Effect of Monoamine Reuptake Inhibitor NS 2330 in Advanced Parkinson's Disease†

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Abstract: **Dopamine reuptake blockers, by enhancing and stabilizing intrasynaptic transmitter levels, could help palliate motor dysfunction in Parkinson's disease. This randomized, double-blind, placebo-controlled study compared the acute effects of the monoamine uptake inhibitor NS 2330 to those of placebo in 9 relatively advanced parkinsonian patients. At the dose administered, no change in parkinsonian scores was found when NS 2330 was given alone or with levodopa. Moreover, NS 2330 coadministration did not appear to alter dyskinesia severity or the duration of the antiparkinsonian response to levodopa. The drug was well tolerated. Under the conditions of this study, the present results failed to support the usefulness of dopamine reuptake inhibition in the treatment of advanced Parkinson's disease.**

Key words: Parkinson's disease; dyskinesia; dopamine; levodopa; striatum; uptake; transporter; clinical trial

In Parkinson's disease (PD), a progressive loss of nigral dopaminergic neurons results in declining striatal dopamine (DA) concentrations and the appearance of core parkinsonian signs. Under normal conditions, a DA transporter (DAT) regulates intrasynaptic levels of the transmitter amine by actively pumping it back into presynaptic dopaminergic terminals.[1,2] Naturally occurring or drug-induced alterations in transporter function, thus, can profoundly affect dopaminergic transmission.[3] With DA neuron destruction and resultant loss of DAT activity in rats, striatal DA uptake diminishes.[4] Progressive failure of this mechanism contributes to the preservation of normal motor function in presymptomatic parkinsonian patients until most of the nigrostriatal system has degenerated.[5] In patients with early symptomatic PD, DA uptake blocker monotherapy thus might be expected to ameliorate motor dysfunction by increasing intrasynaptic monoamine levels. In experimental animals with severe neurotoxin-induced dopaminergic neuron loss or effective pharmacologic DAT blockade mimicking conditions in advanced PD, levodopa treatment produces far higher elevations in extracellular DA than normally occur.[4] For this reason, DAT inhibitors should act clinically to potentiate the antiparkinsonian action of L-dopa. Moreover, because a reduction in DA reuptake prolongs its striatal half-life,[6,7] motor fluctuations of the wearing-off type as well as dyskinesias and other adverse consequences of the intermittent stimulation of striatal DA receptors might diminish.[8] Recent studies in parkinsonian primates appear to support these possibilities.[9] In this proof-of-concept study, we examined the hypothesis that a potent new DAT inhibitor, given alone or in combination with L-dopa, will improve motor function in patients with moderately advanced PD.

PATIENTS AND METHODS

Study Population

A study in 16 parkinsonian patients was planned, but a decision to discontinue further accessions was made by the drug manufacturer, for nonclinical reasons, after interim analysis of blinded data from the first 9 subjects. All patients (4 women, 5 men; 65 ± 12 years of age, mean ± SD) consented to participate in this randomized, controlled, pilot evaluation, in accordance with NINDS Institutional Review Board and Food and Drug Administration regulations (Table 1). Symptom duration averaged 14 ± 5 years. Each subject had received a stable regimen of L-dopa/carbidopa alone or in combination with pramipexole or ropinirole for at least 4 weeks. All manifested motor fluctuations and peak-dose dyskinesias. The duration of prior L-dopa treatment was 11 ± 6 years, and the dose of L-dopa before study initiation was 1,128 ± 851 mg. Patients were excluded on the basis of the presence or history of any medical condition that could reasonably be expected to subject them to unwarranted risk, a history of intracranial surgical procedures for PD, an inability to satisfactorily discontinue any study-forbidden medication (essentially, any centrally acting medication other than the allowed antiparkinsonian drugs, i.e., ropinirole and pramipexole), or exposure to any other investigational drug within 2 months of randomization.

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TABLE 1. *Patient demographics*

Patient no.	Sex	Age (yr)	H&Y score	Disease duration (yr)	Meds	Levodopa (mg/day)
1	F	47	4.0	7.0	ld, pr	850
2	M	68	4.5	12.0	ld, pr	1250
3	M	73	3.5	20.0	ld, pr	850
4	F	69	3.0	15.0	ld, pr	400
5	M	68	4.5	14.0	ld, pr	2150
6	M	52	3.5	11.0	ld, pr	2900
7	F	51	3.0	18.0	ld	500
8	M	76	4.5	18.0	ld, pr	550
9	F	77	3.5	8.0	ld, ro	700
Mean		64.6	3.8	13.7		1128
SD		11.5	0.6	4.6		851

m, male; f, female; ld, levodopa; pr, pramipexole; ro, ropinirole; H&Y, Hoehn and Yahr scale. Levodopa dose refers to that taken regularly on nonefficacy assessment days; it does not take into account concomitant agonist treatment.

Study Design

The acute effects of orally administered NS 2330,[10] a potent DA uptake inhibitor with a long plasma half-life (178–220 hours; NeuroSearch, Ballerup, Denmark) were evaluated under double-blinded, placebo-controlled conditions in a study lasting 4 weeks. Blinding was achieved by keeping raters and patients unaware of the study design, as well as by giving patients a constant number of identically appearing placebo- or NS 2330-containing tablets. Blinding was further ensured by using an unbalanced, computer-generated block randomization design, with two parallel groups receiving either NS 2330 or placebo alone, in a 3:1 ratio. Individuals randomly assigned to NS 2330 treatment were given an initial 1-week placebo run-in, followed by a treatment phase consisting of eight doses of 1.5-mg each, administered three times weekly. The cumulative total dose of 12 mg was selected to achieve plasma drug concentrations in therapeutic range, based on preliminary pharmacokinetic data obtained by the drug manufacturer in an earlier clinical study. Remaining patients received placebo throughout the entire study. Subjects underwent efficacy evaluations at the end of the first (placebo) phase and again at the end of the study, according to a method that has been described previously.[11] At each evaluation, motor function was assessed: (1) when NS 2330 was administered alone, (2) when NS 2330 was coadministered with an optimal-dose, steady-state intravenous L-dopa infusion, and (3) every 30 minutes after discontinuation of the L-dopa infusion. During intravenous L-dopa administration, carbidopa (50 mg every 3 hours) was coadministered orally. Patient's oral antiparkinsonian medications were withheld at consistent times from the night before until completion of the efficacy evaluations.

Efficacy Evaluations

Parkinsonism was scored using part III (Motor subscale) of the Unified Parkinson's Disease Rating Scale (UPDRS). Dyskinesia severity was evaluated on a scale of 0 to 4 using UPDRS item 33, modified in accordance with Abnormal Involuntary Movement Scale terminology for each of five body parts (all four extremities plus trunk/face). The efficacy half-time for the antiparkinsonian action of L-dopa, a measure of the severity of wearing-off fluctuations, was defined as the time to achieve 50% of the *off* state (baseline) UPDRS score, after discontinuing the L-dopa infusion. Plasma NS 2330 levels were measured on venous blood samples collected just before dosing throughout the course of this study.

Safety Monitoring

Primary outcome measures for safety were the adverse event frequency, vital signs, and clinical laboratory values, monitored on a weekly basis.

Statistics

Results are reported as means ± SEM. Nonparametric *t* tests were used for within-patient analysis of efficacy parameters, comparing placebo baseline scores (Day 7) to those at the highest tolerated NS 2330 dose (usually Day 27) for each patient.

RESULTS

Of 15 patients screened for protocol participation, 6 did not meet accession criteria. All 9 participants completed the study, 7 of whom were randomly assigned to receive NS 2330 and 2 to placebo therapy. In the 7 NS 2330-treated patients, who received a mean cumulative dose of 11 ± 0.9 mg, plasma NS 2330 concentrations peaked at 9.0 ± 2.7 ng/ml. Treatment in 2 of these 7 individuals was discontinued after administration of total cumulative doses of 6 and 9 mg, due to recurrence of preexisting conditions (syncope and depression, respectively). Efficacy analysis was based on data from only 6 patients, as posttreatment data from 1 who received a cumulative dose of 6 mg could not be obtained. The 2 remaining patients were randomly assigned to receive only placebo therapy.

Compared to placebo baseline scores, NS 2330 monotherapy failed to improve parkinsonian signs ($P > 0.05$, Table 2). Moreover, administration of this drug did not alter the antiparkinsonian or the dyskinesiogenic effects of optimal dose L-dopa (both $P > 0.05$). NS 2330 also had no consistent effect on the duration of antiparkinsonian action of L-dopa (Table 2). There was no apparent relation between circulating plasma NS 2330 levels and degree of change of any of the outcome measures. The 2 placebo-only

TABLE 2. *Effect of NS 2330 on Motor Function*

Treatment	Placebo (Day 7)	NS 2330 (Day 27)	Difference (Days 27 − 7)	*P*
Parkinsonian severity (UPDRS III score)				
NS 2330 monotherapy	46 ± 4.7	39 ± 6.8	−6.7 ± 7.0	0.41
NS 2330 plus levodopa	15 ± 2.1	17 ± 2.9	2.5 ± 3.1	0.28
Dyskinesia severity (modified UPDRS Item 33 score)				
NS 2330 plus levodopa	5.3 ± 1.4	6.5 ± 1.8	1.2 ± 1.6	0.50
Efficacy halftime (min)				
NS 2330 plus levodopa	72 ± 21.0	57 ± 7.3	15 ± 14.0	0.31

Values are the means ± SEM for 6 NS 2330-treated patients. None of the differences between NS 2330 and placebo baseline scores were significant. UPDRS, Unified Parkinson's Disease Rating Scale.

treated patients had no significant changes in motor function during the course of the study (data not shown). Side effects possibly or probably related to NS 2330 treatment were limited to mild, transitory nausea (one occurrence), dizziness (one), headache (one), hypotension (one), and hallucinations (one).

DISCUSSION

Under the conditions of this study, we were unable to document any significant change in the severity of parkinsonian signs with NS 2330 monotherapy. Similarly, when NS 2330 was given with optimal dose L-dopa, there were no consistent alterations in the duration of its antiparkinsonian action or in the severity of dyskinesias. The drug was generally well tolerated, and adverse effects did not seriously complicate its administration to relatively advanced PD patients.

The foregoing observations could be construed as suggesting that drugs acting to interfere with DA uptake have little, if any, effect on motor function in advanced parkinsonian patients. NS 2330 is a highly potent inhibitor of striatal DA uptake when present in the low nanomolar range.[12] Whereas DAT antagonists have antiparkinsonian activity in primate models of PD,[9] there have been no previous controlled studies of drugs with this pharmacologic profile in parkinsonian patients. NS 2330 also exerts an inhibitory effect on both serotonin and norepinephrine uptake.[12] Nevertheless, countervailing motoric effects of these pharmacologic actions are unlikely to contribute to the apparent lack of NS 2330 efficacy, because drugs acting mainly through these mechanisms ordinarily do not induce parkinsonism in normal individuals nor exacerbate parkinsonian signs in PD models or patients.[13–15] On the other hand, it is not known whether brain NS 2330 concentrations attained during the course of this study were sufficient to achieve a significant degree of striatal DAT blockade. The dosing schedule used, however, was designed to raise levels of this very long acting drug into the putative therapeutic range at the end of the 2.5-week treatment period. It is also unknown whether the density of DATs, which are primarily expressed on striatal DA neuron terminals, is sufficient in relatively advanced PD patients to have a substantial effect on dopaminergic transmission.[16]

The present study, involving a small population of advanced parkinsonian patients, failed to provide evidence that DA reuptake mechanisms are an important determinant of motor dysfunction and do not support the utility of dopamine uptake blockade as a pharmacologic approach to the treatment of this patient group. On the other hand, the possibility that central drug concentrations did not reach the pharmacologically effective range cannot be excluded.

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Rhythmic Movement Disorder and Cyclic Alternating Pattern During Sleep: A Video-Polysomnographic Study in a 9-Year-Old Boy

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Abstract: **We report on polysomnographic findings in a 9-year-old boy affected by rhythmic movement disorder. The subject's rhythmic movements were found to be intimately linked to unstable nonrapid eye movement N-REM sleep, as shown by their close association with the A phases of the cyclic alternating pattern. We examine the complex interactions between arousal mechanisms and rhythmic movements occurring during sleep.** © 2004 Movement Disorder Society

Key words: sleep; arousal; CAP; rhythmic movement disorder

The term rhythmic movement disorder (RMD) embraces a variety of clinical conditions characterized by repetitive rhythmic banging or rolling of the whole body or of one or more of its parts, such as the head, arms, or legs.[1] This grouping of heterogeneous phenomena stems from the fact that, for a long time, the term was used in reference to predominantly clinical findings. However, the few video-polysomnographic (video-PSG) studies conducted to date[2–4] show clearly that some forms of RMD constitute true movement disorders occurring both in nonrapid eye movement (non-REM) and, not uncommonly, in REM sleep. This kind of RMD must be dif-

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