Induction by Dopamine D₁ Receptor Agonist ABT-431 of Dyskinesia Similar to Levodopa in Patients With Parkinson Disease

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Background: Dyskinesias are a frequent adverse effect of long-term levodopa therapy. The relative contribution of dopamine D₁ and D₂ receptor function to the pathophysiology of levodopa-induced dyskinesias remains a matter of controversy.

Objective: To establish whether a selective D₁ dopamine agonist induces more or less dyskinesia than levodopa in primed dyskinetic patients with Parkinson disease.

Methods: We studied ABT-431, the prodrug of a fully selective D₁ agonist, in 20 subjects with advanced Parkinson disease and a fluctuating response to levodopa complicated by dyskinesias. Eight patients were studied in a double-blind, randomized design (French centers); 12, in an open, randomized design (US centers). We assessed and compared the antiparkinsonian (Unified Parkinson’s Disease Rating Scale) and dyskinetic (response induced by an acute challenge of a suprathreshold dose of levodopa and by 4 different ascending doses (3, 10, 20, and 40 mg) of ABT-431 during the 6 hours after the challenge).

Results: The separate analysis of the double-blind and open data led to the same findings, ie, the antiparkinsonian and dyskinetic responses induced by ABT-431 were dose related. At the most effective doses (20 and 40 mg), ABT-431 exhibited similar antiparkinsonian benefit and produced similar dyskinesias as levodopa.

Conclusion: Dopamine D₁ agonists can induce a full antiparkinsonian response but do not support previous hypotheses suggesting that D₁ agonists are more or less likely to produce dyskinesias than levodopa.

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LONG-TERM levodopa replacement treatment is associated with the development of long-term motor response complications, including fluctuations and dyskinesias, in most patients with Parkinson disease who respond to levodopa. The mechanisms that cause such complications remain poorly understood. Despite numerous studies, the relative contribution of dopamine D₁ and D₂-receptor stimulation to the antiparkinsonian and dyskinetic responses obtained with levodopa is still a matter of controversy. Because levodopa undergoes decarboxylation to dopamine itself, it is considered nonselective, stimulating D₁- and D₂-like families of receptors. Early experimental data suggested that D₂ receptors are responsible for the antiparkinsonian effects, whereas dyskinesias might be mediated by the D₁ receptors. However, more recent results obtained in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkey have challenged this assumption, showing that an agent that is selective and a full agonist at the D₁ receptor might produce equivalent antiparkinsonian efficacy as levodopa with less dyskinesia than that associated with stimulation of D₂ receptors. We studied ABT-431, the diacetyl prodrug of A-86929, ie, (5aR-trans)-4,5,5a,6,7,11b-hexahydro-2-propylbenzof[thieno[2,3-c]quinoline-9,10-diol, diacetate (ester), hydrochloride. The drug is converted rapidly and completely in vivo to A-86929 by nonspecific plasma esterases with an elimination half-life of less than 60 seconds. A full agonist for the D₁ receptor, A-86929, has an elimination half-life of approximately 2 hours. Preclinical data indicate that ABT-431, or its active entity A-86929, has comparable efficacy to levodopa in several animal models of Parkinson disease, including MPTP-treated primates. In a recent pilot placebo-controlled clinical study, we showed...
PATIENTS AND METHODS

Patients were qualified for admission to the study during a 1-day screening visit if they had received a diagnosis of idiopathic Parkinson disease and if they demonstrated, compared with their practically defined medication-free state, a significant clinical improvement but with substantial dyskinesias (score of at least 2 on ≥2 areas on a dyskinesia scale derived from that published by Marconi et al13) in response to their usual first morning dose of oral levodopa (+ carbidopa) plus an additional 50 mg of levodopa. In patients treated with an agonist combined with levodopa, the investigator was allowed to increase this dose of levodopa by up to 100 mg based on his or her clinical judgment. Patients scoring less than 23 on the Mini-Mental State Examination, patients with hypertension or symptomatic orthostatic hypotension, patients taking enzyme-inducer medications, and patients with any significant abnormality on history or results of physical examination, blood chemistry, hematologic studies, electrocardiography (ECG), and electroencephalography were excluded from the study.

Once qualified, patients spent 5 days in a clinical research unit. Each morning, they underwent testing after all antiparkinsonian drugs had been withheld during the 12 previous hours. Each day, the patients underwent challenge with an intravenous dose of ABT-431 (successively 5, 10, 20, and 40 mg); 1 day, they received levodopa (+ carbidopa) instead. The levodopa day was randomly assigned. The dose of levodopa was the same as that determined during the screening session. Because of the scarcity of clinical safety data for ABT-431, the 4 doses of ABT-431 were administered in rising order. The next higher dose was administered only if the patient tolerated the previous dose without significant adverse events. Because of insufficient oral bioavailability, ABT-431 was administered intravenously (1-hour infusion).

The response to treatments was assessed during the 6 hours after the challenge. The antiparkinsonian response was assessed before challenge and then every 60 minutes thereafter using the motor examination of the United Parkinson’s Disease Rating Scale (UPDRS)11 (maximal score, 108), whereas dyskinesias were assessed before challenge and every 30 minutes thereafter using the severity scale derived from that published by Marconi et al,11 which rates the abnormal movements from 0 (none) to 4 (severe with markedly impaired function) in 6 different parts of the body (face, neck and trunk, and 4 limbs) (maximal score, 24).

If the subject showed no clinical improvement in the 3 hours after the challenge, or if clinical improvement lasted less than 3 hours, the usual established antiparkinsonian therapy was resumed and clinical scoring was discontinued.

Safety and tolerability were assessed at regular intervals using clinical inquiry, vital signs (heart rate and blood pressure), laboratory assessments, and ECG.

The study was randomized and double blinded in the 2 French centers (Toulouse and Marseille) using a double-placebo procedure, one for the ABT-431 infusion and the other for oral levodopa. Initially, it was planned that the US centers (Portland, Ore; Chicago, Ill; and Charlottesville, NC) would use intravenous rather than oral levodopa in a double-blind single-placebo design. Because of unexpected regulatory limitations, however, intravenous levodopa could not be used in the US centers. The US patients therefore underwent challenge with open-label oral levodopa (+ carbidopa) (no oral placebo being available) and were randomized into the ascending doses of ABT-431.

Active drugs, placebo, and randomization were provided by Abbott Laboratories, Abbott Park, Ill. Patients gave written informed consent after the study had been approved by the appropriate human research ethic committees.

To analyze the 2 major outcomes of the study (UPDRS and dyskinesia scores), changes from predose to postdose evaluations were calculated for each patient. Comparisons between the effects of levodopa and the different ABT-431 doses were performed using a mixed repeated-measures model, including terms for patients as a random effect and dose of ABT-431 as a fixed effect. Results were expressed as median (range) changes from baseline of the best UPDRS improvement and as the median of the worst dyskinesia response after dosing.

Because of the blinded design in the French centers and the open design in the US centers, the results were analyzed separately.

Eight patients were studied in the French centers and 12 in the US centers. The demographic data of the French and US patients are listed in Table 1. Both groups were similar.

BLIND DATA (FRENCH CENTERS)

Of the 8 French patients studied in a double-blind design, 7 completed the study as planned, and 1 was discontinued because of ECG changes when receiving the 10-mg dose of ABT-431. Figure 1A shows the results expressed as median scores in the patients analyzed as a group, for levodopa and the 4 doses of ABT-431. At the 2 lower doses of ABT-431, the antiparkinsonian (best improvement) and dyskinetic (worst score) responses were
significantly smaller than those produced by levodopa. Conversely, at the 2 higher dosages, there was no statistical difference in amplitude of antiparkinsonian and dyskinetic responses induced by ABT-431 and levodopa. Clinically, the ABT-431– and levodopa-induced dyskinesias were indistinguishable.

**Figure 2** and **Figure 3** present the individual subject UPDRS scores (assessed every hour) and dyskinesia scores (assessed every 30 minutes) at each dose of ABT-431 and levodopa. These data show that all patients except patient 105 responded with 1 or more doses of ABT-431. The patient who did not respond with ABT-431 was using the highest daily dose of levodopa (1500 mg/d). Of the 6 patients who responded to ABT-431 and completed the study, 3 patients fully responded to the 10-mg and higher doses of ABT-431; 2 patients to the 20-mg and higher doses; and 1 patient only to the 40-mg dose (a *full response* being defined as a maximal UPDRS motor improvement within 10% of that seen after receiving levodopa). The amplitude of the antiparkinsonian response did not significantly increase with larger doses in most subjects, if one compares only the doses producing an effect. This observation suggests that the maximal amplitude of the response (comparable to that induced by levodopa) was reached with the smallest dose capable of inducing a response in the subject, without further improvement because of a ceiling effect. Conversely, increasing the dose increased the number of patients who responded and prolonged the duration of the antiparkinsonian response (Figure 2). The severity of ABT-431–induced dyskinesias was comparable to that induced by levodopa, at the dosages of ABT-431 inducing a full antiparkinsonian response (Figure 3).

Adverse effects of ABT-431 and levodopa were similar (**Table 2**), with a noticeable exception. The exception is the subject who was discontinued because of an asymptomatic ST-segment depression on ECG during the infusion of the 10-mg dose of ABT-431. The ECG abnormality reversed spontaneously and was not associated with elevation of cardiac enzyme levels.

**OPEN DATA (US CENTERS)**

Figure 1B shows the results of the 12 US patients analyzed as a group. These open results are quite similar to those of the French double-blind study, ie, at the 2 lower doses of ABT-431, the antiparkinsonian and dyskinetic responses were smaller than those with levodopa, whereas no significant difference was observed at both higher dosages.

Two patients failed to respond to any of the doses of ABT-431 used. As in the French study, these patients were taking the largest daily doses of levodopa. Of the 7 responders who completed the study, 3 patients fully responded to the 5-mg and higher doses of ABT-431, 3 responded to the 10-mg and higher doses, and 1 responded to the 20- and 40-mg doses. In these 7 responders, the severity of dyskinesias induced by ABT-431 at the lower dosage inducing a full antiparkinsonian response was comparable to that induced by the supra-threshold dosage of levodopa (data not shown).

**Table 1. Demographic Data**

<table>
<thead>
<tr>
<th></th>
<th>French Centers</th>
<th>US Centers</th>
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<tbody>
<tr>
<td>Sex ratio, M/F</td>
<td>7:1</td>
<td>8:4</td>
</tr>
<tr>
<td>Age, y</td>
<td>62 (51-71)</td>
<td>64 (38-75)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69 (41-116)</td>
<td>70 (48-88)</td>
</tr>
<tr>
<td>PD duration, y</td>
<td>13 (6-20)</td>
<td>13 (6-18)</td>
</tr>
<tr>
<td>Levodopa therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, y</td>
<td>12 (4-20)</td>
<td>10 (4-14)</td>
</tr>
<tr>
<td>Daily dose, mg/d</td>
<td>750 (600-1500)</td>
<td>900 (400-2600)</td>
</tr>
<tr>
<td>Challenge dose, mg</td>
<td>300 (200-350)</td>
<td>200 (100-400)</td>
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<tr>
<td>Screening UPDRS III†</td>
<td>43 (25-55)</td>
<td>54 (36-70)</td>
</tr>
<tr>
<td>Screening dyskinesia score‡</td>
<td>6 (4-12)</td>
<td>7 (6-16)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean (range). PD indicates Parkinson disease; UPDRS, United Parkinson’s Disease Rating Scale. † Measured while not receiving levodopa. ‡ Measured during therapy.

Adverse events were also quite similar to what was observed in the French centers (**Table 2**). Three US patients withdrew from the study before its completion because of adverse events, ie, symptomatic hypotension in 2 subjects at the 10-mg dose of ABT-431 and nausea in the third at the 5-mg dose of ABT-431. One US patient also had an asymptomatic ST-segment depression on ECG associated with nausea, vomiting, and hypotension during the infusion of 40 mg of ABT-431. This abnormality reversed spontaneously within a few hours.

**ANTIPARKINSONIAN RESPONSE**

We have compared the effects of a selective and efficacious D₄ agonist, ABT-431, with those of levodopa in 20 subjects with advanced Parkinson disease and a fluctuating response to levodopa complicated by dyskinesias. We analyzed the French and US data separately because the French study was double-blind, whereas a last-minute administrative problem mandated an open design in the US study. Apart from this difference, the design of the protocols was identical in both groups. The fact that both group analyses provided similar results strongly reinforces the consistency of our findings, and we therefore will discuss them further as a whole. Our data show that the short-term administration of ABT-431 was as effective as levodopa in alleviating parkinsonism, but that this result was achieved with a similar amount of dyskinesia.

The hypothesis that the stimulation of D₄ receptors may have relevant antiparkinsonian effects has been tested previously with partial D₄ agonists like SKF 82958 or CY 208-243. These drugs were shown to produce, at best, only mild antiparkinsonian effects. Later D₄ agonists with greater intrinsic agonist activity fully relieved parkinsonism in MPTP-treated primates. A prodrug of the full dopamine D₄ agonist A-86929, ABT-431, induced a similar effect in patients with Parkinson disease. The present study demonstrates that the ABT-431 response has an equivalent...
magnitude to that of a suprathreshold levodopa dose. Blanchet and colleagues also reported that 1 patient showed a definite motor improvement with another full D₃ agonist, dihydrexidine. Therefore, it is likely that selective D₃ agonists are as potent as levodopa in alleviating human parkinsonian symptoms, as they have been shown to be in MPTP-treated monkeys. One French patient and 2 US patients did not respond

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**Figure 1.** Median scores (range) of dyskinesias and United Parkinson's Disease Rating Scale (UPDRS) for levodopa and the 4 doses of ABT-431 in the 8 patients studied in double-blind conditions in the French centers (A) and the 12 patients studied in an open design in the US centers (B). The UPDRS scores are expressed as absolute score changes from baseline to the peak of the antiparkinsonian responses (best improvement). Dyskinesia scores are expressed as absolute score changes from baseline to the peak of the dyskinetic response (worst score). Asterisk indicates P < .05; dagger, P < .01.

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**Figure 2.** Temporal profile of United Parkinson's Disease Rating Scale (UPDRS) scores in each individual French subject with Parkinson disease after a suprathreshold dose of oral levodopa and 5, 10, 20, and 40 mg of intravenous ABT-431, as measured during the 5 days of assessment (subject 108 only received 5 and 10 mg of ABT-431).

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**Figure 3.** Temporal profile progression of dyskinesia scores in the same patients as in Figure 2.
with any dose of ABT-431. We suggest that this lack of responsiveness is best explained by the fact that these subjects may have needed a larger dose of ABT-431 because they were using the highest daily doses of levodopa.

DYSKINETIC RESPONSE

The important finding of the present study is that when ABT-431 produced a full antiparkinsonian effect, it was at the cost of the same amount of dyskinesias as produced with levodopa.

The relative contribution of dopamine D₁ and D₂ receptors to the dyskinetic response induced by levodopa remains a matter of controversy. Some arguments suggest that D₂ receptors are a major contributor to the dyskinetic response. For example, the low dyskinetic potential of bromocriptine mesylate in levodopa-naive MPTP-treated monkeys⁵ and patients with Parkinson disease⁶⁰–⁶³ might be due to its D₂ antagonistic (partial agonistic) properties. Similarly, the antidyskinetic properties of the atypical neuroleptic clozapine might be explained by its D₂ antagonistic effects.⁶⁴–⁶⁶

However, recent data from MPTP-treated monkeys suggest that D₁-selective agonists, including A-86929, the active metabolite of ABT-431, produced less dyskinesias than levodopa or D₂-selective agonists in monkeys that had been primed with levodopa to exhibit dyskinesias.⁶³,⁶⁷

Our present study, designed to address directly the question about dyskinesias in patients with Parkinson disease, failed to demonstrate that ABT-431 was less prone than levodopa to induce dyskinesias at doses demonstrating equivalent antiparkinsonian efficacy. Blanchet and colleagues¹⁹ reached a similar conclusion in a single patient treated with another D₁ agonist, dihydrexidine.

The D₁ selectivity of ABT-431, especially at the highest tested doses, is a major concern when discussing the present results. It is rapidly (1 minute) and completely converted in vivo to a single known active metabolite, A-86929. This compound has a high affinity for the human D₁ receptor, with an inhibition constant of 51 nmol/L. It has a full functional efficacy compared with dopamine (concentration at which it is half-maximally effective [EC₅₀], 9 nmol/L).⁶⁸ The metabolite A-86929 has a 200:1 selectivity for the D₁ vs the D₂ human receptor in binding and adenylate cyclase assays.⁶⁹ The produg ABT-431 retains full selectivity for the dopamine D₁ receptor at high doses in the 6-hydroxydopamine lesioned rat model of parkinsonism, where its effects are fully inhibited by the D₂ receptor antagonist SCH23390, but not by the D₁ antagonist haloperidol decanoate.⁷⁰ Therefore, although we do not have direct evidence in humans, we assume that the behavioral effects of ABT-431, including its antiparkinsonian and dyskinetic ones, are selectively mediated by D₁ receptors.

It is well known, in levodopa-treated dyskinetic patients with advanced Parkinson disease, that the threshold for antiparkinsonian and dyskinetic responses are closely related.⁷¹,⁷² The same observation was true for ABT-431. However, the analysis of individual responses showed some instances when these 2 thresholds apparently differed. Some patients responded without dyskinesias at low doses (eg, patients 101 and 108 at the 5-mg dose in Figures 2 and 3), whereas others exhibited some dyskinesias, probably of the diphasic type, without responding (eg, patient 105 at the 5-, 20-, and 40-mg doses and patient 106 at the 20-mg dose in Figures 2 and 3). The same dissociation of the threshold can be seen with levodopa at doses that are near thresholds.

We pooled for analysis the effects of each dose of ABT-431. However, dramatic differences between patients in motor responses to a given dose of levodopa or dopamine agonists is a common observation. A given dose of ABT-431 also induced quite different responses in different patients (Figures 2 and 3). For example, the lowest dose of ABT-431 (5 mg) led to response in some patients (patients 101 and 104), whereas the highest ABT-431 dose (40 mg) did not in others (patient 105). Nevertheless, if one looks carefully at each patient when receiving the lowest dose of ABT-431 that induced a full response, one can notice that this dose always induced nearly the same amount of dyskinesias as the suprathereshold dose of levodopa. This was observed in the French and the US patients.

ADVERSE EVENTS

The adverse events related to ABT-431 were quite usual for dopamine receptor agonists (Table 2). These included mostly hypotension, nausea, and flushing. Hypotension limited testing of dihydrexidine in several patients studied by Blanchet and colleagues¹⁰ but was rarely a clinical problem in patients receiving ABT-431. No clear dose- or study day–related effects were apparent except for nausea, which tended to appear early in the study at low doses of ABT-431, and dissipated thereafter, as if tolerance occurred, after which ABT-431 was generally well tolerated. A worrisome adverse event was evidence of cardiac ischemia. Asymptomatic ST-segment depression on ECG during ABT-431 infusions that reversed within a couple of hours developed in 2 patients without any evidence of coronary artery disease. A similar observation was also reported in 1 subject in the initial placebo-
controlled study. This adverse effect could be related to hypotension. However, the mean drop in systolic blood pressure induced by ABT-431 did not appear to be significantly larger than that induced by levodopa in the French and US patients (Table 2), and blood pressure was not more affected in subjects with development of ECG ST-T changes. This will require close surveillance as D1 agonists are further evaluated.

Our data provide convincing evidence that a short-term challenge with ABT-431 induces the same antiparkinsonian and dyskinetic effects as levodopa in patients with Parkinson disease. This observation questions the importance of D1 vs D2 receptors in the motor effects of antiparkinsonian medications. It remains to be determined if a long-term treatment with D1 agonists or if initial therapy in patients not undergoing priming with levodopa would or would not reduce the risk for or the severity of dyskinesias.

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