Effect of Low Concentrations of Apomorphine on Parkinsonism in a Randomized, Placebo-Controlled, Crossover Study

Steven A. Gunzler, MD; Caroline Koudelka, MPH; Nichole E. Carlson, PhD; Misha Pavel, PhD; John G. Nutt, MD

Objective: To determine whether low concentrations of a dopamine agonist worsen parkinsonism, which would suggest that activation of presynaptic dopamine autoreceptors causes a super-off state.

Design: Randomized, double-blind, placebo-controlled, crossover clinical trial.

Setting: Academic movement disorders center.

Patients: Patients with Parkinson disease and motor fluctuations.

Intervention: Fourteen patients with Parkinson disease and motor fluctuations were randomized to receive 1 of 6 possible sequences of placebo, low-dose (subthreshold) apomorphine hydrochloride, and high-dose (threshold to suprathreshold) apomorphine hydrochloride infusions. Subthreshold doses of apomorphine hydrochloride (12.5 µg/kg/h every 2 hours and 25 µg/kg/h every 2 hours), threshold to suprathreshold doses of apomorphine hydrochloride (50 µg/kg/h every 2 hours and 100 µg/kg/h every 2 hours), and placebo were infused for 4 hours daily for 3 consecutive days.

Main Outcome Measures: Finger and foot tapping rates.

Results: There was no decline in finger or foot tapping rates during the low-dose apomorphine hydrochloride infusions relative to placebo. The high-dose infusions increased foot tapping (P < .001) and trended toward increasing finger tapping compared with placebo infusions.

Conclusions: Subthreshold concentrations of apomorphine did not worsen parkinsonism, suggesting that presynaptic dopamine autoreceptors are not important to the motor response in moderate to advanced Parkinson disease.

Trial Registration: clinicaltrials.gov Identifier: NCT00472355

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PATIENTS WITH PARKINSON DISEASE (PD) often have motor fluctuations, which are shifts between on states, in which patients have better motor function, and off states, in which they function poorly. Some fluctuating patients transiently decline below their baseline off motor function to what we will refer to as the super-off state.1-4 The super-off state can be divided into a beginning-of-dose inhibitory effect1,3 and an end-of-dose inhibitory effect,1,4 depending on whether it occurs before or after levodopa or apomorphine has reached a threshold (or therapeutic) plasma concentration. The super-off state is often very distressing, and patients may adjust their PD medications to avoid the super-off state as much as to achieve the on state.

Low doses of dopaminergic medications can suppress locomotor activity in rodents.5 This presumed presynaptic inhibition of dopaminergic neurotransmission, occurring at low plasma dopaminergic medication concentrations, is postulated to cause beginning-of-dose and end-of-dose inhibitory effects.6-10 To explore this possible mechanism for the super-off motor state, we examined the effects of subthreshold, threshold, and suprathreshold infusions of apomorphine hydrochloride (a D1/D2 dopamine agonist) in a randomized, double-blind, placebo-controlled, crossover study.

METHODS

Our protocol was approved by the institutional review board at Oregon Health & Science University (OHSU). All patients gave informed consent while in the on state. Apomorphine hydrochloride infusions were...
conducted with Investigational New Drug approval through one of the investigators.

PARTICIPANTS

Twenty-two patients with a clinical diagnosis of idiopathic PD were recruited from the Parkinson Center of Oregon clinics at OHSU between March 2006 and January 2007. Eligible patients were aged between 35 and 85 years and had PD for at least 3 years and at least 1 year of levodopa treatment. Patients had motor fluctuations and were required to exhibit a 10% or greater improvement in finger and foot tapping rates from the off state to the on state. Mini-Mental State Examination scores had to be 24 or higher.

Exclusion criteria were unstable cardiac or cerebrovascular disease, hypotension or hypertension, bradycardia, a prolonged QT interval, and treatment with a serotonin 3-receptor antagonist or vasodilating medication. Other exclusion criteria were drug abuse, psychosis, and any other medical or psychiatric illness that could pose a risk to the patient or to interpretation of the data.

DESIGN

Patients were screened in the OHSU outpatient clinics to determine whether they had measurable motor fluctuations and met no exclusion criteria; they were subsequently admitted for 3 days to the inpatient Oregon Clinical and Translational Research Institute (OCTRI). Blocks of 6 participants were randomized to the 6 possible sequences of placebo, low-dose apomorphine hydrochloride, and high-dose apomorphine hydrochloride infusions (Figure 1).

PROTOCOL

Participants were premedicated with 20 mg of domperidone 3 times daily for 3 days prior to admission and were treated in the OCTRI for the 3 days. The evening prior to the first infusion, participants were admitted to the OCTRI to practice the parkinsonism ratings 3 times. Parkinson disease medications, except anticholinergic drugs and monoamine oxidase type B inhibitors, were discontinued at 10 PM the night before each infusion and were resumed each day at about 3:30 PM. Each morning, plasma levodopa level ensured compliance with the protocol.

Parkinsonism was scored every 20 minutes for the first 6 participants. Because fatigue developed with this schedule, the remaining 8 participants were scored every 30 minutes. Measurements occurred for 1 hour before the infusions (baseline), for 4 hours during the infusions, and for 2 hours following the infusions before the participant started their regular antiparkinsonism medications. Anxiety, mood, and fatigue were self-reported by analog scales every 20 to 30 minutes. Continuous cardiac telemetry and vital signs were monitored. Two milliliters of plasma were drawn every 20 to 30 minutes via an indwelling catheter to determine apomorphine concentrations by high-pressure liquid chromatography.11

INFUSIONS

In our previous experience with intravenous apomorphine hydrochloride infusions, 50 µg/kg/h was therapeutic in all but 1 patient.12 We therefore used 50 µg/kg/h as a threshold dose and 100 µg/kg/h as a suprathreshold dose (high doses). The subthreshold doses were 12.5 and 25 µg/kg/h (low doses).

Placebo and apomorphine hydrochloride were administered by subcutaneous infusion for 4 hours each day (9 AM-1 PM) on 3 consecutive days. Treatments were (1) saline infused for 2 hours and then double the rate for 2 hours (placebo); (2) apomorphine hydrochloride infused at 12.5 µg/kg/h for 2 hours and then at 25 µg/kg/h for 2 hours; and (3) apomorphine hydrochloride infused at 50 µg/kg/h for 2 hours and then at 100 µg/kg/h for 2 hours.

OUTCOME MEASURES

Finger and foot tapping were used as primary outcome measures because they are objective, rapid, repeatable, and simple indices of bradykinesia. Finger tapping was measured as the number of times a participant tapped the index finger of his or her more affected hand back and forth between 2 counters 20 cm apart in 1 minute.4,13 As a new outcome measure, foot tapping with the more affected foot was measured between 2 pedals spaced 30 cm apart for 15 seconds. A tap was counted if
there was a 20% depression of the foot pedal. Trained nurses rated dyskinesia on a scale (0-4) for each of 6 body regions.13

DATA ANALYSIS

Our power analysis indicated that with 14 participants, we would be able to detect a difference of 7.1 taps in finger tapping per minute with 80% power and an alpha level of 0.025 (adjusting for 2 comparisons: high-dose apomorphine hydrochloride vs placebo and low-dose apomorphine hydrochloride vs placebo), assuming an SD of 5.55 taps for placebo and 8.91 taps for subthreshold days and a correlation of 0.50 between observations in the same participant. The 7.1-unit difference was approximately 60% of the maximal difference observed within the placebo period in our previous experience.4

Data were analyzed prior to unblinding of investigators. Measurements at 8 AM, 8:30 AM, and 9 AM the morning of the infusion served as baseline; these were averaged then subtracted from each subsequent 30-minute observation. For participants who were examined every 20 minutes, the average of the 20- and 40-minute observations served as the 30-minute data. Data were then divided into 3 time intervals for each study day: the first 2-hour infusion, the second 2-hour infusion, and the 2-hour postinfusion washout. Mean finger tapping, foot tapping, and dyskinesia scores were calculated for each time interval. Repeated-measures analysis of variance was used to assess time interval and treatment assignment differences. Pairwise comparisons were performed using linear contrasts. Given the sample size, adjustments for multiple comparisons were not performed, as we were interested in the pattern of differences rather than statistical significance. An additional subanalysis was performed stratifying by participants' prior reports of beginning-of-dose inhibitory effects.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Twenty-two participants were screened; 14 met inclusion criteria and were admitted to the OCTRI (Figure 1). Baseline characteristics of the 13 participants who completed at least 2 study days and were included in the statistical analysis are listed in Table 1. Mean age was 61 years. The average patient had PD for 16 years, 11 years of levodopa treatment with 9 years of motor fluctuations, and 7 years of dyskinesia. Four of the 13 participants reported a history of beginning-of-dose inhibitory effects when asked whether they sometimes experienced increased parkinsonism after taking levodopa, before its beneficial effects were noticeable. Beginning-of-dose inhibitory effects, by patient report, occurred 15 to 30 minutes after taking levodopa and lasted 10 to 45 minutes.

PHARMACOKINETICS

Mean apomorphine concentration curves for the first 3 infusions are shown in Figure 2. Apomorphine concentrations responded quickly to changes in infusion rate and appeared to plateau within 2 hours. Maximum plasma concentration was linearly related to infusion rate (3.68, 8.31, 19.42, and 39.16 ng/mL for the 12.5-, 25-, 50-, and 100-µg/kg/h infusions, respectively [R²=0.99]). Time to maximum plasma concentration was 80 minutes for the 12.5- and 50-µg/kg/h infusions and 120 minutes or longer for the 25- and 100-µg/kg/h infusions, suggesting that time to maximum plasma concentration may have been influenced by order of infusions.

Levodopa concentrations, drawn each morning, ranged from undetectable to 0.33 µg/mL (mean, 0.09 µg/mL). These levodopa concentrations are subthreshold in patients with motor fluctuations.15

RESPONSES TO INFUSIONS

Response of finger and foot tapping to subthreshold apomorphine hydrochloride infusions (12.5 and 25 µg/kg/h) did not differ from the response to placebo infusions (Figure 3 and Table 2). With data divided into 4 time intervals for statistical analysis (baseline, first 2 hours of infusion, last 2 hours of infusion, and wash-
out), threshold and suprathreshold apomorphine hydrochloride infusions increased foot tapping during the first 2 hours ($P = .007$) and the last 2 hours ($P < .001$) of infusion relative to placebo (Table 2). Threshold and suprathreshold apomorphine hydrochloride levels showed a trend toward increased finger tapping compared with placebo ($P = .15$).

The subgroup of 4 participants who reported beginning-of-dose inhibitory effects had increased finger tapping ($P = .03$, first 2 hours of infusion; $P = .009$, last 2 hours) and foot tapping ($P = .03$, first 2 hours; $P = .02$, last 2 hours) during high-dose apomorphine hydrochloride infusion relative to placebo. The remaining 9 participants only showed a difference in foot tapping during the last 2 hours.

Table 2. Finger and Foot Tapping Rates in Participants Receiving Apomorphine Hydrochloride vs Placebo Infusion

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (SE)</th>
<th>Mean (SE)</th>
<th>Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First 2 Hours of Infusion (9:30-11 AM)</td>
<td>Last 2 Hours of Infusion (11:30 AM-1 PM)</td>
<td>Washout Period (1:30-3 PM)</td>
</tr>
<tr>
<td>Low-dose apomorphine hydrochloride</td>
<td>137.60 (8.63)</td>
<td>133.89 (8.09)</td>
<td>129.31 (9.05)</td>
</tr>
<tr>
<td>High-dose apomorphine hydrochloride</td>
<td>144.62 (8.58)</td>
<td>142.72 (9.56)</td>
<td>129.97 (8.48)</td>
</tr>
<tr>
<td>Placebo</td>
<td>137.04 (7.67)</td>
<td>137.77 (8.37)</td>
<td>133.66 (7.89)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (SE)</th>
<th>Mean (SE)</th>
<th>Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finger Tapping Rate, Taps/min</td>
<td>Foot Tapping Rate, Taps/15 s</td>
<td></td>
</tr>
<tr>
<td>Low-dose apomorphine hydrochloride</td>
<td>33.35 (2.53)</td>
<td>33.14 (2.94)</td>
<td>31.08 (2.27)</td>
</tr>
<tr>
<td>High-dose apomorphine hydrochloride</td>
<td>37.05 (2.46)$^a$$^b$</td>
<td>39.08 (2.16)$^c$$^d$</td>
<td>33.50 (2.14)</td>
</tr>
<tr>
<td>Placebo</td>
<td>32.14 (2.94)</td>
<td>32.10 (2.88)</td>
<td>32.00 (2.52)</td>
</tr>
</tbody>
</table>

$^a$Baseline-adjusted value different from low-dose apomorphine, $P = .02$.

$^b$Baseline-adjusted value different from placebo, $P = .007$.

$^c$Baseline-adjusted value different from low-dose apomorphine, $P < .001$.

$^d$Baseline-adjusted value different from placebo, $P < .001$.
of high-dose apomorphine hydrochloride infusion \( (P = .002) \).

Dyskinesia, as measured by the research nurses, was low and sporadic, with a mean score below 0.20 (on a 0-24 scale) throughout the low-dose and placebo days. During the high-dose apomorphine hydrochloride infusion, mean dyskinesia score increased to higher than 1.00. Mean (SD) maximum dyskinesia scores were 0.54 (0.95) for the placebo day, 0.23 (0.60) for the low-dose day, and 4.54 (4.42) for the high-dose day. Analog scales of mood, anxiety, and fatigue were not affected by any of the treatments.

**ADVERSE EFFECTS**

Adverse effects were mild (Table 3). One participant left the study after 2 days (low-dose apomorphine hydrochloride and placebo) because of a persistent off state. Another participant completed only the high-dose infusion because of anxiety while in the off state during the washout period. Infusions were briefly stopped twice because of orthostatic hypotension, though mean blood pressure and pulse did not differ between treatment types.

**COMMENT**

Despite evidence in animals that low doses of dopaminergic medication can inhibit motor function, we found no evidence that subthreshold apomorphine hydrochloride worsened parkinsonism. This observation contrasts with some anecdotal reports of worsening parkinsonism with low-dose dopamine agonists. However, clinical trials of low-dose pergolide mesylate or apomorphine hydrochloride did not find evidence that subthreshold doses worsened parkinsonism or reduced the effects of levodopa. The lack of effect of subthreshold doses of apomorphine hydrochloride in our study may be because the presynaptic D2 autoreceptor is dysfunctional or absent in advanced PD.

There are several other reasons why subthreshold apomorphine hydrochloride infusions may not have worsened parkinsonism. One possibility is that the super-off state may be present only in certain subgroups of PD patients. One of our participants who had reported a history of beginning-of-dose inhibitory effects did have a pattern that might be consistent with beginning-of-dose inhibitory effect. Alternatively, there may be something different about giving a continuous subthreshold infusion of apomorphine hydrochloride rather than a suprathereshold bolus. As described in the methylphenidate literature, rapidity of drug administration can influence response to medication. A rapid bolus or threshold dose of apomorphine hydrochloride may be necessary to demonstrate beginning-of-dose and end-of-dose inhibitory effect. It is conceivable that the autoreceptor mechanism does not underlie the super-off state. End-of-dose inhibitory effect could instead be explained by a withdrawal or rebound phenomenon. However, this would not be a feasible explanation for beginning-of-dose inhibitory effect.

This was the first study to systematically explore the effects of subthreshold doses of dopaminergic medication in PD. Subthreshold apomorphine hydrochloride neither improved nor worsened parkinsonism in our participants with moderately severe PD. This suggests that a presynaptic or autoreceptor action of dopaminergic agents is not important in more advanced PD and is not an explanation for super-off states. It does not question the existence of super-off phenomena but instead deepens the mystery about their origin. An understanding of the etiology behind the super-off state may help us to better manage motor fluctuations and reduce the severity of off time in PD.

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**Author Affiliations:** Parkinson’s Disease Research, Education, and Clinical Center, Portland VA Medical Center, Portland, Oregon (Drs Gunzler and Nutt); and Parkinson Center of Oregon (Drs Gunzler and Nutt), Oregon Clinical and Translational Research Institute (Ms Koudelka), Division of Biostatistics, Department of Public Health & Preventive Medicine (Dr Carlson), and Department of Biomedical Engineering (Dr Pavel), Oregon Health & Sciences University, Portland. Dr Gunzler is now with the Movement Disorders Center, University Hospitals Case Medical Center and Case Western Reserve University School of Medicine, Cleveland, Ohio.

**Correspondence:** Steven Gunzler, MD, Movement Disorders Center, Neurological Institute, University Hospitals Case Medical Center and Case Western Reserve University School of Medicine, 11100 Euclid Ave, Cleveland, OH 44106 (steven.gunzler@uhhospitals.org).

**Author Contributions:** Drs Gunzler and Nutt had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gunzler, Carlson, and Nutt. Acquisition of data: Gunzler and Pavel. Analysis and interpretation of data: Gunzler, Koudelka, Carlson, and Nutt. Drafting of the manuscript: Gunzler, Carlson, and Nutt. Critical revision of the manuscript for important intellectual content: Koudelka, Carlson, Pavel.
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