Effects of Serotonin 5-HT1A Agonist in Advanced Parkinson's Disease

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Abstract: Intermittent stimulation of striatal dopaminergic receptors seems to contribute to motor dysfunction in advanced Parkinson's disease (PD). With severe dopaminergic denervation, exogenous levodopa is largely decarboxylated to dopamine in serotonergic terminals. If 5-HT1A autoreceptors regulate dopamine as well as serotonin release, in parkinsonian patients inhibition of striatal serotonergic neuron firing might help maintain more physiological intrasynaptic dopamine concentrations and thus ameliorate motor fluctuations and dyskinesias. To evaluate this hypothesis, effects of a selective 5-HT1A agonist, sarizotan, given orally at 2 and 5 mg twice daily to 18 relatively advanced parkinsonian patients, were compared with baseline placebo function during a 3-week, double-blind, placebo-controlled, proof-of-concept study. Sarizotan alone or with intravenous levodopa had no effect on parkinsonian severity. But at safe and tolerable doses, sarizotan coadministration reduced levodopa-induced dyskinesias and prolonged its antiparkinsonian response ($P \leq 0.05$). Under the conditions of this study, our findings suggest that 5-HT1A receptor stimulation in levodopa-treated parkinsonian patients can modulate striatal dopaminergic function and that 5-HT1A agonists may be useful as levodopa adjuvants in the treatment of PD. © 2005 Movement Disorder Society

Key words: 5-HT1A receptor; serotonin; dopamine; Parkinson's disease; dyskinesias, levodopa; striatum

The treatment of advanced Parkinson's disease (PD) is associated generally with progressive alterations in the response to dopaminomimetic therapy. Increasing evidence suggests that nonphysiological, pulsatile stimulation of striatal dopamine (DA) receptors contributes to the appearance of these disabling dyskinesias and motor fluctuations.[1–4] According to this hypothesis, striatal medium spiny neurons undergo reactive changes first as a result of the denervation produced by natural disease progression and later due to the intermittent stimulation associated with current therapeutic regimens.[5–7] The aberrant activation of signaling cascades within these striatal neurons linking their dopaminergic receptors to nearby ionotropic glutamatergic receptors then seems to augment their synaptic efficacy in ways that compromise motor function.[5,8] These possibilities have encouraged the search for alternative approaches to the palliation of parkinsonian symptoms that avoid exposing striatal dopaminergic receptors to long-term nonphysiological stimulation.[9]

With progressive degeneration of dopaminergic neurons in PD, DA formation from exogenous levodopa (L-dopa) increasingly takes place in striatal serotonergic nerve terminals.[10,11] It is thus not surprising that pharmacologic agents affecting serotonergic nerve impulse activity, by interacting with 5-HT1A autoreceptors, can regulate serotonin release under normal conditions and DA release in L-dopa-treated parkinsonian animals.[12–15] In the latter circumstances, drugs that stimulate these autoreceptors tend to attenuate peak striatal concentrations of DA and prolong its half-life.[12] If 5-HT1A agonists produce the same pharmacologic effects in PD patients, then a reduction in peak-dose dyskinesias and wearing-off fluctuations might be expected. Recent

observations in parkinsonian animals support this possibility.[16]

Sarizotan is a novel chromane derivative with a high affinity for 5-HT1A receptors where it acts as a nearly full agonist.[17,18] In phase I studies, sarizotan seemed to be safe and tolerable at doses up to at least 20 mg per day. To evaluate the hypothesis that pharmacologic attenuation of striatal serotonergic nerve impulse activity will benefit L-dopa-induced motor complications, we administered this 5-HT1A agonist to individuals with relatively advanced PD. We also sought to determine whether sarizotan influences the antiparkinsonian action of L-dopa, as well as assess its acute safety and tolerability at clinically effective doses.

SUBJECTS AND METHODS

Subjects

Study participants in this study comprised 18 patients (8 women; 10 men; mean age $\pm$ SD, 58 $\pm$ 11 years) diagnosed with PD in accordance with standard criteria, at moderate to advanced stages (Hoehn and Yahr 2.5–4.0 in the *off* state). Consent was obtained from all participants in this study, which was conducted in accordance with NINDS IRB and FDA guidelines. Symptom duration averaged 10 $\pm$ 4 years, L-dopa treatment duration was 6.1 $\pm$ 3.0 years, and the daily dose of L-dopa was 1,135 $\pm$ 348 mg. All subjects manifested motor fluctuations and peak-dose dyskinesias. Each was receiving a stable regimen of carbidopa/L-dopa, alone or in combination with pramipexole or ropinirole, for at least 4 weeks before the study. Patients were excluded based on the presence or history of any medical condition that could reasonably be expected to subject them to unwarranted risk, a history of intracranial procedures for PD, an inability to discontinue any study-forbidden medication (essentially, any centrally acting medication other than the allowed antiparkinsonian drugs), or exposure to any investigational drug within 2 months of random assignment.

Study Design

The acute effects of sarizotan (EMD 128130; E. Merck, Darmstadt, Germany) were evaluated under double-blind, placebo-controlled conditions in a study lasting 3 weeks. Participants first received a 1-week placebo run-in, followed by a dose-escalation treatment phase lasting 2 weeks (1 week at 2 mg b.i.d. and then 1 week at 5 mg b.i.d.). All participants underwent efficacy evaluations at the end of the first (placebo baseline), second, and third study weeks.[19] Motor function was assessed: (1) when sarizotan was given alone; (2) when sarizotan was coadministered with steady-state intravenous L-dopa infusions, at both low and optimal doses, together with oral carbidopa, 50 mg every 3 hours; and (3) at 30-minute intervals after discontinuation of the optimal L-dopa dose infusion to evaluate wearing-off severity.[19] An optimal dose was defined as one producing a good antiparkinsonian response with consistent, ratable dyskinesias (a score of 3 or more for Item 33 of the modified Unified Parkinson's Disease Rating Scale [UPDRS], as described in the following section). A low L-dopa dose was defined as one producing minimal antiparkinsonian response with negligible or no dyskinesias. Patients' oral antiparkinsonian medications were withheld at consistent times from the night before until completion of all efficacy evaluations.

Efficacy Evaluations

Efficacy was assessed using part III (motor subscale) of the UPDRS and a modification of Item 33 (Dyskinesias) on the UPDRS. Dyskinesia severity was scored on a 0-to-4 scale, according to Abnormal Involuntary Movement Scale terminology, for each of five body parts (all four extremities plus trunk/face).[19] Duration of L-dopa action (efficacy half-time) was defined as the time to achieve 50% of the *off* state (baseline) UPDRS motor score after discontinuing the L-dopa infusion.

Safety Monitoring

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

Statistics

Results are reported based on a within-patient analysis of UPDRS score changes from the end of study Week 1 to the end of Weeks 2 and 3. A sample size of 15 patients receiving placebo followed by sarizotan was estimated, to provide approximately 80% power using a two-tailed paired *t* test at the 0.05 significance level. The Wilcoxon signed-rank test was employed for statistical analyses of primary (dyskinesias) and secondary (parkinsonism and wearing-off) efficacy outcome measures, comparing baseline placebo scores with those at the best dose (most effective and best tolerated dose) of sarizotan for each patient. This proof-of-principle study was not powered for between-group comparisons. Efficacy results are presented as the means $\pm$ standard error of the mean (SEM).

Blinding

Blinding was achieved by keeping raters and patients unaware of the study design as well as giving patients a constant number of identically appearing placebo- or
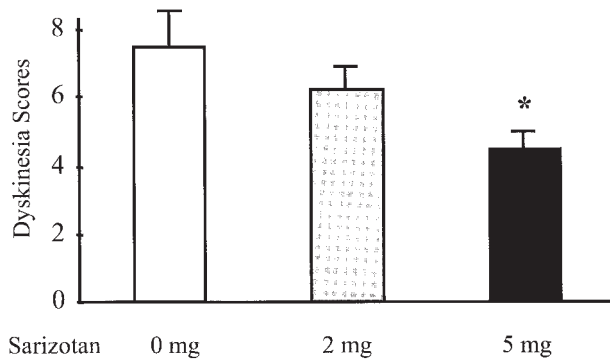
FIG. 1. Serotonin 5-HT1A agonist effects on L-dopa-induced dyskinesias. The figure shows mean ± SEM for choreiform dyskinesia severity (UPDRS dyskinesia score) for 15 subjects assigned randomly to sarizotan treatment. All patients were receiving optimal dose of L-dopa. At 5 mg, sarizotan significantly improved L-dopa-induced dyskinesias; *$P < 0.05$.

sarizotan-containing capsules. Blinding was ensured further by randomly assigning additional patients to receive placebo throughout the entire study, using an unbalanced block randomization design (1:5 ratio), which minimized the total number of subjects admitted to this study. To the best of our knowledge, the integrity of the blind was never compromised in the study.

Assignment

Patients were assigned randomly in blocks of five using a computerized procedure carried out by the drug manufacturer. Allocation was concealed by means of a covered tear-off tab held at the NIH Pharmaceutical Development Service before and after the time of assignment.

RESULTS

Sarizotan monotherapy failed to improve parkinsonian scores (45 ± 5.2 and 43 ± 4.2, at 2 and 5 mg, respectively), compared with those at placebo baseline values (40 ± 3.6) in the 15 patients randomly assigned to active drug therapy ($P > 0.05$). Moreover, sarizotan did not alter the antiparkinsonian action of optimal-dose (13 ± 1.7 vs. 14 ± 2.0) or low-dose L-dopa (34 ± 4.2 vs. 30 ± 3.6). Although at the lower dose (2 mg b.i.d.), sarizotan did not influence the dyskinesiogenic effect of L-dopa (6.3 ± 2.5), at the higher dose (5 mg b.i.d.) it reduced L-dopa-induced dyskinesias by 40% (4.5 ± 0.5), when compared with L-dopa alone (7.5 ± 1; $P < 0.05$; Fig. 1). L-Dopa efficacy half-time values increased by an average of 38%, from 87 ± 8 min at baseline to 121 ± 20 min at each patient's best dose of sarizotan ($P = 0.05$; Fig. 2).

Of 3 patients who were assigned randomly to receive only placebo, 1 was subsequently withdrawn due to

recurrence of a preexisting condition. The other 2 patients showed no significant change in motor function measures during the course of the study (data not shown).

Adverse events reported by patients included palpitations (1 occurrence), nausea (2), constipation (2), headache (2), coughing (1), insomnia (2), depression (1), and increased *off* time (1). Most were considered to be unrelated to sarizotan, as they occurred during the placebo phase of the study, except for a bout of depression and insomnia during Week 3 of study in a patient with a previous history of these symptoms. No somnolence, mental changes, or abnormalities in standard laboratory tests were observed.

DISCUSSION

Results in this cohort of rather advanced PD patients showed that sarizotan, when coadministered with L-dopa, reduces dyskinesias and prolongs the duration of antiparkinsonian action without diminishing antiparkinsonian efficacy. Post-hoc analysis did not reveal any other consistent difference between those having the most favorable response to sarizotan and remaining members of the study group. In particular, sarizotan efficacy did not correlate with disease duration or severity. These findings replicate results from earlier studies in animal models of PD. In 6-OHDA-lesioned rats, sarizotan reversed the shortening in motor response duration (an index of wearing-off severity) induced by chronic intermittent L-dopa treatment.[16] In MPTP-lesioned monkeys, sarizotan reduced L-dopa-induced choreiform dyskinesias by over 90%.[16] Although the response magnitude seemed
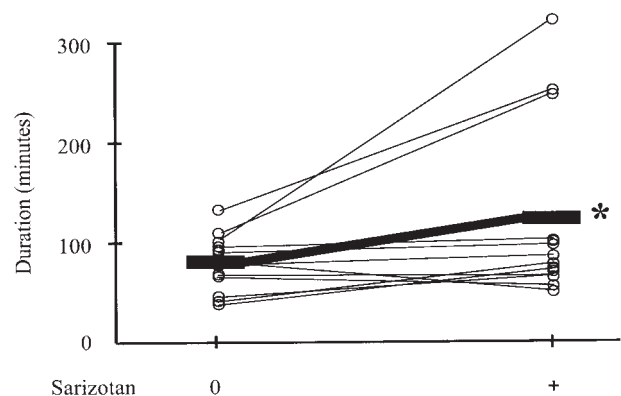
FIG. 2. Individual data showing effect of the best dose of sarizotan on L-dopa motor response half-time (i.e., time for antiparkinsonian effect to decline by 50% after withdrawal of optimal-dose, steady-state L-dopa infusion). Drug dose symbols are 0 (placebo) and + (best dose of sarizotan). Compared with placebo, sarizotan prolonged the L-dopa effect by an average of 34 minutes (38%). The dark bars indicate mean effects; *$P = 0.05$.

less in parkinsonian patients than it did in parkinsonian rodents or primates, the apparent dose–response effect in the present study suggests that higher doses might have proven more beneficial. Safety observations support exploration of this possibility, because at the doses and durations administered, sarizotan produced no clinically consequential adverse effects. Our results with sarizotan are consistent with the antidyskinetic effects in L-dopa-treated parkinsonian patients of drugs such as buspirone and clozapine[20–23] that, among various other pharmacologic actions, also activate 5-HT1A receptors.

The clinical effects of sarizotan observed here most likely relate to the drug's potent ability to activate 5-HT1A autoreceptors. In rodent and primate models of PD, functional activity at this site probably accounts for the amelioratory effects on L-dopa-induced motor response alterations, because they disappeared when sarizotan was coadministered with WAY 100635, a highly selective 5-HT1A antagonist.[16] Moreover, in parkinsonian rats 5-HT1A receptor stimulation blunts peak concentrations and prolongs the half-life of striatal DA.[12,24–27] Clearly, such an action could explain the observed ability of sarizotan to attenuate peak-dose dyskinesias and diminish the cause of the wearing-off fluctuations in parkinsonian patients as it does in parkinsonian animals. Our results are thus consistent with the participation of vesicular storage and release for DA in human striatal serotoninergic terminals and support preclinical data suggesting that serotoninergic terminals are an important site for the decarboxylation of exogenous L-dopa to DA, and the major source of DA released into the striatum during L-dopa treatment of parkinsonian states.[10,11]

In addition to 5-HT1A agonist effects, other potential mechanisms for the antidyskinetic effect of sarizotan warrant consideration. Although sarizotan also acts as an antagonist at D2 family dopaminergic receptors,[16,17] its ability to diminish dyskinesias is unlikely to reflect D2, D3, or D4 receptor blockade.[28] In vitro binding assays indicate the affinity of sarizotan at cloned human D2 DA receptors to be an order of magnitude less than that at 5-HT1A receptors.[18] In parkinsonian primates, an action primarily at serotonergic rather than dopaminergic receptors is suggested further by the ability of sarizotan to block L-dopa-induced dyskinesias at doses that had no effect on dyskinesias induced by a direct-acting D2 receptor agonist.[16] In addition, a functionally important effect at dopaminergic receptors is incompatible with the absence of any reduction in the antiparkinsonian action of L-dopa and the tendency to prolong rather than shorten the motoric effects of L-dopa observed in parkinsonian animals,[16] as well as in patients admitted to this study.

Because sarizotan acts to decrease serotonergic neuronal firing and thus serotonin release, it is possible that some of its effects represent a reduced stimulation at other serotonergic receptors.[29–31] On the other hand, the presence of a sarizotan effect on L-dopa-induced dyskinesias but not on D2 agonist-induced dyskinesias in these animals favors a direct action on DA release from serotonergic terminals rather than an indirect effect at 5-HT2 receptors on striatal spiny neurons.

At present, there are no entirely satisfactory pharmacologic treatments for the motor response changes that complicate L-dopa treatment of PD.[32] The present results suggest a new potential target for pharmacologic intervention. Hopefully, the findings of this limited, proof-of-concept study should stimulate efforts to determine whether serotonergic drugs of the type used here can safely benefit those with advanced disease.

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