Effects of Methylphenidate on Response to Oral Levodopa

A Double-blind Clinical Trial

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Objective: To determine if repeated dosing with methylphenidate hydrochloride (MPD) (Ritalin; Novartis Pharmaceuticals, East Hanover, NJ), an inhibitor of the dopamine transporter, would augment the effects of oral levodopa in patients with Parkinson disease.

Design: The study was a double-blind, randomized, placebo-controlled crossover trial.

Setting: The trial was conducted at the General Clinical Research Center (GCRC) as an inpatient study.

Subjects: Thirteen people with idiopathic Parkinson disease and a fluctuating motor response to levodopa were recruited from movement disorder clinics as a convenience sample. One subject was excluded because he did not have a 10% increase in tapping speed in response to levodopa. The remaining 12 subjects completed the protocol.

Interventions: A 0.4-mg/kg dose of MPD was administered orally at 8 AM, noon, and 4 PM in conjunction with the subjects’ normal oral antiparkinsonian medications. Oral levodopa dosage was decreased as clinically feasible during the first 4 days in the GCRC during open-label administration of MPD and hourly monitoring of parkinsonism and vital signs between 7 AM and 8 PM. Subjects were discharged taking their usual antiparkinsonian medications without MPD. They returned 1 and 2 weeks later to the GCRC for 1 day of hourly monitoring of their response to the medication regimen derived during the 4 days in the GCRC, once with MPD and once with identical-appearing placebo, in a randomized sequence and double-blind conditions.

Main Outcome Measures: The main outcome measure was the duration of “on” time between 9 AM and 8 PM measured by an increase in tapping speed by 10% over the average of the 7 AM to 8 AM predosing tapping speed measurements. Secondary measures were estimates of “on” time obtained with the timed walking task, tremor scores, and dyskinesia scores. In addition, averages of hourly tapping speeds, walking speed, tremor scores, dyskinesia scores, vital signs, and analog scale scores for mood, anxiety, and fatigue between 9 AM and 8 PM were examined. Adverse events on the double-blinded days were compared.

Results: Methylphenidate tended to increase the time “on” as measured by tapping ($P = .09$) but not by walking time or dyskinesia scores ($P = .40$ and .42, respectively). Methylphenidate tended to increase average tapping speed, decrease time to perform walking task, decrease tremor, and increase dyskinesia score but only the decrease in tremor reached significance. Neither the investigators nor the subjects could reliably identify active drug. Methylphenidate was well tolerated.

Conclusions: The effects of 0.4 mg/kg of MPD 3 times per day on the motor response to levodopa were small and variable and judged to be clinically insignificant.

Trial Registration: clinicaltrials.gov Identifier: NCT00359723

Arch Neurol. 2007;64:319-323

THE EFFECTS OF DOPAMINE IN the brain are terminated largely by reuptake into presynaptic dopamine terminals by the dopamine transporter.1 Although dopamine transporters are reduced by 30% or more in Parkinson disease (PD), imaging data indicate that 30% to 50% of transporters remain in moderately severe PD.2 In animals, reduction of dopamine transporters by treatment with the neurotoxin 6-hydroxydopamine leads to higher striatal extracellular concentrations of dopamine after administration of levodopa than produced in the striata of normal animals.3 Similarly, blocking the dopamine transporters with nomifensine in intact animals augments extracellular levels of dopamine after administering levodopa.4 However, in animals with 98% reduction in striatal dopamine induced by 6-hydroxy-
dopamine treatment, nomifensine does not increase extracellular dopamine concentrations induced by levodopa administration beyond the increases related to loss of terminals. A clinically relevant question is whether blockade of the estimated 30% to 50% of dopamine transporters remaining in severely PD would augment the effects of orally administered levodopa.

Methylphenidate hydrochloride (MPD) inhibits the dopamine transporter and dopamine reuptake without inducing dopamine release. At doses of 0.25 mg/kg in humans, MPD occupies half of the dopamine transporters. Methylphenidate doses of 0.5 mg/kg intravenously or 0.8 mg/kg orally have been shown by imaging techniques to raise dopamine concentrations in the brains of normal humans.

In a previous study, we found that a single oral dose of 0.4 mg/kg of MPD, administered to subjects with PD who were “off” after overnight without antiparkinsonian medications, had no motor or subjective effects. However, when this dose of MPD was administered with concomitant intravenous levodopa, the motor and subjective effects of levodopa were enhanced, particularly for levodopa infusion rates that were threshold for an antiparkinsonian response. Further, this dose of MPD was well tolerated.

The results from our study suggested that blockade of the dopamine transporter might be a clinically useful manner to augment the response to levodopa. As the next step to explore the utility of MPD in levodopa-treated people with PD, we have examined the response to 0.4 mg/kg of MPD administered 3 times per day in conjunction with the normal antiparkinsonian medication regimen in subjects with PD.

Figure 1. Flow of subjects through the protocol. GCRC indicates General Clinical Research Center; MPD, methylphenidate hydrochloride.

METHODS

SUBJECTS

Thirteen subjects with idiopathic PD by clinical criteria and a fluctuating motor response to levodopa enrolled in a protocol approved by the Oregon Health and Science University institutional review board and the General Clinical Research Center (GCRC) Scientific Advisory Committee. One subject failed screening; the other 12 completed the protocol. The 12 subjects included 4 women and 8 men, with a mean age of 65 years (range, 56-72 years), mean duration of PD of 14 years (range, 9-20 years), and mean duration of levodopa treatment of 12 years (range, 6-20 years). In addition to levodopa, 7 subjects were using entacapone, 10 were using a dopamine agonist, and 4 were using amantadine hydrochloride. Drug regimens were based on numerous titrations of drugs over the previous years and the subjects were considered to be optimally treated. Eight of the 12 subjects had tremor, but in only 3 was it scored greater than 1 on a scale of 0 to 4 for 7 body parts. All subjects had levodopa-induced dyskinesia. Based on our previous study, 12 subjects were calculated to give a power of 0.90 to detect a 10% increase in duration of response in a crossover study using a paired t test and an α of .05.

PROTOCOL

The flow of subjects through the protocol is illustrated in Figure 1. Subjects gave consent in the outpatient clinic and then were screened for inclusion criteria (idiopathic PD, responsive to levodopa, normal vital signs, and general medical history and examination) and exclusions (unstable medical problems, hypertension, cardiac arrhythmias, Mini-Mental State Examination score <24, or use of monoamine oxidase inhibitors). Tapping speed had to increase 10% in “on” state.

Subjects were admitted to the GCRC for 4 days of adjustment of levodopa dose with concomitant MPD (0.4 mg/kg) at 8 AM, noon, and 4 PM. The subjects’ usual schedules of antiparkinsonian medications were modified so that all subjects began their medications at 8 AM and all medications were administered on the hour so that hourly scoring of parkinsonism signs and subjective effects would capture end-of-dose clinical states. We assumed that concomitant MPD would allow reduction of levodopa dose so we attempted to decrease levodopa in all subjects. Further, in our previous study, MPD effects appeared to be more prominent on smaller levodopa doses and it was reasoned that the effects of MPD would be more apparent if levodopa doses were decreased. Daily doses of dopamine agonists and amantadine were unchanged. In 1 subject, entacapone dosage was decreased. At the end of the 4 days in the GCRC, the MPD administration was stopped and the subjects were returned to their levodopa dose schedules on entry to the GCRC and then were discharged.

The subjects returned to the GCRC for a full day of monitoring response to medications 1 and 2 weeks later. The 1-week interval between GCRC admissions for the double-blind phase of the study was to assure washout of MPD between admissions. Levodopa and other medications were administered according to the schedule derived from the first GCRC admission. Under double-blind conditions, 0.4 mg/kg of MPD was administered at 8 AM, noon, and 4 PM on 1 admission and identical appearing placebo on the other admission. The order of active drug and placebo was randomized by the statistician using a computer-generated schedule. Parkinsonism was scored with tapping speed, timed get-up-and-go task, dyskinesia scores, and tremor scores at 7 AM, 7:30 AM, and 8 AM and then hourly until 8 PM. Analog scales (0-115 mm) for depressed/happy, calm/happy, and fatigued/energized were scored by the subject each time parkinsonism was scored. Six milliliters of blood were collected each hour from 8 AM to 8 PM for assays of plasma concentrations of MPD and levodopa.

ANALYSIS

Monitoring response from 8 AM to 8 PM included 3 dose cycles of MPD and 3 to 6 dose cycles of levodopa. The 11 hours of monitoring thus included “on” and “off” times. Estimates of “on” time were calculated as the time that tapping scores exceeded baseline by 10%, the walking time decreased 20% from baseline, and dyskinesia was present. Secondary analysis of the data included the means of the hourly 9 AM to 8 PM measurements and the area

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under the time-action curve (AUC) from 9 AM to 8 PM using the average of the baseline scores (7 AM to 8 AM) from that day as zero. Statistical comparisons between the double-blind MPD and placebo days were made with paired t tests or with Wilcoxon signed rank tests if the normality test failed. Data in text and tables is presented as means and standard deviations.

### RESULTS

Thirteen subjects were recruited for the study; 1 subject failed screening. The other 12 subjects completed the protocol, although 1 subject had MPD dosing reduced to 0.4 mg/kg twice per day at 8 AM and 2 PM because of anxiety evoked by the MPD. Levodopa dose was decreased from 871 ± 482 mg/d (mean ± SD) at entry to the GCRC to 638 ± 323 mg/d while taking MPD (P = .005). The range of decreases of daily levodopa dose was 0 (2 subjects) to 750 mg/d.

### MOTOR EFFECTS

Methylphenidate tended to increase the time “on” as measured by tapping speed (P = .09) but the increase did not approach significance as measured by the walking task or presence of dyskinesia (Table 1).

Secondary methods of calculating the effects of MPD used average scores and AUCs for 9 AM to 8 PM. Methylphenidate nonsignificantly increased average tapping speed from 132 to 136 taps/min (mean ± SD difference, 4.1 ± 9.2 taps/min [95% confidence interval (CI), −1.8 to 10.0]; P = .15). The AUC for tapping, which adjusted for 7 AM to 8 AM baseline tapping speed, was increased 5.2 ± 6.6 taps/min (mean ± SD) with MPD (95% CI, 1.1 to 9.3) (P = .02). The average time to arise, walk 6 m, and return and sit for 9 AM to 8 PM was reduced from a median of 11.6 to 11.1 seconds with MPD (P = .11, Wilcoxon signed rank test). The average tremor score was decreased from a median of 0.25 to 0.08 with MPD (P = .02, Wilcoxon signed rank test). The mean dyskinesia score for 9 AM to 8 PM increased from 1.4 to 2.0 (mean ± SD difference, 0.6 ± 1.3 [95% CI, −0.2 to 1.4]; P = .11). Areas under the curve for walking time and tremor and dyskinesia scores yielded the same significance levels as did the averages.

### SUBJECTIVE EFFECTS

Methylphenidate had no significant effects on analog scale scores for subjective effects. Methylphenidate minimally raised average subjective mood scores from 59.4 to 60.7 (P = .35), increased anxiety scores from 38.7 to 40.6 (P = .48), and increased energy scores from 54.0 to 55.4 (P = .44). The same pattern was seen with the time-action AUCs for these measures.

On the double-blind days, 7 of 9 subjects identified placebo as placebo and 2 identified placebo as active drug. Six of 10 subjects identified active drug as placebo during the double-blind phase and 4 correctly identified the active drug.

### VITAL SIGNS

Average heart rate was higher with MPD (81.8 beats/min vs 76.4 beats/min with placebo [mean ± SD difference, 5.4 ± 6.2 (95% CI, 1.5 to 9.4); P = .01]). Average systolic blood pressure tended to be higher with MPD (124.4 mm Hg vs 120.3 mm Hg with placebo [mean ± SD difference, 4.12 ± 7.63 (95% CI, −0.7 to 9.0); P = .09]). Average diastolic blood pressure was unaffected. Compared with the 7 AM to 8 AM baseline, when subjects had been overnight without antiparkinsonian treatment, systolic and diastolic blood pressures were lower throughout the remainder of the day with placebo or MPD. In 1 subject, MPD appeared to augment orthostatic hypotension induced by levodopa.

### PHARMACOKINETICS

Plasma levodopa concentrations were measured in 8 subjects. Median plasma levodopa AUC was 40.7 nmol/mL with placebo and 42.5 nmol/mL with MPD (P = .74, Wilcoxon signed rank test). Methylphenidate hydrochloride administered at 0.4 mg/kg at 8 AM, noon, and 4 PM produced plasma concentrations within the therapeutic range reported for other conditions, as shown by the mean hourly MPD plasma concentrations between 8 AM and 8 PM in the 11 subjects receiving the drug 3 times per day (Figure 2). No MPD was detected on the placebo days.

Adverse events were more frequent on the MPD double-blind day than the placebo double-blind day but were generally mild and well tolerated (Table 2). During the open-label phase of the study, MPD-induced anxiety necessitated reducing the frequency of MPD dosing to twice per day in 1 subject.
suggests that reuptake of dopamine into remaining nerve terminals in PD is quantitatively unimportant or that this dose of MPD was not sufficiently efficacious.

What is the explanation for the difference between the results of this study and our previous study? In the previous study, the effects of MPD were most apparent with levodopa infused at a threshold rate, a rate at which approximately half the subjects had no antiparkinsonian response.9 At this threshold rate, a small increment in efficacy of levodopa induced by MPD might have a relatively large clinical effect. In the current study, oral doses were administered at suprathreshold doses, that is, doses that generally produced an antiparkinsonian action, despite our efforts to reduce levodopa doses in all subjects.

The reduction in daily levodopa dose by a mean±SD of 233±231 mg during the first GCRC admission with open-label MPD in our “optimally treated subjects” initially was interpreted as suggesting a beneficial effect of MPD. However, the small differences between MPD and placebo on the double-blind days indicated that the reduction in levodopa was probably not related to augmentation of levodopa effects by MPD. The reduction in levodopa may, however, explain the observation that the subjects were “on” less than half of the time between 9 AM and 8 PM. Finally, our data also show that concomitantly administered MPD did not alter plasma levels of levodopa so that a pharmacokinetic interaction is unlikely to explain any clinical effects of MPD in our study.

Although PD is associated with a decrease in dopamine transporters, a considerable concentration of the transporter remains in moderately advanced subjects.2–4,13,14 The 0.4-mg/kg dose of oral MPD administered was predicted to block greater than 50% of dopamine transporters.5 The plasma levels achieved with the 3 doses of 0.4 mg/kg of MPD at 4-hour intervals in our study produced plasma MPD concentrations that were in the range of clinically effective doses for attention-deficit/hyperactivity disorder.15,16

In humans, the clinical effects of MPD vary markedly. As reviewed by Volkow et al,17 there is evidence that the clinical effects of MPD may depend on more than just occupation of the dopamine transporter. Dopamine tone or spontaneous rate of dopamine release, behavioral context (which may influence dopamine release), age, and dopamine D2 receptor concentrations are likely critical as well. These variables are undoubtedly different in humans with PD, and conceivably, there are other differences in the dopamine transporters in PD.18 Indeed, unlike normal subjects,5 0.8 mg/kg of MPD failed to elicit dopamine release in subjects with PD, as judged by imaging studies.19

The failure to find clinically significant augmentation of levodopa effects with MPD is consistent with other small clinical trials that reported no benefit with blockade of the dopamine transporter.20 These trials do not exclude the possibility that higher doses of dopamine transporter inhibitors and more complete blockade of the transporters might be effective. Although controlled-release preparations of MPD might produce more sustained dopamine transporter blockade, the plasma concentrations during our study with immediate-release MPD produced levels that would be predicted from clinical ex-

Table 2. Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo</th>
<th>MPD</th>
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<tbody>
<tr>
<td>Anxiety/panic</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>More dyskinesia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
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Abbreviation: MPD, methylphenidate hydrochloride.

The pattern of MPD effects on our 4 measures of parkinsonism, although small, are consistent with an augmentation of levodopa effects by MPD. The results of this study confirm our earlier studies indicating that MPD augments the actions of levodopa.6,12 Given that the main pharmacological effect of MPD is blockade of the dopamine transporter, these results suggest that there are some remaining dopamine terminals that take up extracellular dopamine and that their blockade raises the extracellular dopamine concentrations derived from administered levodopa and thereby augments the antiparkinsonian effects of levodopa.

The magnitude of the augmentation of effects of orally administered levodopa by MPD in subjects with PD was, however, smaller and more variable than we predicted from our experience with MPD in conjunction with intravenously administered levodopa and the effects were judged to be clinically nonsignificant. This observation suggests that reuptake of dopamine into remaining nerve terminals.
perience with other disorders to have clinical effects throughout the 11 hours they were monitored.

Adverse events were generally mild and usually did not identify active drug during the double-blind phase of the study. Methylphenidate increased heart rate in our subjects but not blood pressure. It is important to recognize the potential for cardiovascular complications with MPD as emphasized by recent publicity about stimulants.21

In conclusion, this study of repeated MPD dosing with concomitant oral levodopa, designed to represent a more typical clinical setting, found minimal augmentation of levodopa effects that were considered to be clinically unimportant.

Accepted for Publication: September 29, 2006.

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Financial Disclosure: None reported.

Funding/Support: This work was supported by the North-west Parkinson’s Disease Research, Education and Clinical Center (PADRECC), National Institutes of Health grant RO1-NS21062, and Public Health Service grant 5 MO1-RR00334.

Acknowledgments: We thank Michele Barnard, BS, for coordinating the study, Lisa Bui, BA, for data management, William Woodward, PhD, for levodopa assays, Tom Cooper, BS, for methylphenidate assays, GCRC nurses for care of subjects, the Oregon Health and Science University research pharmacy for preparation of methylphenidate capsules and placebos, and Amy Sterenberg, BA, for preparation of the manuscript.

REFERENCES