A Pilot Placebo-Controlled Study of Chronic *m*-CPP Administration in Alzheimer's Disease

Brian A. Lawlor, Trey Sunderland, Alan M. Mellow, Susan E. Molchan, Rick Martinez, and Dennis L. Murphy

Meta-Chlorophenylpiperazine (m-CPP), a serotonin agonist and metabolite of the antidepressant trazodone, was administered chronically to eight moderate to severely affected Alzheimer patients to determine whether it would produce improvement in behavioral symptoms complicating this illness. In doses up to 80 mg/day for 16 days, m-CPP was well tolerated and resulted in small but significant increases in anergy and depression-related symptoms compared with placebo. The effects of chronic m-CPP in this study contrast with the reported beneficial effects of the parent compound trazodone and selective 5-HT reuptake inhibitors in treating behavioral symptoms in Alzheimer patients.

Introduction

A number of recent studies have documented the existence of significant biochemical and neuroanatomic abnormalities in the serotonin (5-HT) system in Alzheimer's disease (AD) (Yamamoto and Hirano 1985; Bowen et al 1983; Cross et al 1984, 1986). The clinical correlates of 5-HT system dysfunction in AD is unknown, but altered 5-HT function may be implicated in the expression of behavioral and cognitive symptoms in this population.

We have been using the 5-HT receptor agonist, meta-chlorophenylpiperazine (*m*-CPP), a metabolite of the heterocyclic antidepressant trazodone, to examine the functional correlates of 5-HT abnormalities in AD. Although the pharmacological effects of *m*-CPP are varied and complex, *m*-CPP appears to act primarily as a 5-HT receptor agonist, with somewhat greater potency at the 5-HT_{1C} than at the 5-HT_{1A} and 5-HT_{1B} sites (Schoeffter and Hoyer 1989). Because of the failure to demonstrate the existence of the 5-HT_{1B} receptor in human brain (Heuring et al 1986; Hoyer et al 1986), *m*-CPP's effects in humans cannot be attributed to agonist activity at the 5-HT_{1B} receptor site.

In earlier studies, we established the safety of single-dose administration of *m*-CPP in an elderly neuropsychiatric population (Lawlor et al 1989a) and also found that AD patients showed increased behavioral responsivity to acute intravenous (IV) administration of this 5-HT agonist (Lawlor et al 1989b). Increased behavioral responsivity was not paralleled by any differences in neuroendocrine responsivity, suggesting that subpopu-

From the Division of Geriatric Psychiatry, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY (BAL), the Laboratory of Clinical Science, Bethesda, MD (TS, SEM, RM, DLM), and the Department of Psychiatry, University of Michigan, Ann Arbor, MI (AMM).
Address reprint requests to Dr. Brian Lawlor, Department of Psychiatry, Box 1230, Mount Sinai Hospital, One Gustave Levy Place, New York, NY 10029.
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lations of 5-HT receptors remained functionally unaffected by the disease process. We postulated that the 5-HT receptors mediating certain aspects of behavior may be hyperresponsive in AD, and that a possible therapeutic strategy could be to downregulate such a hyperresponsive receptor system by chronic treatment with an agonist or with a 5-HT reuptake inhibitor. Furthermore, therapeutic benefit was observed during chronic *m*-CPP administration in a small number of depressed patients (Mellow et al 1990).

In this study, *m*-CPP was administered on a chronic basis to AD patients in a pilot double-blind, crossover study to determine whether it might be behaviorally active and whether direct agonist administration might produce behavioral or other improvement in this population.

Methods

Eight patients meeting strict NINCDS–ADRDA criteria for "probable Alzheimer's disease" (McKhann et al 1984) were entered into the study. All subjects were inpatients during the course of the study and were medically healthy as determined by physical examination and normal blood chemistries prior to beginning the study. The mean age of the patients was 68.0 ± 2.5 years, with a mean duration of illness of 5.8 ± 0.8 years. All were moderately to severely affected, with ratings on the Global Deterioration Scale (GDS) (Reisberg et al 1982) and Clinical Dementia Rating Scale (CDR) (Hughes et al 1982) of 5.9 ± 0.1 and 2.4 ± 0.2, respectively. Although none of the patients met criteria for Major Depression on entry to the study, patients did have measurable levels of mild depression, as evidenced by baseline depression-related items from the 17-item Dementia Mood Assessment Scale (DMAS) (Sunderland et al 1988, 1989) of 32.2 ± 3.3.

Subjects received *m*-CPP or placebo in a double-blind, placebo-controlled, crossover fashion, randomized for order. Initial doses of *m*-CPP were 20 mg/day, and *m*-CPP was increased in 20-mg increments over the following 3–5 days to a maximum of 80 mg/day. Capsules were administered four times a day, at 9:00 AM, 1:00 PM, 6:00 PM, and 10:00 PM. The duration of the placebo and active drug administration in this preliminary study varied from patient to patient; the goal was to administer *m*-CPP for at least 2 weeks to each subject. At the completion of the drug treatment phase, the dose of *m*-CPP was halved and then discontinued completely the following day. There was no washout between active drug and placebo treatment phases.

Behavioral measures included weekly ratings carried out by trained raters blind to the treatment condition using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), modified Global Rating Scales (Bunney and Hamburg 1963), the DMAS, and nightly sleep checks documenting the number of hours of uninterrupted sleep. Patients also had blood drawn twice a week for routine hematology and biochemistries (including liver function tests). *m*-CPP blood levels (drawn at 7:30 AM prior to the morning dose) were measured in five of the eight subjects at the end of the chronic treatment phase.

Data Analysis

The group behavioral data were analyzed using paired *t*-tests comparing mean BPRS, Global Ratings, and DMAS ratings at the end of drug and placebo treatments. The sleep data were analyzed by repeated measures analysis of variance (ANOVA). All data are expressed as mean ± SEM, unless otherwise stated.

Table 1. Behavioral Ratings in Eight Alzheimer Patients Following *m*-CPP and Placebo[a]

Pt	Age	Sex	Drug	Treatment duration (days)	BPRS	DMAS-17	Global depression	Global sadness	Global anxiety	Global anger	Global psychosis	Global functional impairment	Global cognitive impairment
1	57	M	Placebo	17	43	21	2	6	4	1	3	10	9
			m-CPP	16	44	25	4	6	5	2	1	10	10
2	67	F	Placebo	17	79	38	3	6	4	9	5	14	13
			m-CPP	14	111	55	5	7	9	13	4	13	13
3	77	F	Placebo	16	42	22	3	4	6	4	1	15	14
			m-CPP	18	51	37	3	5	7	6	5	14	14
4	64	M	Placebo	11	64	24	3	6	6	4	1	9	10
			m-CPP	20	81	33	2	4	8	6	1	9	9
5	75	F	Placebo	6	67	33	4	8	4	1	1	13	12
			m-CPP	13	69	31	2	7	4	1	2	13	13
6	65	F	Placebo	12	98	46	7	9	9	9	7	14	14
			m-CPP	23	76	42	5	7	7	6	9	13	13
7	75	F	Placebo	8	67	49	4	5	10	7	3	10	10
			m-CPP	7	72	62	4	6	11	9	3	12	12
8	64	M	Placebo	11	56	28	5	6	5	4	1	11	12
			m-CPP	18	66	42	6	8	5	5	6	11	11

[a]BPRS, Brief Psychiatric Rating Scale; DMAS, Dementia Mood Assessment Scale. Global Ratings (Bunney–Hamburg) range from 0–15.

Results

m-CPP was tolerated by all subjects and no side effects related to drug treatment were reported or observed by the staff. There were no changes in blood indices during the course of the *m*-CPP trial that could be attributed to drug treatment. One female subject with x-ray evidence of osteoporosis at baseline (patient 7, Table 1) had elevations of alkaline phosphatase (with normal SGOT and SGPT) while on *m*-CPP, but this was attributed to microfractures of the pelvis, as diagnosed by bone scan.

The duration of active treatment for each individual patient is shown in Table 1. The mean daily dose of *m*-CPP was 55.3 ± 4.2 mg and the mean durations of *m*-CPP treatment and placebo were 16.13 ± 1.72 and 12.25 ± 1.46 days, respectively. The mean plasma *m*-CPP concentration (only available for five subjects) measured at the completion of the chronic treatment phase was 84.0 ± 42.0 ng/ml.

Behavioral Ratings

Individual scores on all behavioral scales for the eight patients following *m*-CPP and placebo are shown in Table 1. Five of eight patients showed increases in the DMAS and BPRS scores (indicating worsening in clinical status) following *m*-CPP compared with placebo. There were no consistent changes along the individual "Global" items, in particular across measures of "cognitive" or "functional impairment."

There was no difference between mean DMAS depression-related items at baseline (prior to drug or placebo treatments) and DMAS following placebo (32.2 ± 3.3 versus 32.6 ± 3.8), indicating that placebo treatment was not associated with any change in DMAS ratings. Following *m*-CPP, there were small but significant increases noted on the 17-item DMAS (32.6 ± 3.8 versus 40.9 ± 4.4; $p < 0.05$), and on the "vegetative"

factor of the DMAS (indicating decreased sleep, appetite, and energy) (1.0 ± 0.3 versus 1.9 ± 0.5; $p < 0.001$). Although there was no overall significant change on the total 24-item BPRS, there was a small but significant increase in the "anergia" factor (indicating increased emotional withdrawal, motor retardation, blunted affect, and disorientation) (3.1 ± 0.5 versus 3.5 ± 0.4; $p < 0.001$) following *m*-CPP compared with placebo.

Sleep Records

When mean nightly sleep records were compared, there was no overall difference between drug and placebo treatment conditions. However, consistent with the behavioral observation in a number of patients, comparison of the immediate *m*-CPP withdrawal phase with the chronic *m*-CPP treatment phase revealed significantly decreased sleep during the our nights following drug withdrawal compared with the chronic treatment phase.

Discussion

In this preliminary study, chronic *m*-CPP, in doses of up to 80 mg/day, was well tolerated and produced no significant changes in hematological or biochemical indices in a group of moderate to severely affected AD subjects. *m*-CPP treatment did result in significant, albeit small, increases in depression-related items and anergy, but produced no significant change in cognitive function in this small group of severely impaired patients. Interestingly, in the only other reported clinical trial with chronic dosing of this agent, we found improvement in depressed mood in a subgroup of depressed patients following chronic *m*-CPP treatment (Mellow et al 1990). One could postulate that the contrasting behavioral effects following *m*-CPP in these two populations could be explained by the serotonergic (and other) neuronal losses in AD. However, it should be noted that the behavioral changes observed in this study were modest, and were found with a small number of subjects. More definitive conclusions must await replication with larger patient numbers.

In conclusion, chronic 5-HT agonist treatment with *m*-CPP produced small but significant increases in depression and anergy ratings in this group of moderate to severely affected AD patients. No beneficial or deleterious effects on cognition were observed in this small group of patients. The overall negative behavioral results in this preliminary study contrast with the reported positive behavioral effects of 5-HT reuptake inhibition in dementia populations (Nyth et al 1988), and of the effects of the parent compound, trazodone, in agitated demented patients (Pinner and Rich 1988; Simpson and Foster 1986). Future studies are warranted to explore whether 5-HT-selective agents (agonists or antagonists) are helpful in the management of noncognitive and cognitive symptoms in AD.

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