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End-of-Dose Akinesia After a Single Intravenous Infusion of the Dopaminergic Agonist Piribedil in Parkinson's Disease Patients: A Pharmacokinetic/Pharmacodynamic, Randomized, Double-Blind Study

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Abstract: This randomized, double-blind trial was designed to define the possible relationship between piribedil plasma concentrations and the decrease of the Unified Parkinson's Disease Rating Scale (UPDRS) motor score or the switch from *off* to *on* state after single intravenous infusion. Ten fluctuating patients with idiopathic Parkinson's disease (PD) received escalating doses of piribedil (2–16 mg) and placebo. Starting from 2 mg, piribedil was effective in reducing the motor deficit (UPDRS, motor score) including akinesia at the first evaluation time point of 15 minutes, and in reversing *off* state of 7 of 10 patients. The doses were equally effective, although the effect was more sustained with the highest dose of 16 mg. Piribedil was well tolerated up to a 16-mg dose and pharmacokinetics were linear up to the 16-mg dose. Plasma levels of piribedil were not correlated to the motor score improvement or switch from *off→on*. In conclusion, a short single infusion of piribedil at 2 to 16 mg was safe and effective in improving motor symptoms, including akinesia, of fluctuating PD patients. © 2005 Movement Disorder Society

Key words: randomized double-blind study; Parkinson's disease; akinesia; piribedil; intravenous; pharmacokinetics/pharmacodynamics

Piribedil is a dopaminergic agonist used in clinical practice for the long-term treatment of idiopathic Parkinson's disease (PD), at oral dose ranges between 80 and 250 mg/day. It acts on postsynaptic dopamine D_2 receptors (Ki = 1.3×10^{-7} mol/L) and on D_3 receptors (Ki = 2.4×10^{-7} mol/L).[1] Piribedil also displays presynaptic α-2 antagonist properties,[2,3] and pharmacology studies have demonstrated an activity in animal models predictive of Parkinson's disease (PD).[4] In particular, piribedil was able to reverse akinesia and rigidity in 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP)-treated common marmosets.[5] Piribedil has proved effective in the treatment of PD patients when used in monotherapy[6] or in combination with levodopa (L-dopa).[7,8]

Little information is known regarding the concentration–effect relationship of piribedil in PD. After oral dosing, the drug undergoes extensive biotransformation, resulting in low availability.[9] In such cases, an intravenous route (i.v.) is preferred to study the concentration–effect relation on motor symptoms. Preliminary studies have been carried out, essentially focused on tremor.[10] The small sample of PD patients receiving slow i.v. administration of piribedil (6 mg over 1 hour) showed a progressive decrease of resting tremor and effective plasma concentrations ranging

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between 10 and 30 ng/mL. The concentration–effect relationship of piribedil in PD requires elucidation with further investigation of all motor components of PD, including akinesia.

The present phase II study was designed to assess the efficacy of a single i.v. infusion of piribedil on motor deficit in PD patients, particularly its effect in reversing akinesia. The relationship of the motor response to plasma concentration of piribedil was investigated. As the safety of short infusion of piribedil higher than 2 mg was unknown in PD patients, the design consisted of escalating doses administered in separate periods, with patients receiving the next dose of piribedil only if the previous one was well tolerated. Short-duration infusion (15 minutes) was chosen to mimic a piribedil plasma peak that would be more appropriate to treat akinesia in PD patients. Finally, a placebo randomized controlled session was included to detect placebo responders[11] and to balance the study of drug effect on motor symptoms.

PATIENTS AND METHODS

General Methods

The study was conducted according to a randomized double-blind design. It was planned that each patient would be treated with four escalating doses of piribedil versus placebo. Patients attended a total of seven visits, including a selection visit, five 24-hour periods separated by a 4- to 14-day interval, and a final visit. Based on a pharmacokinetic viewpoint and considering the design of the study, 10 patients were included.

The study was approved by the Ethics Committee of Marseille Hospital. All patients provided written informed consent before participation.

Inclusion Criteria

Patients with PD were qualified for inclusion if they presented with motor fluctuations responding to L-dopa. They had to demonstrate, compared with their practically medication-free state, an improvement on the motor examination of the Unified Parkinson's Disease Rating Scale (mUPDRS)[13] in response to 150% of the usual morning dose of L-dopa. Antiparkinsonian treatment had to be effective and unchanged for at least 1 month before inclusion. Patients with uncontrolled high blood pressure or symptomatic postural hypotension, uncontrolled diabetes, renal or hepatic impairment, or any clinically significant abnormality on blood tests and electrocardiography (ECG) could not be included in the study.

Concomitant Treatment

Antiparkinsonian treatments including L-dopa, dopamine agonists, and COMT inhibitors were allowed during the study. Anticholinergics were allowed if initiated more than 1 month before study entry. During each study treatment period, PD treatment was withheld 12 hours before and up to 3 hours after the infusion phase.

Domperidone (60 mg/day, orally) was given starting 3 days before the study and throughout the entire study to prevent potential dopaminergic adverse effects related to piribedil. β-Blockers, neuroleptics, and monoamine oxidase inhibitors (MAOIs) were forbidden during the entire study.

Study Treatment

Study products (piribedil and placebo) and randomization were provided by IRIS-Servier, Courbevoie France. At each period, the patients underwent a single i.v. dose of piribedil in the monomethane sulfonate (MMS) form at 2, 4, 8, or 16 mg. For one randomly assigned period, they received placebo instead. Piribedil was administered at escalating doses, where the next higher dose was administered only if the patient tolerated the previous dose without significant adverse events. If the patient developed signs of intolerance considered minor by the investigator, the treatment sequence was switched toward an intermediate dose sequence (3, 6, and 12 mg instead).

All antiparkinsonian treatments were withheld in the evening, 12 hours before the infusion phase. On the subsequent morning, domperidone was administered 30 minutes before the infusion started. Study treatments started at 8:00 AM on fasting patients. All doses were administered in the same infusion volume and rate for a total duration of 15 minutes. After 3 hours, the patient evaluation was discontinued and the usual antiparkinsonian treatment was resumed.

Investigations

Clinical Response to Treatment.

The antiparkinsonian response was assessed at baseline and 15 minutes, 1 hour, 2 hours, and 3 hours after the start of the infusion, using the mUPDRS. The switch from the *off* to the *on* state was determined (Yes/No) as well as the time of onset. Patients were evaluated and scored by the same investigating physician throughout the study.

The evaluation criteria determined during the motor examination were the mUPDRS (main parameter (min, max; range 0–108), the UPDRS akinesia subscore (items 19, 23, 24, 25, 26, 31; min, max; range 0–24), and the occurrence of the switch from *off* to *on* state.

Safety.

Safety was assessed during the entire periods using clinical inquiry for adverse events and vital signs (supine and standing blood pressure and heart rate). ECG and laboratory tests for hematology and biochemistry were carried out at the inclusion visit and at the final visit.

Pharmacokinetics.

Blood samples were drawn before the start of the infusion, at 7.5 minutes, 15 minutes, 30 minutes, and 1 hour, with blood sampling times randomly assigned between patients and periods up to 12 hours (seven to eight samples per patient per session). In total, 35 ml of blood per session was collected from each patient. Plasma piribedil concentrations were measured using gas chromatography coupled to mass spectrometry detection (GC/MS).[9] The detection limit of the assay was 0.10 ng/mL.

Analysis

All results were presented as mean values ± standard deviation (SD). Descriptive statistical analyses were carried out for pharmacokinetics and pharmacodynamics of piribedil. A model-dependent Bayesian approach using a three-compartment model was carried out to estimate the pharmacokinetic parameters, with the NONMEM (Nonlinear Mixed Effect Models) v5.1 software (GloboMax, Hanover, MD). For concentration–effect relationship, analyses were carried out between pharmacokinetics (plasma concentration, maximal concentration [Cmax], area under the curve [AUC], secondary parameters calculated from the primary parameters, clearance [CL], volumes of distribution of the central, second, and third compartment [V1, V2, and V3], and intercompartmental clearances [Q2 and Q3]) and pharmacodynamics (mUPDRS, UPDRS akinesia subscore, and time of onset of the switch from *off→on*). Safety analysis was carried out on the intention-to-treat population.

RESULTS

Patients

In this study, 10 patients (7 men; 3 women) were included between April 2000 and October 2001. Their mean (± SD) age was 66.2 ± 3.2 years (age range, 61–71 years), the means disease duration was 8.5 ± 5.1 years (range, 1–18 years), and their mean Hoehn and Yahr stage in the *off* condition was 3.1 ± 0.3 (range, 3–4). The mean UPDRS global score at inclusion was 58.6 ± 18.9 (range, 25–86). None of the patients had been exposed previously to piribedil. One patient was treated with a dopamine agonist in monotherapy (ropinirole, 18 mg/day) and nine were on L-dopa medication (mean daily dose, 689 mg; dose range, 300–1,600 mg). In addition to L-dopa, 6 patients received a dopamine agonist (3, bromocriptine; 3, ropinirole; 1, apomorphine), 3 received amantadine, 1 was using an anticholinergic (trihexyphenidyl), and 2 were using entacapone. Laboratory and ECG screening results were within the normal range.

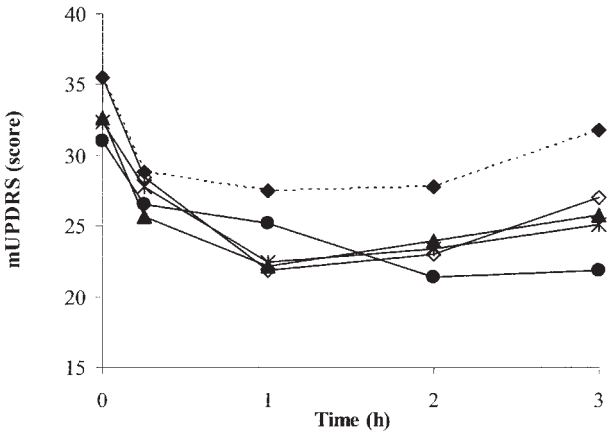

FIG. 1. Clinical response to treatment: evolution of the UPDRS motor score per dose. Data of the 12-mg dose (from 1 patient) is analyzed with that of the 16-mg dose. Placebo (n = 10), filled diamonds; 2 mg (n = 10), open diamonds; 4 mg (n = 9), filled triangles; 8 mg (n = 9), asterisks; 16 mg (n = 8), filled circles.

In total, 8 patients completed all five treatment periods: 7 received all treatment sequences as planned and one received the 12-mg dose instead of 16 mg at the fifth period (the patient presented abdominal pain at the fourth period, considered minor in severity). The 2 patients who withdrew before completion did so for personal reasons unrelated to safety: 1 patient attended two periods (piribedil 2 mg and placebo) and the other attended four periods (all study doses except 16 mg and placebo).

Clinical Response to Treatment

The time course of the mUPDRS (main parameter) per dose is reported in Figure 1. Mean UPDRS motor scores at baseline for each dose, including the placebo, ranged from 31.0 to 35.5. All i.v. doses of piribedil produced an improvement on the motor score within 3 hours of evaluation.

The drug effect was observed at the first evaluation point at 15 minutes, starting with the 2-mg dose. The maximal gain from baseline occurred at 1 hour with this dose (mean gain, 41.1%). The effect on the motor score observed with intermediate doses (4 and 8 mg) was similar. The effect observed with the 16 mg dose was more sustained, with important gains still being observed

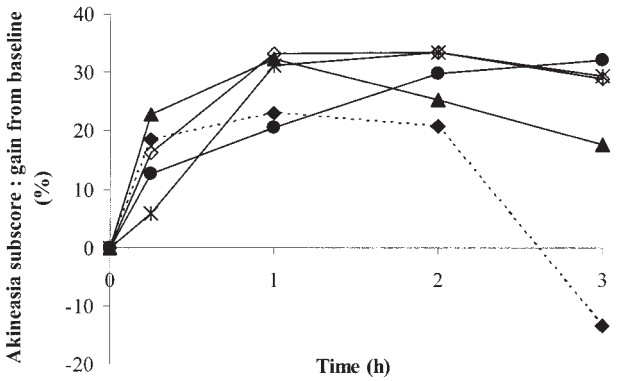

FIG. 2. Improvement of the UPDRS akinesia subscore per dose: gain from baseline (%). Data of the 12-mg dose (from 1 patient) is analyzed with that of the 16-mg dose. Placebo (n = 10), filled diamonds; 2 mg (n = 10), open diamonds; 4 mg (n = 9), filled triangles; 8 mg (n = 9), asterisks; 16 mg (n = 8), filled circles.

at 3 hours (mean gain, 32.6%). Placebo also decreased the mUPDRS score but in contrast, the effect did not last (maximal mean decrease at 1 hour, 23.8%, at 2 hours, 21.8%; and at 3 hours, 14.4%).

The effect of the study drug on the UPDRS akinesia subscore paralleled that of the mUPDRS (Fig. 2). Mean akinesia subscores ranged from 13 to 16 at baseline of each period. After study drug administration, an improvement of the akinesia subscore was observed from the 2-mg dose. Intermediate doses had a similar effect. The magnitude of gain from baseline was maximal at 3 hours with the 16-mg dose of piribedil (mean gain, 32.2%) whereas akinesia subscores were worse than baseline values with placebo (mean gain, −13.5%).

The effect of the study drug on the switch from *off* to *on* state was analyzed (Table 1; Fig. 3). Data from Patient 1 in the fifth period and Patient 2 in the fourth period were discarded from analysis of the switch as not being *off* at baseline. Finally, with the 2-mg dose of piribedil, 7 of 10 patients (70%) turned *on* within a time interval of 15 to 63 minutes after the infusion start. The switch rate and time interval for switch were not different with higher doses.

TABLE 1. *Clinical response to treatment: switch from* off→on *state per dose*

Parameter	Placebo	Dose (mg)			
		2	4	8	16
Total n	10	10	8[a]	8	7[a]
Switch *off→on,* n (%)	3 (30)	7 (70)	4 (50)	5 (55.6)	5 (71.4)
Mean onset (min)	32.7	48.6	52.8	30.6	39.4
Range (min)	18–60	15–63	20–120	20–47	19–53

[a]Patient 1/period 5 and Patient 2/period 4 were not *off* at baseline, and thus were not included in this analysis.

On a case-by-case analysis of patient status, 8 of 10 patients (80%) were considered responders to piribedil (Patients 1–6, 8, and 9; Fig. 3). At all doses and times analyzed, the maximal mUPDRS score improvement was greater than 70% in 2 patients (Patients 3 and 8), between 50 and 70% in 3 patients (Patients 4, 6, and 9) and between 30 and 50% in 3 patients (Patients 1, 2, and 5). Of 10 participants, 2 patients (Patients 7 and 10), presenting with a less than 30% improvement in the mUPDRS regardless of dose or evaluation time, were considered nonresponders to treatment. Finally, 3 patients (Patients 2, 3, and 10) were found placebo responders.

Safety

Short infusion of piribedil up to the 16-mg dose was well tolerated in this study. All patients complied with the escalating design except 1 who switched to an intermediate last dose (12 mg). In total, seven adverse events possibly related to the treatment were reported in 5 patients during study periods: one adverse event was reported with placebo (headache); three were reported in 2 patients with the 16-mg dose (flush, nausea, and vomiting); one was reported with the 12-mg dose (abdominal pain); and two with the 8-mg dose (somnolence and abdominal pain). They were considered mild to moderate. All resolved rapidly and spontaneously. No clinically significant changes in cardiac parameters or laboratory tests were reported at the final visit.

Pharmacokinetics: Concentration Effect

Pharmacokinetic parameters are presented in Table 2. Piribedil kinetics were linear from 2 to 16 mg. The pharmacokinetic results were in agreement with those described previously.[9]

No direct relationship was established between piribedil plasma concentrations and the evolution of patient UPDRS motor scores/akinesia subscores. Plasma concentration threshold inducing the patient switch *off→on* could not be determined. There was no relationship between secondary pharmacokinetic parameters (Cmax, and exposure up to the time of switch) and switch onset. Finally, no pharmacokinetics/pharmacodynamics modeling could be applied in this study. The maximal effect on mUPDRS was reached starting from the 2-mg dose, with mean corresponding plasma levels of 23 ng/ml.

DISCUSSION

The study provided evidence that intravenous infusion of piribedil starting from a 2-mg dose was effective in reducing the motor deficit and in reversing *off* state in PD patients. The maximal motor improvement occurred

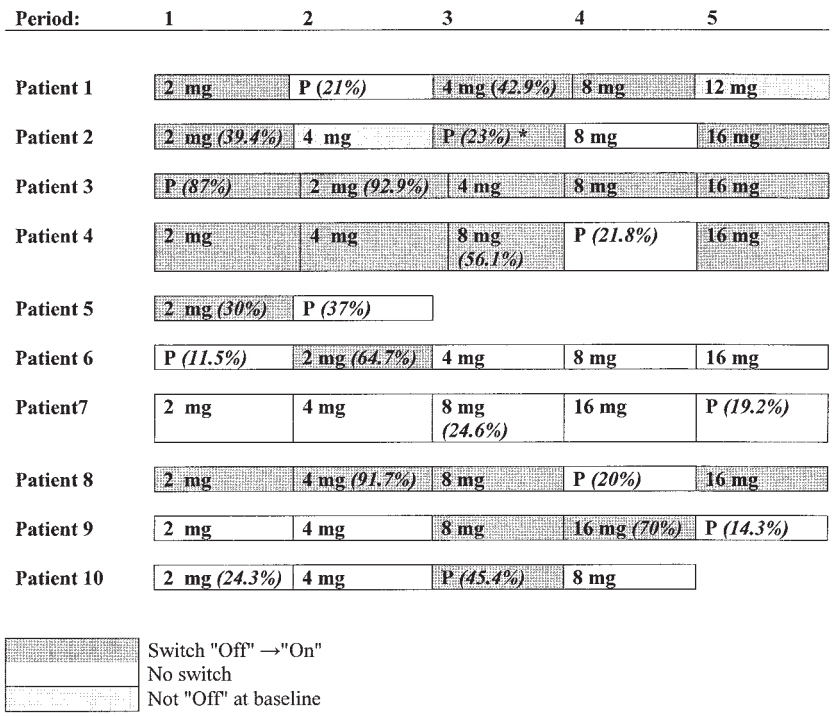

FIG. 3. Clinical response to treatment: patient status per period. The maximal improvement (% from baseline) of the mUPDRS score is indicated (in parentheses) for the most effective dose of piribedil and for placebo (P). Patient 2 showed a switch from *off* to *on* state, despite maximal improvement in the mUPDRS of only 23%, and was considered a placebo responder.

within the time interval from 15 minutes to 1 hour. The doses were equally effective, although the effect was more sustained with the highest dose (16 mg). In addition to its effect on resting tremor shown in previous studies,[10,14] piribedil administered intravenously was effective in treating the motor deficit in fluctuating PD patients. Short infusion of piribedil up to the 16-mg dose was well tolerated. Cardiovascular assessments remained stable throughout the study. Only six related adverse events were reported with piribedil, confirming that concomitant treatment with domperidone was effective in preventing the dopaminergic side effects.[4] Piribedil kinetics were linear from 2 to 16 mg. No direct relationship could be determined, however, between plasma concentrations and patient clinical status and no pharmacokinetics/pharmacodynamics model could be applied in this study.

Dose Range and Time Interval

The design of this exploratory study consisted of a fixed dose range as compliance and tolerance to the study doses were considered a priority. As a result, the lowest dose of piribedil (2 mg) was safe and already pharmacologically active in patients. Intermediate and the highest doses (16 mg) were also effective and well tolerated in the study population. The results suggest that wider dose ranges with doses even higher than 16 mg might be tested to assess further the efficacy of intravenous piribedil in PD patients.

The patient motor status improved from the first evaluation time point (15 minutes), although the maximal benefit on motor deficit was present on average at the 1-hour point after the infusion (2-mg dose). In addition, the time interval for improvement of UPDRS motor score/akinesia subscore was consistent with the onset of switch from *off* to *on* state. Suggestively, the maximal effect of piribedil may have occurred earlier than at 1 hour during the interval from 15 minutes to 1 hour; however, too many blood collections and safety assess-

TABLE 2. *Pharmacokinetic parameters of piribedil after a 15-minute intravenous infusion*

	Dose (mg)			
Piribedil infusion	2	4	8	16
$T_{1/2,z}$ (hr)				
Mean (SD)	11.9 (9.6)	11.8 (9.9)	11.8 (10.7)	12.9 (11.5)
Range	10.8–14.3	10.8–14.3	10.5–14.3	10.9–15.1
AUC_∞ (hr* μg/L)				
Mean (SD)	23.9 (22.7)	47.1 (23.8)	96.7 (30.7)	253.4 (32.1)
Range	17.3–37.8	37.8–71.7	70.2–157.6	150.0–266.3
Cmax (μg/L)				
Mean (SD)	23.2 (51.8)	46.5 (44.6)	86.0 (60.7)	222.3 (46.8)
Range	9.8–46.8	27.9–85.8	39.0–193.0	84.3–374.0

$T_{1/2}$, half life; Cmax, maximal concentration, AUC, area under the curve.

ments were carried out and thus prevented any additional clinical evaluation on patients during that interval. The patient motor improvement was kept stable up to 3 hours. At this final evaluation point, the difference in gain of the UPDRS akinesia subscore was maximal with the 16-mg dose compared with that with placebo (up to a mean 45.7% difference). Finally, the finding of a rapid and sustained activity of 2 to 16 mg of intravenous piribedil is supportive of the need for dopaminergic agents that provide maintained dopamine stimulation to limit motor fluctuations in PD patients.

Patient Treatment Response

The mean maximal improvement achieved in the mUPDRS was 41.1% (1 hour after 2-mg piribedil). This effect is superior in magnitude to the 30% cut-off recommended in clinical trials with dopamine agonists for defining an improvement or a deterioration of the mUPDRS from baseline.[15]

The changes in motor scores expressed as a mean of the global population did not actually reflect what happened during the evaluation periods. When they received piribedil infusion, most patients experienced a nearly normal motor response that was noticed both by the patient and the evaluating physician. As a result, 8 patients (80%) were responders to piribedil: 2 showed an mUPDRS improvement of greater than 70%; 3 had an improvement ranging from 50 and 70%; and 3 had an improvement between 30 and 50%. Two patients were considered non-responders. They were similar to the others with regard to disease duration, severity of the disease, or clinical response to L-dopa and they did not present any side effects with piribedil. Nonresponder patients have been mentioned in the same proportion in other studies with a dopamine agonist infusion.[16–18]

The finding of two placebo-responder patients (>30% of patients) in this study was not surprising. The mean maximal mUPDRS improvement with placebo was 23.8% (range, 5–87%), as described previously in similar experimental conditions with fluctuating PD patients.[12] There is ample evidence for a strong placebo effect in PD.[11,19] Positron emission tomography (PET) studies carried out in PD patients indicated that the placebo administration is associated with the release of dopamine in the striatum.[20] It has been suggested that the placebo effect might be related to reward (clinical benefit) mechanisms.[19]

Concentration–Effect Relationship

Plasma concentrations of piribedil increased proportionally to the administered intravenous dose. In contrast, the motor improvement was maximal starting from the lowest dose. Subsequently, the study failed to find a correlation between plasma level of piribedil and motor improvement (mUPDRS) or switch *off→on* after infusion. The effect of piribedil on motor status was not related directly to its plasma levels, nor could the variability in time to obtain maximal motor improvement be explained solely by pharmacokinetic parameters. It is suggested that in fluctuating PD patients the motor response to piribedil depends not only on pharmacokinetics factors, i.e., delivery of the study drug, but also has a pharmacodynamic basis. Finally, the mean plasma level of piribedil (23 ng/mL) corresponding to a maximal improvement of the motor score was similar to the levels found to alleviate resting tremor (10–30 ng/mL) in PD patients.[10]

In conclusion, administration of a short infusion of piribedil at 2 to 16 mg was well tolerated, effective in reducing motor deficit, and effective in reversing *off* state of parkinsonian patients. Improvement of patient motor status was observed shortly after piribedil infusion. The effect of piribedil on motor deficit including akinesia was maintained after 3 hours during the final evaluation.

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