cause a significant increase in somatic symptoms and fatigue, as measured by the POMS.

The obsessive-compulsive symptoms at baseline as assessed with the YBOCCS, referred to as the “actual YBOCCS”, were (mean ± SD) 8.3 ± 7.9 for sumatriptan and 9.7 ± 8.2 for placebo. The baseline values on the two tests were not statistically different. Multivariate analysis of variance with repeated measures on time did not show significant effects for the actual YBOCCS. The mean YBOCCS change from baseline (Table 2) after sumatriptan and placebo was not significantly different. Twelve patients on sumatriptan and nine patients on placebo could be classified as responders to the test as assessed with the YBOCCS. The response rate among the treatment conditions was not significantly different.
When the YBOCCS was administered after asking the patients to imagine an aversive situation, referred to as the “imagining YBOCCS”, substantial higher baseline values were obtained as compared to “actual YBOCCS”. The mean ± SD baseline values for the two conditions were not statistically different (sumatriptan $23.6 \pm 6.1$; placebo $23.1 \pm 7.4$). Multivariate analysis of variance with repeated measures on time did not show any significant effect. Using this procedure, one patient responded on sumatriptan and three on placebo challenge. The response rate between the challenge conditions was not significantly different.

Mean baseline scores for the six subscales of the POMS (Table 2) revealed no significant differences between sumatriptan and placebo. Multivariate analysis of variance with repeated measures on time revealed significant drug by time interactions for the subscales “somatic symptoms” ($F = 3.57$, df = 2.82, $p = 0.024$) and “fatigue” ($F = 3.28$, df = 2.24, $p = 0.046$). All other subscales were not different for the two conditions.

### Table 2. Mean (± SD) maximum change in symptoms from baseline.

<table>
<thead>
<tr>
<th></th>
<th>Sumatriptan</th>
<th>Placebo</th>
<th>p-value</th>
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<tr>
<td><strong>YBOCCS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>actual</td>
<td>4.0 ± 4.2</td>
<td>3.3 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>imagining</td>
<td>1.4 ± 1.9</td>
<td>1.6 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td><strong>POMS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anxiety</td>
<td>1.3 ± 2.3</td>
<td>0.5 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>depression</td>
<td>0.7 ± 1.1</td>
<td>0.3 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>hostility</td>
<td>0.4 ± 1.1</td>
<td>0.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>vigour</td>
<td>0.5 ± 1.1</td>
<td>0.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>fatigue</td>
<td>1.1 ± 1.3</td>
<td>0.6 ± 0.9</td>
<td>0.046</td>
</tr>
<tr>
<td>somatic symptoms</td>
<td>1.2 ± 1.9</td>
<td>0.7 ± 1.2</td>
<td>0.024</td>
</tr>
</tbody>
</table>

YBOCS = Yale Brown Obsessive-compulsive Scale, POMS = Profile of Mood Scale, NS = not significant

### Physiological effects

There were no significant differences at baseline for pulse rate, systolic and diastolic blood pressure during the sumatriptan and placebo challenge. Multivariate analysis of variance with repeated measures on time showed no significant effect for any of these physiological parameters.
Discussion

The major finding of this challenge study is that administration of the 5-HT1D receptor agonist sumatriptan did not induce an exacerbation of obsessive-compulsive symptoms in OCD patients. Moreover, sumatriptan did not alter mood or anxiety symptoms in these patients. Thus, the present data do not hint at a role for 5-HT1D receptor in the pathophysiology of OCD. The data of the present study are at variance with a preliminary report of Zohar, who described an exacerbation of obsessive-compulsive symptoms in OCD patients challenged with sumatriptan.

In the present study, oral administration of sumatriptan caused a marked rise in the plasma drug levels, reaching a peak value at 60 minutes after administration. This finding is in keeping with data reported previously and concurs with the observed side effects as assessed with the POMS. Similar side effects have been reported by others.

The significant rise in plasma GH levels reported in this study is also in accordance with early reports. Although the GH data do suggest a central effect, the extent to which sumatriptan reaches brain regions thought to be implicated in the pathophysiology of OCD remains questionable, as sumatriptan does not seem readily to cross the blood-brain barrier. There is anecdotal evidence for sumatriptan inducing psychiatric symptoms. In a small trial (n = 8), patients treated with sumatriptan for migraine attacks reported symptoms resembling those of panic disorder patients. In another report, an acute onset of depressive symptoms was described after treatment with sumatriptan for migraine, in a patient with a history of recurrent depression. It has been postulated that, despite its poor penetration of the blood-brain barrier, sumatriptan might exert central cerebral effects in areas not shielded by the blood-brain barrier, such as the area postrema, choroid plexus, dorsal root ganglia or hypophysal circulation or in subjects in whom the blood-brain barrier is less efficient due to the disease process. Selective 5-HT1D receptor agonists or antagonists with better penetrating properties for the blood-brain barrier are warranted, to further explore the role of the 5-HT1D receptors in the pathophysiology of OCD.

The rationale for the present study was primarily based on data reporting that mCPP exacerbated obsessive-compulsive symptoms, however, the literature is not unequivocal in this respect. Not all investigators reported mCPP to induce obsessive-compulsive symptoms in OCD patients. One explanation for these discrepant findings is that mCPP induces obsessive-compulsive symptoms in a subgroup of OCD patients only. The data published thus far do not allow firm conclusions to be drawn in this respect. Another possibility is that the effect of mCPP depends on the procedure.
and particularly on the environmental conditions during the test. Challenge procedures in OCD patients may be context-dependent; unforeseen symptom provoking triggers during the test, persistent effects of provocative events preceding the challenge, or the “reassuring” presence of the investigator or the environment (a hospital room) might influence the outcome. Patients frequently experience their symptoms when performing certain tasks or in certain situations. To mimic these situations experimentally, patients were asked to imagine a situation in which they usually suffer most from obsessive-compulsive symptoms. The YBOCCS administered during this imagination period, referred to as “imagining” YBOCCS, was an attempt to take these specific conditions into account. It should be emphasized, however, that the rating scale employed has not been validated using this procedure. The results show substantially higher baseline scores with this procedure, supporting the notion that the outcome may be context-dependent, but there was no effect of the outcome of the challenge. On the contrary, the change from baseline and the number of responders on placebo and sumatriptan were smaller as compared to the “actual” test, suggesting that test effects, if any, might have been overruled by symptoms elicited by the imagination procedure.

Patients included in this study represented a heterogenous sample with regard to the symptomatology, medication history and response to treatment. Therefore, it cannot be ruled out that sumatriptan may induce obsessive-compulsive symptoms in a subgroup of patients. Although it must be said that the present study is subject to the risk of type II error from the aforementioned sources, the behavioral effects of sumatriptan were too low and inconsistent to be useful as a challenge agent in studies with a sample size which is feasible in most centers.

In conclusion, the 5-HT₁D receptor agonist sumatriptan did not induce obsessive-compulsive symptoms during a placebo-controlled cross-over challenge paradigm in OCD patients. Sumatriptan did cause a significant rise in plasma GH levels, indicating that the dose was high enough to induce hypothalamic-pituitary effects. In view of the poor blood-brain barrier penetrating properties of sumatriptan, it cannot be ruled out that sumatriptan levels in brain regions thought to be implicated in the pathophysiology of OCD, have been too low to be effective. Selective 5-HT₁D receptor agonists with better penetrating properties for the blood-brain barrier are warranted to further our understanding with respect to the role of this receptor subtype in OCD.
References


3. Pigott TA, Hill JL, Grady TA, L’Heureux F, Bernstein SE, Rubenstein CS, Murphy DL. 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. Biol Psychiatry. 1993;33:3-14.


Chapter 4
