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The Behavioral Effect of m–Chlorophenylpiperazine (mCPP) and Methylphenidate in First-Episode Schizophrenia and Normal Controls

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Although there has been renewed interest in the serotonin (5-HT) system in schizophrenia, direct evidence for 5-HT dysfunction is limited. This study compares the responses of m-chlorophenyl-piperazine (mCPP), a 5-HT agonist, in first-episode schizophrenia and a known psychotogenic dopamine agonist, methylphenidate. Eighteen patients experiencing their first episode of psychosis and eight healthy controls received methylphenidate (0.5 mg/kg) and mCPP (0.1 mg/kg) intravenously. Behavioral assessments were done before and after the procedure, and a peak response to each agent was rated. Methylphenidate, but not mCPP, produced psychotic symptoms in patients. mCPP did decrease anxiety, hallucinations, and anger and increased agitation, somatic concern, and impaired understandability. Both agents had limited effects on controls. In conclusion, unlike methylphenidate, mCPP did not produce psychotic symptom activation in schizophrenic patients in, and its effects appeared to be nonspecific. **© 1997 American College of Neuropsychopharmacology [Neuropsychopharmacology 16:61–68, 1997]**

KEY WORDS: *Schizophrenia; Serotonin; Dopamine; First-episode schizophrenia; Pharmacology; Probes*

Next to dopamine (DA), serotonin (5-HT) has historically been the neurotransmitter most often implicated in schizophrenia (Lieberman and Koreen 1993). Renewed interest in the 5-HT system has been stimulated by the development of atypical antipsychotic drugs that, in addition to their DA antagonizing effects, have potent 5-HT blocking activity (Meltzer 1989). Compounds such as clozapine and risperidone have unique clinical properties that some have attributed to their combined effects on the DA and 5-HT systems (Meltzer 1989, 1991). However, direct evidence for 5-HT system dysfunction in schizophrenia is limited.

M-chlorophenylpiperazine (mCPP) is a 5-HT agonist and a metabolite of the antidepressant trazodone. Although mCPP binds to other neurotransmitter receptors (Hamik and Perutka 1989), the temperature, neuroendocrine, and behavioral response to mCPP appear to be mediated by 5-HT receptor stimulation (Kahn and Wetzler 1991; Owen et al. 1993). mCPP readily crosses the blood–brain barrier (Caccia et al. 1982; Rurak and Melzacka, 1983) and binds to 5-HT-$_{1D}$, 5-HT$_{1C}$, and 5-HT$_2$ receptors in humans (Hamik and Perutka 1989). Its greatest affinity is for the 5-HT$_{1C}$ receptor (Kahn and Wetzler 1991). Although it binds to a variety of serotonin receptors and can act as an agonist, antagonist and reuptake inhibitor and thus has limited utility as a probe of the serotonin system, it has been used to understand the role of serotenergic dysregulation in a variety of disorders, including depression (Kahn et al. 1988; 1990), ob-

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sessive-compulsive disorder (Zoher et al. 1987; Charney et al. 1988), alcoholism (Benkelfat 1991), Alzheimer's disease (Lowla et al. 1989, 1989b), and panic disorder (Charney et al. 1987; Kahn et al. 1988, 1990). It also has been one of the most extensively used probes of serotonin function. Although many of these studies, even those looking at homogeneous populations, have obtained conflicting results due most likely to differences in methodology (i.e., route of administration, dose, observation period), individual variability as well as a number of yet unidentified factors (Pigolt et al. 1993), there have been no reports of mCPP provoking psychotic symptoms in healthy subjects or in nonpsychotic psychiatric patients. Instead, various nonpsychotic behavioral symptoms have been reported, including anxiety, depression, euphoria, panic attacks, and altered self-reality, as well as a variety of somatic effects, including nausea, perspiration, piloerection, hot and cold flashes, lacrimation, faintness, weakness, tremors, vertigo, and parasthesias (Murphy et al. 1989).

Several studies of behavioral response to mCPP in schizophrenia have produced differing results. Krystal et al. (1991) and Iqbal et al. (1991) found that mCPP produced increases in psychotic symptoms in schizophrenia that in one study could be antagonized by ritanserin and clozapine (Krystal et al. 1991). In contrast, Kahn et al. (1992) and Szymanski et al. (in press) reported mild behavioral worsening characterized by increased anxiety and somatic symptoms that did not include increases in psychotic symptoms, and Owen et al. (1993) found a full range of behavioral effects but no statistically significant changes. Whether these disparate results are due to differences in methodology, in the interpretation of symptoms, or in samples is unclear. To attempt to clarify whether mCPP produces psychotogenic effects, this study completed the responses of mCPP in a relatively homogeneous population and of a known psychotogenic agent, methylphenidate. Methylphenidate is an indirect acting DA agonist that binds to the DA transporter and has been shown to provoke psychotic symptoms in 40 to 60% of patients with schizophrenia (Lieberman et al. 1987).

SUBJECTS

Subjects were drawn from a larger, ongoing prospective study of psychobiology in first-episode schizophrenia, the design and procedures of which have been previously described (Lieberman et al. 1993a, 1993b). In summary, the sample was drawn from patients admitted to the inpatient service of Hillside Hospital. Eligible patients met Research Diagnostic Criteria (Spitzel et al. 1977) for schizophrenia or schizoaffective disorder (mainly schizophrenic), were in the acute phase of their first episode of psychosis, and had no or had had no more than 12 weeks (lifetime) prior neuroleptic treatment. Subjects were between 14 and 40 years of age and had no neuromedical contraindications to antipsychotic drug treatment and no known history of neurological or endocrine disorder. All patients and their families were advised of the nature of the study and signed informed consent. Healthy volunteers were recruited from the community as control subjects. Those with significant neuromedical or psychiatric illness on a screening interview were excluded. Subjects underwent a standardized medical and psychiatric interview, laboratory examinations, and a physical exam. Only volunteers who were medically and psychiatrically healthy and who did not have a family history of psychiatric illness were included.

METHODS

Patients underwent two separate challenge procedures under single-blind conditions at least 48 hours apart, as previously described (Lieberman et al. 1993a; Szymanski et al. in press) with methylphenidate (methyl) and mCPP between 8:00 and 11:00 a.m. under standardized conditions (Jody et al. 1990). (The order of the infusions was fixed with patients receiving mCPP on the first day and methyl on the second day, but patients were blind to the order of infusions). These included a low monoamine diet for 16 hours prior to testing (since some of the biological measures we were looking at are affected by diet), an overnight fast, and a restriction of activity and smoking prior to testing. Prior to testing patients also had been free from psychotropic medication for at least 1 week. If they were on neuroleptic medication, this was discontinued at least 1 week prior the infusion. Chloral hydrate and/or sodium amytal was used during this time to control agitation.

For the procedure, an indwelling catheter was placed into an arm vein and connected to a slow-running heparinized saline infusion system with the patient in the supine position. After a 45-minute adaptation period, baseline behavior ratings were completed by a research psychiatrist who used selected items from the Schedule for Affective Disorder and Schizophrenia (SADS C+PD) (Endicott and Spitzer 1978), the scale for assessment of Negative Symptoms (SANS) (Andressen 1983), and the Clinical Global Impression Scale (CGI) (Guy 1976). Control subjects were similarly studied with the challenge procedures.

After the adaptation period methyl (0.5 mg/kg) or mCPP (0.1 mg/kg) was administered intravenously in the contralateral arm. The patient was interviewed and observed continuously for 90 minutes following the infusion. The patient's peak behavioral response was rated on the SADS C+PD, SANS, and CGI. Blood pressure, heart rate, temperature, and cardiac rhythm were monitored throughout the infusion procedure.

STATISTICS

Repeated-measures analysis of variance (ANOVA) was used to test for differences between schizophrenia and control subjects on change in symptoms pre- and post-infusion. These analyses were followed by paired *t*-tests that looked at change within patient and control groups.

RESULTS

Characteristics of Study Sample

Eighteen patients underwent an mCPP infusion, 14 of whom also underwent a methyl infusion. Ten patients (55%) were male, five (28%) were white, eight (44%) were black, two (11%) were hispanic, and 11 (61%) had completed at least some college. Fourteen (78%) of the patients met RDC criteria and four (22%) met RDC criteria for schizoaffective disorder, mainly schizophrenia subtype. Schizophrenia subtypes were determined to be paranoid for 11 patients (61%), disorganized for 1 (6%) and undifferentiated for 2 (11%).

The healthy controls consisted of three males and five males, of whom seven (88%) were white and one (12%) was Asian; all had completed at least some college. The mean age (SD) at study entry for the patients was 28.5 (6.8 ±) years and 26.1 (6.6 ±) years for the control group. The patients were less educated ($p = 0.02$), but otherwise there were no significant differences between patients and control.

At baseline, patients had significant psychopathology with a mean GAS ± standard deviation (SD) of 37.6 ± 8 and a mean CGI (± SD) of 4.9 ± 0.9. Delusions, in particular, were prominent with a mean (± SD) on the delusion item of the SADS of 4.4 ± 0.7. Hallucinations, impaired understandability, and anger also were present, and pa-

Table 1. Schizophrenics' and Controls' Response to mCPP (mean SD)

Symptom	Schizophrenia	Control	*p* Value[a]
Psychotic symptoms[b]			
Pre	2.4 (1.0)	1.0 (0.0)	
Post	2.5 (1.2)	1.0 (0.0)	0.49
GAS			
Pre	34.2 (6.1)	91.9 (2.6)	
Post	32.9 (9.6)	92.5 (2.7)	0.30
CGI Severity of illness			
Pre	5.1 (0.8)	1.0 (0.0)	
Post	5.3 (1.0)	1.0 (0.0)	0.46
CGI change score			
Post infusion	4.5 (0.9)	4.1 (0.4)	0.20
Depression			
Pre	2.4 (1.1)	1.3 (0.4)	
Post	2.3 (1.4)	1.2 (0.4)	0.88
Anxiety			
Pre	2.5 (1.1)	1.4 (0.2)	
Post	2.5 (1.6)	1.6 (0.7)	0.86
Bizarre behavior			
Pre	1.7 (1.5)	1.0 (0.0)	
Post	1.9 (1.8)	1.0 (0.0)	0.35
Impaired understandability			
Pre	1.9 (1.0)	1.0 (0.0)	
Post	2.2 (1.3)	1.0 (0.0)	0.30
Delusions			
Pre	4.6 (0.5)	1.0 (0.0)	
Post	4.6 (0.7)	1.0 (0.0)	1.00
Hallucinations			
Pre	2.4 (1.8)	1.0 (0.0)	
Post	2.0 (1.7)	1.0 (0.0)	0.50
Anger			
Pre	1.4 (0.8)	1.4 (0.5)	
Post	1.3 (0.6)	1.3 (0.5)	0.36
Agitation			
Pre	1.1 (0.3)	1.0 (0.0)	
Post	2.3 (2.0)	1.0 (0.0)	0.11

[a]Diagnosis–time interaction.
[b]Mean of critical psychotic items (severity of delusions, hallucinations, impaired understandability, and bizarre behavior) of the SADS.

tients experienced moderate levels of anxiety and depression.

Response to mCPP and Methylphenidate of Patients and Controls

The behavior responses of patient and control subjects to mCPP and methylphenidate administration are reflected on the rating scales described in Tables 1 and 2. mCPP caused little change in any of the symptoms for the control group and only an increase in agitation ($t = 2.54$; df = 17, $p = .02$) and a decrease in anger ($t = 1.93$, df = 16, $p = 0.07$) for patients. Repeated-measures ANOVAs revealed no significant differences between the schizophrenia or control groups responses to mCPP on any of the behavioral measures.

In patients methyl caused an increase in overall positive symptoms [severity of delusions, severity of hallucinations, impaired understandability and bizarre behavior ($t = 2.39$, df = 13, $p = .03$), anxiety ($t = 1.89$, df = 11, $p = .09$), agitation ($t = 2.50$, df = 12, $p = .03$), and delusions ($t = 2.80$, df = 11, $p = .02$)] and a decrease in anger ($t = 2.73$, df = 11, $p = .02$). Controls experienced no significant symptom response to methyl. Repeated-measures ANOVAs revealed significant differences between the schizophrenia and control groups in methyl response on several items. Schizophrenics had a greater increase in delusions ($F = 4.47$, df = 1.17, $p = .05$), global worsening (CGI change score, $t = 2.38$, df = 18, $p = .03$), and a greater decrease at the trend level in subjective anger ($F = 3.61$, df = 1.16, $p = .08$) than controls.

Analyses of cardiac data for the mCPP infusion

Table 2. Schizophrenics' and Controls' Response to Methyl (mean SD)

Symptom	Schizophrenia	Control	*p* Value[a]
Psychotic symptoms[b]			
Pre	2.3 (0.8)	1.0 (0.0)	
Post	2.9 (1.2)	1.1 (0.1)	0.14
GAS			
Pre	36.3 (6.9)	92.9 (3.9)	
Post	29.8 (11.0)	85.0 (11.5)	0.77
CGI Severity of illness			
Pre	4.9 (0.9)	1.0 (0.0)	
Post	5.4 (0.9)	1.4 (0.8)	0.82
CGI change score			
Post infusion	5.3 (1.3)	4.0 (0.8)	0.03
Depression			
Pre	2.3 (1.1)	1.1 (0.4)	
Post	2.3 (0.9)	1.1 (0.1)	0.95
Anxiety			
Pre	2.3 (1.2)	1.2 (0.4)	
Post	3.3 (1.4)	1.2 (0.4)	0.18
Bizarre behavior			
Pre	1.2 (0.6)	1.0 (0.0)	
Post	1.6 (1.5)	1.0 (0.0)	0.45
Impaired understandability			
Pre	1.9 (1.0)	1.0 (0.0)	
Post	2.6 (1.3)	1.3 (0.8)	0.47
Delusions			
Pre	4.4 (0.7)	1.0 (0.0)	
Post	4.8 (0.8)	1.0 (0.0)	0.05
Hallucinations			
Pre	2.3 (1.6)	1.0 (0.0)	
Post	2.7 (1.8)	1.0 (0.0)	0.68
Anger			
Pre	1.9 (1.2)	1.0 (0.0)	
Post	1.0 (0.0)	1.0 (0.0)	0.08
Agitation			
Pre	1.2 (0.4)	1.0 (0.0)	
Post	2.2 (1.5)	1.0 (0.0)	0.09

[a] *p* Value is for the interaction term that tests whether the change in symptoms with the methylphenidate infusion differed from the change in symptoms with the mCPP infusion; diagnosis–time interaction.

[b] Mean of critical psychotic items (severity of delusions, hallucinations, impaired understandability, and bizarre behavior) of the SADS.

Table 3. Schizophrenics' Response to Methyl vs. mCPP (mean SD)

Symptom	Methylphenidate	mCPP	*p* Value[a]
Psychotic symptoms[b]			
Pre	2.3 (0.8)	2.4 (1.0)	
Post	2.9 (1.2)	2.5 (1.2)	0.08
GAS			
Pre	36.3 (6.9)	34.2 (5.9)	
Post	29.8 (11.0)	32.9 (9.6)	0.06
CGI Severity of illness			
Pre	4.9 (0.9)	5.1 (0.8)	
Post	5.4 (0.9)	5.2 (1.0)	0.06
CGI change score			
Post infusion	4.9 (1.1)	4.5 (0.9)	1.00
Depression			
Pre	2.3 (1.1)	2.4 (1.1)	
Post	2.3 (0.9)	2.3 (1.4)	0.79
Anxiety			
Pre	2.3 (1.2)	2.5 (1.1)	
Post	3.3 (1.4)	2.5 (1.6)	0.12
Bizarre behavior			
Pre	1.2 (0.6)	1.7 (1.5)	
Post	1.6 (1.5)	1.9 (1.8)	0.43
Impaired understandability			
Pre	1.9 (1.0)	1.9 (1.0)	
Post	2.6 (1.3)	2.2 (1.3)	0.27
Hallucinations			
Pre	2.3 (1.6)	2.4 (1.8)	
Post	2.7 (1.8)	2.0 (1.6)	0.23
Delusions			
Pre	4.4 (0.7)	4.6 (0.5)	
Post	4.8 (0.8)	4.5 (0.7)	0.03
Anger			
Pre	1.9 (1.2)	1.4 (0.8)	
Post	1.0 (0.0)	1.3 (0.6)	0.04
Agitation			
Pre	1.2 (0.4)	1.1 (0.3)	
Post	2.2 (1.5)	2.3 (2.0)	0.84

[a] *p* Value is for the interaction term that tests whether the change in symptoms with the methylphenidate infusion differed from the change in symptoms with the mCPP infusion.

[b] Mean of critical psychotic items (severity of delusions, hallucinations, impaired understandability, and bizarre behavior) of the SADS.

showed a trend level difference in systolic blood pressure (BP) between patients and controls. The systolic BP in control patients increased by 4.0 mmHg points postinfusion and decreased by 1.3 mmHg (F = 3.30, df = 1.24, p = .08). No differences were observed for diastolic BP, pulse rate, or temperature, all of which increased slightly in both groups. Analyses of cardiac date for the methyl infusion indicated that the diastolic and systolic BP and heart rate increased significantly above baseline in both groups (all at the p = .0001 level) but revealed no differences between patients and controls.

Response of Patients to Methyl versus mCPP

Repeated-measures ANOVAs revealed a trend for a greater increase in the mean of all the positive symptoms (F = 3.52, df = 1,13, p = .08), GAS (F = 4.17, df = 1,13, p = 0.06), and global severity of illness (F = 4,45, df = 1,13, p = .06) in the patients' responses to methyl than to mCPP. Methyl also caused a significantly greater increase in delusions (F = 6.60, df = 1,11, p .03) and a decrease in anger (F = 5.21, df = 1,11, p = .04) than mCPP (Table 3).

DISCUSSION

This study compares the behavior responses of mCPP and methylphenidate in first-episode schizophrenic patients and normal control subjects to asses the potential role of serotonin in the pathophysiology of schizophrenia. In summary, methylphenidate, but not mCPP, produced psychotogenic effects in first-episode schizophrenic patients. mCPP decreased anger and increased agitation

in the patients. Both agents had a minimal effect on the psychopathological symptom items in normal subjects. Cross-tabulation of individual patients and controls on specific items revealed a heterogenous response to many items in both groups, but more so in schizophrenics. On many items the full range of responses from a worsening to an improvement in the symptom was seen.

Our results are consistent with the studies of Szymanski et al. (in press) and Kahn et al. (1992) that reported a nonspecific (change in nonpsychotic symptoms) behavioral change and the Owen et al. (1993) study that reported a full range of responses with no significant effects. These results differ from those of Krystal et al. (1993) who found increases in psychotic symptoms with mCPP. The discrepant results do not appear to be the result of differences in the patient sample (e.g., chronicity, diagnosis, or route of administration) as studies of chronic patients given IV mCPP (Krystal et al. 1991 versus Owens et al. studies) yielded different results. However, the rate of drug administration, and thus the rate of increase of mCPP in the central nervous system (CNS) may have been a factor as in the studies that showed an increase in psychosis mCPP was delivered more slowly (IV over 20 minutes or PO vs. IV over 90 s). This effect was also seen with panic attacks, where it was found that IV mCPP at a number of doses did not induce panic attacks when given over 90 s but did in 32% of normal subjects when given over 20 minutes. Protocols in which the speed of administration is fast may be stimulating different serotonergic and nonserotonergic receptors from those in which the mCPP was delivered more slowly or may produce a different pharmacodynamic effect at the same 5-HT-$_{2a}$ and 5-HT-^{2c} receptors by virtue of different concentration gradients of the exogenous stimulant. The relationship between 5-HT receptor subtypes, behavior effects of mCPP, and rate of rise of drug concentration in the CNS is unknown. Many of the mCCP effects, hormonal, behavioral, and physical, appear to be dose related, and the differences among studies may thus be related in part to this.

A priori we had hypothesized that mCPP would stimulate anxiety and somatic effects (e.g., flushing, headache) and that these nonpsychotic effects could lead to increases in psychotic symptoms. In our study, however, mCPP did not affect anxiety levels. Still, given the broad range of response, we did have a few patients who experienced increased anxiety. In fact, one of the few patients who did show a psychotic reaction initially had a panic attack and then became preoccupied with her physical symptoms, became frightened, and then had an increase in somatic and paranoid delusions. It is possible that the first-episode population is unique in this regard. However, this is unlikely as similar results were found in chronic multiepisode patients (Szymanski et al. in press).

Prior antipsychotic drug treatment as well as variable, and thus perhaps incomplete, washout periods could also have influenced previous results and certainly could affect not only the anxiety response but also the psychotic response. Szymanski et al (in press) found no difference between the mCPP responses of first-episode and chronic patients other than an increase in bizarre behavior in the chronic sample. However, it is difficult to compare studies that use chronic patients given the variability of response found.

Three limitations of this study should be mentioned. Behavioral ratings during the infusions were not blind, this study lacked a placebo control, and a fixed IV dose of mCCP was used. Still, this study was designed with an active control (methylphenidate) that in a previous placebo-controlled study (Lieberman et al. 1987) was shown to be significantly different from placebo. In fact, placebo response (defined as the development of mild but definitely present psychotic symptoms) was 0% in that study indicating a very low placebo response rate to methylphenidate. Thus, we are confident that any effect, in particular an increase of psychotic symptoms, can be attributed to the pharmacological effects of methylphenidate. Ideally, a double-blind placebo-controlled would have been preferred, but given the invasive nature of the procedure and the fact the patients were already undergoing two infusions, a placebo control was not included.

Because dose, route of administration, diagnoses, and perhaps the duration of administration could influence mCPP effects, these need to be standardized when comparing studies. From this study it can be reported that IV mCCP given over 90 s does not have a psychotogenic effect, but whether this would be true if a first-episode patient received IV mCPP over 20 minutes of PO mCCP is not known. The mCPP effect may be very variable, and even subtle differences individually as well as methodologically may result in the stimulation of different receptors or receptor subtypes. Patient response to mCPP, reflecting receptor sensitivity, may be indicative of the extent of serotonergic dysfunction. However, from these results the effect of mCCP appears to be nonspecific. Consequently, further studies with larger samples and standardized methods may be needed.

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