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Brief Report

# A Randomized, Double-Blind Study of a Skin Patch of a Dopaminergic Agonist, Piribedil, in Parkinson's Disease

*Jean-Louis Montastruc, MD, PhD, †Marc Ziegler, MD, *Olivier Rascol, MD, PhD, and ‡Muriel Malbezin, MD, on Behalf of the Study Group

**Service de Pharmacologie Clinique, Faculté de Médecine, Hôpitaux de Toulouse, Toulouse, France; †Unité James Parkinson, Hôpital Léopold Bellan, Paris, France; and ‡Centre d'Investigation Clinique (CIC) du Centre Hospitalier Universitaire de Toulouse, Toulouse, France*

**Summary:** This randomized, double-blind trial was designed to evaluate the efficacy of a transdermal system of piribedil on the motor symptoms of Parkinson's disease during 3 weeks of treatment administered to three different groups: placebo, one piribedil patch (1 PP), and two (2 PP) piribedil patches. Twenty-seven patients with idiopathic Parkinson's disease, treated with L-dopa but not sufficiently controlled, were included in this trial. The test treatment did not demonstrate any clinical efficacy on either the main end point (Unified Parkinson's Disease Rating Scale motor score) or the secondary end points (rigidity, bradykinesia, postural, and resting tremor scores). The main adverse events were nausea (11%), vomiting (7.4%), and malaise (7.4%) mainly observed in the placebo group (four of seven patients). The local acceptability of the transdermal system was good. Plasma piribedil concentrations at the end of treatment were 6.74 ± 1.10 and 9.31 ± 3.33 ng/mL in the 1 PP and 2 PP groups, respectively. These plasma levels could account for the lack of clinical efficacy, because a previous pharmacokinetics-PD study conducted in parkinsonian patients and treated with the intravenous route demonstrated that the critical limits of activity on tremor were between 10 and 30 ng/mL. **Key Words:** Piribedil—Parkinson's disease—Transdermal patch.

The motor symptoms of Parkinson's disease are mainly explained by dopaminergic nigrostriatal neuron degeneration.[1] L-dopa is converted to dopamine and is thus effective in treating the motor symptoms of Parkinson's disease. Although recognized as the standard therapy, its long-term use is often associated with side effects such as fluctuation of activity, dyskinesia, and psychiatric symptoms.[2,3] Dopaminergic agonists such as bromocriptine,[4] lisuride,[5,6] pergolide,[7,8] and apomorphine[9] also act on the motor deficits of parkinsonian patients. Although not as effective as L-dopa, they have the advantage of fewer side effects. These drugs stimulate central dopaminergic D2 receptors. Some also stimulate D1 receptors.[10]

Piribedil is a dopaminergic agonist active on all central (nigrostriatal, mesocortical, tubero-infundibular, and mesolimbic) dopaminergic pathways.[11,12] It acts essentially by stimulating post-synaptic D2 receptors. Animal pharmacology studies demonstrated activity in both psychopharmacologic tests and models predictive of Parkinson's disease.[13] In particular, in the marmoset monkey, piribedil is able to improve the signs induced by the neurotoxin MPTP (1 methyl-4-phenyl-1,2,3,6 tetrahydropyridine).[14] Clinical studies with piribedil administered orally[15] or intravenously[16] have validated its activity on parkinsonian symptoms. However, after oral dosing, the drug undergoes a major hepatic first-pass effect. Bioavailability is consequently low, less than 10%.[17] To minimize the hepatic first-pass effect and achieve stable effective plasma concentrations, a 50-mg transdermal patch formulation was developed.

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Address correspondence and reprint requests to Jean-Louis Montastruc, MD, PhD, Service de Pharmacologie Clinique, Faculté de Médecine, Hôpitaux de Toulouse, 37 allées Jules Guesde, 31073 Toulouse cedex, France.

The aim of this phase II study was to evaluate the pharmacologic activity of one and two transdermal patches of piribedil in combination with L-dopa on the motor symptoms of Parkinson's disease.

## METHODS

### General Methods

The study was conducted according to a randomized, double-blind design versus placebo in three parallel groups. Each group was treated with two transdermal patches: two piribedil patches (2 PP), two placebo patches (placebo), or one piribedil patch plus one placebo patch (1 PP). Clinical stability and patch adhesion were tested in a 2–4-week selection period. At inclusion, patients were randomized to treatment for 3 weeks. The four study visits took place at selection, inclusion, and after treatment for 1 and 3 weeks.

### Ethics

The study was approved by the Ethics Committee of Cochin Hospital, Paris. Patients freely gave their informed written consent as required by the French Huriet Law.

### Inclusion Criteria

Men and women aged 35–80 years with idiopathic Hoehn & Yahr stage I–III Parkinson's disease were eligible for inclusion if their history did not exceed 10 years and they had been receiving L-dopa for at least 6 months at a dosage of $\leqslant$800 mg per day divided into $\leqslant$6 doses. Further criteria were clinical stability (defined as an L-dopa regime unchanged for at least 1 month before inclusion and unchanged motor status and mood over the previous 2 weeks in terms of both Hoehn & Yahr staging and investigator impression) and an inadequate clinical response to current therapy as shown by persistent parkinsonian symptoms. Exclusion criteria were neurodegenerative disorders, other nonidiopathic Parkinson's disease, systemic diseases (as revealed by medical or laboratory examination), and patients whose placebo patches failed to stick during the selection period.

### Laboratory Investigations

A routine hematologic and biologic examination was performed before and at the end of the study. Because the investigations were performed by different laboratories, results were standardized to each laboratory's normal range.[18] Assuming X = found value and $X_L$ and $X_U$ = laboratory lower and upper limits of normal, the standardized variable (Z) was calculated as follows : $Z = (X - X_L)/(X_U - X_L)$. The standardized parameter value was calculated using a reference laboratory standard range $(X_{Lref} - X_{uref})$, that is, $X_{Std} = Z\,(X_{Uref} - X_{Lref}) + X_{Lref}$. The reference laboratory chosen was that which had analyzed blood samples from the greatest number of patients.

### Concomitant Treatments

Patients treated with dopamine agonists were only eligible if these drugs had been withdrawn at least 1 month beforehand. The same treatments were also forbidden during the study. Anticholinergics and selegiline were only permitted if initiated more than 1 month previously and if given at the same dosage throughout the study. Centrally acting antihypertensives, neuroleptics, barbiturates, and some antidepressants (MAOIs, amineptine, fluoxetine, medifoxamine, and nortriptyline) had to have been withdrawn at least 1 month before inclusion and were forbidden during the study. Other antidepressants could only be administered if initiated at least 2 months before inclusion and nonbarbiturate anxiolytics and hypnotics at least 1 month before inclusion.

### Study Treatment

The transdermal patch was a 30-$cm^2$ matrix containing 50 mg micronized piribedil and an adhesive strip. The placebo was of matching appearance. Two patches were applied daily at the same time on the dorsal surface of the arm, one below the other, on alternating arms at each application. If a patch became unstuck over more than half its area before the scheduled removal time, a replacement patch was applied to the same site. During the selection period, patients were treated for 7 days with two placebo patches. At inclusion, they were randomized into three parallel treatment groups to receive two patches: two piribedil patches (2 PP), two placebo patches, or one piribedil and one placebo patch (1 PP).

### Investigations

#### Efficacy

Clinical efficacy was determined using the Unified Parkinson's Disease Rating Scale (UPDRS) at each visit.[19] The Hoehn and Yahr scale (scored 0–5), measured at the selection and inclusion visits, was used to document clinical stability and hence eligibility. The primary measure was the UPDRS motor score. The secondary measures were four UPDRS subscores determined during the motor examination (rigidity: item 22, bradykinesia: items 23–27, rest tremor: item 20, postural tremor: item 21), dopaminergic score (items 20 and 22–27), and the Schwab & England activities of daily living index (degree of independence). The daily L-dopa dose was checked at each visit. Therapeutic activity was as-

sessed using Week 0 scores and numerical values as baseline. Patient and investigator gave their overall impressions of efficacy at the final visit.

### Patch Adhesion and Skin Tolerance

Patch adhesion was evaluated during the selection period and later during the active treatment periods by the frequency and degree of detachment: total, >50%, <50%. Patch detachment was recorded daily by the patient in a diary issued at each treatment period. Patients with frequent early patch detachment >50% during the selection period were ineligible for inclusion. Local tolerance was determined at each visit by the investigator after removing the patches. Signs were scored as follows: erythema, edema, and desquamation = 0–3; erosion or ulceration = 0–1; and fissuring or chapping = presence/absence. These parameters were measured immediately, 30 minutes, and 1 hour after patch removal in the areas covered by the matrix and adhesive strip.

### Adverse Events

Clinical examination, including measurement of blood pressure (supine and standing) and heart rate, was performed at each visit. Adverse events were investigated by indirect questioning. Patient and investigator gave their overall impressions of acceptability at the final visit.

### Compliance

Compliance was calculated at each treatment visit by the ratio (percentage, mean ± standard deviation [SD]) of actual versus prescribed number of patches applied, excluding replacement patches.

### Plasma Piribedil Assay

Plasma piribedil concentrations were determined by gas chromatography mass spectrometry (GC-MS)[20] at Week 0 to control for background at 0 dose, then at Week 1 and Week 3 just after patch removal. The limit of quantification was 0.1 ng/mL. Reproducibility at this level was 10%.

**TABLE 1.** *Demographic data of the 27 patients included, inclusion diagnosis and disease duration per treatment group (mean values ± standard deviation)*

| Demographic data | Placebo (n = 8) | 1 PP (n = 10) | 2 PP (n = 9) |
|---|---|---|---|
| Sex (% men) | 62.5 | 30.0 | 66.7 |
| Age (yrs) | 70.1 (6.6) | 66.0 (10.8) | 68.6 (6.9) |
| Clinical symptoms | | | |
| Akineto-hypertonic (%) | 0 | 0 | 33.3 |
| Tremor (%) | 0 | 10.0 | 11.1 |
| Akinesia + hypertonia + tremor (%) | 100.0 | 90.0 | 55.6 |
| Hoehn and Yahr stage (medians-range) | 2.75 (1.5–3) | 2.75 (1.5–3) | 2.75 (1.5–3) |
| Mean daily levodopa (mg) | 306 (182) | 360 (163) | 560 (182) |
| Duration (yrs) | 5.1 (2.9) | 4.8 (2.8) | 6.9 (2.6) |

Placebo, two placebo patches; 1 PP, one piribedil patch + one placebo patch; 2 PP, two piribedil patches.

### Statistics

All results were presented as mean values ± standard deviation. A 5% significance level was used in all tests. For efficacy, given the small number of patients per group, the data were tested for dose-effect rather than for significant difference versus placebo using analysis of variance of Week 3–Week 0 values in protocol-compliant patients. For hemodynamics, groups were compared using one-way analysis of variance of the differences between the last value on treatment versus baseline. For acceptability, end point analysis was performed in the intention-to-treat population (end point value on treatment). The incidence of each adverse event was calculated per treatment group and in the overall population and was determined by the ratio of the number of patients included per group or those in the entire included population displaying the same event.

## RESULTS

### Patients

Twenty-seven patients (14 men, 13 women; aged 68.1 ± 8.4 years, range 44–84 yrs) were included, eight in the placebo group, 10 in the 1 PP group, and nine in the 2 PP group. One patient was selected but not included because of poor skin adhesion. Mean duration of Parkinson's disease was 5.6 years (range 2–10 yrs). Mode of onset was tremor in 52%. The median Hoehn and Yahr inclusion score was 2.5 (range 1.5–3). Mean daily use of L-dopa was 411 ± 201 mg (range 150–800 mg) in three to five divided doses. Table 1 shows the demographic data, inclusion diagnosis, and disease duration per treatment group. Laboratory screening results were normal.

### Efficacy

Efficacy was analyzed in the protocol-compliant population: n = 5 in the placebo group, and n = 8 in both the 1 PP and 2 PP groups. Six patients were excluded because of major protocol violation (n = 4) and drop-out (n = 2).

No significant changes in motor score (primary measure) were observed in any group (Table 2). Week 3–Week 1 differences in overall motor scores were not significantly different. The dose-effect relationship observed between the different doses was a regression line

**TABLE 2.** *Clinical parameter response per treatment group (mean ± standard deviation) (*N = *21)*

| | Placebo (n = 5) | 1 PP (n = 8) | 2 PP (n = 8) |
|---|---|---|---|
| UPDRS motor score | | | |
| Week 0 | 24.8 ± 7.0 | 22.4 ± 6.3 | 24.2 ± 6.9 |
| Week 1 | 23.0 ± 8.5 | 20.1 ± 6.1 | 22.6 ± 7.6 |
| Week 3 | 21.0 ± 8.3 | 17.5 ± 8.3 | 21.6 ± 7.1 |
| Week 3−Week 0 difference | −3.8 ± 5.0 | −4.9 ± 6.6 | −2.6 ± 4.3 |
| 95% CI | (−10.0; 2.4) | (−10.4; 0.6) | (−6.2; 1.0) |
| dose effect | | 0.637 | |
| Postural tremor | | | |
| Week 0 | 1.0 ± 1.0 | 0.7 ± 1.0 | 0.5 ± 0.8 |
| Week 1 | 1.0 ± 1.0 | 0.7 ± 0.7 | 0.5 ± 0.8 |
| Week 3 | 1.0 ± 1.0 | 0.7 ± 0.7 | 0.5 ± 0.8 |
| Week 3−Week 0 difference | 0.0 ± 0.0 | 0.0 ± 0.5 | 0.0 ± 0.0 |
| 95% CI | — | (−0.4; 0.4) | — |
| dose effect | | — | |
| Bradykinesia | | | |
| Week 0 | 9.8 ± 3.6 | 10.5 ± 2.6 | 10.4 ± 3.7 |
| Week 1 | 9.0 ± 3.8 | 8.9 ± 2.1 | 9.5 ± 4.6 |
| Week 3 | 7.8 ± 4.6 | 7.2 ± 3.8 | 9.1 ± 3.3 |
| Week 3−Week 0 difference | −2.0 ± 2.8 | −3.2 ± 4.1 | −1.2 ± 2.1 |
| 95% CI | (−5.5; 1.5) | (−6.7; 0.2) | (−3.0; 0.5) |
| dose effect | | 0.6 | |
| Rest tremor | | | |
| Week 0 | 3.2 ± 1.6 | 2.7 ± 2.2 | 2.7 ± 2.9 |
| Week 1 | 2.6 ± 1.9 | 2.5 ± 2.4 | 2.6 ± 2.6 |
| Week 3 | 2.2 ± 1.8 | 2.4 ± 2.3 | 2.5 ± 2.7 |
| Week 3−Week 0 difference | −1.0 ± 1.0 | −0.4 ± 0.7 | −0.2 ± 0.9 |
| 95% CI | (−2.2; 0.21) | (−1.0; 0.2) | (−1.0; 0.5) |
| dose effect | | 0.16 | |
| Rigidity | | | |
| Week 0 | 4.2 ± 2.7 | 1.9 ± 0.6 | 2.4 ± 1.9 |
| Week 1 | 4.0 ± 2.8 | 1.4 ± 0.7 | 2.2 ± 1.9 |
| Week 3 | 3.8 ± 2.5 | 1.0 ± 0.8 | 1.5 ± 1.7 |
| Week 3−Week 0 difference | −0.4 ± 0.9 | −0.9 ± 0.8 | −0.9 ± 1.0 |
| 95% CI | (−1.5; 0.7) | (−1.6; −0.2) | (−1.7; 0.1) |
| dose effect | | 0.4 | |
| Dopaminergic status | | | |
| Week 0 | 17.2 ± 6.9 | 15.1 ± 4.1 | 15.5 ± 4.9 |
| Week 1 | 15.6 ± 8.0 | 12.7 ± 3.7 | 14.4 ± 5.3 |
| Week 3 | 13.8 ± 8.1 | 10.6 ± 5.5 | 13.1 ± 4.2 |
| Week 3−Week 0 difference | −3.4 ± 4.4 | −4.5 ± 5.3 | −2.4 ± 3.4 |
| 95% CI | (−8.9; 2.1) | (−9.0; −0.03) | (−5.2; 0.4) |
| dose effect | | 0.6 | |
| Schwab & England scale (%) | | | |
| Week 0 | 78.0 ± 4.5 | 77.5 ± 8.9 | 71.2 ± 13.6 |
| Week 1 | 78.0 ± 4.5 | 77.5 ± 8.9 | 72.5 ± 12.8 |
| Week 3 | 78.0 ± 4.5 | 78.7 ± 9.9 | 73.7 ± 13.0 |
| Week 3−Week 0 difference | 0.0 ± 7.1 | 1.2 ± 3.5 | 2.5 ± 8.9 |
| 95% CI | (−8.8; 8.8) | (−1.7; 4.2) | (−4.9; 9.9) |
| dose effect | | 0.5 | |

of 0 slope. The score thus showed no evidence of linear dose effect. The placebo effect was the same as that on both doses of active treatment. Secondary measure results were identical to those for the primary measure, that is, they confirmed the absence of a linear dose effect (Table 2). In the placebo, 1 PP, and 2 PP groups, the global evaluation of treatment by investigators was moderate or good for 57.1%, 77.8%, and 88.9% of them, respectively ($p = 0.153$).

### Patch Adhesion

Patch adhesion was good in all patients, notably improving after treatment for 1 week. One selected patient was not included as a result of poor patch adhesion during the selection period. Maximal (full) adhesion of the upper patch increased from 74–96% of applications from Week 0 to Week 3. Corresponding figures for the lower patch were 73–100% (Table 3).

Local skin tolerance was good overall in all patients. It was considered excellent by 73% of patients, whereas 85% of investigators observed no adverse local skin event. However, one patient in the 1 PP group discontinued treatment at Week 1 because of local intolerance to the previous two applications. One skin reaction with edema and induration was observed in relation to the lower patch with redness over the application site and a burning sensation. All these signs disappeared in a few days.

Mild and transient matrix-related erythema was observed in 18.2%, 3.4%, and 9.2% of applications in the placebo, 1 PP, and 2 PP groups, respectively. The corresponding figures for mild to moderate adhesive strip-related erythema were 23%, 27%, and 26%, respectively. Occasional moderate matrix-related edema (two of 40 applications) was observed in the 1 PP group.

### Adverse Events

Six patients reported 10 adverse events. One placebo patient dropped out because of malaise, nausea, and vomiting rated as *moderate* and *probably treatment-related.*[21] Symptoms fully regressed after treatment withdrawal. In the overall population, the most frequent events were nausea (11% of patients), vomiting (7%), and malaise (7%). The investigators rated 70% of these events as moderate. All regressed spontaneously. They were most frequent in the placebo group (50% of events) and least frequent in the 2 PP group (22%). A total of 92% of patients rated treatment acceptability excellent, and 98% of investigators observed no treatment-related adverse events. Clinical examination was normal at each visit in the majority of patients: 85% at Week 0 and 92% at Week 3. No emergent events were observed during the 3 treatment weeks. There were no statistically significant intergroup differences in hemodynamic variables (heart rate and blood pressure) before and after treatment and no significant change occurred during the trial.

### Compliance

Treatment compliance was 105% ± 8.2 (mean ± SD) at Week 1 and 99% ± 5.4 at Week 3. Compliance exceeded 100% at Week 1 because six patients used two extra patches in addition to the number prescribed.

**TABLE 3.** *Transdermal patch adhesion (% applications)*

| | Upper patch (% adhesion) | | | | Lower patch (% adhesion) | | | |
|---|---|---|---|---|---|---|---|---|
| | 100% | >50% | <50% | 0% | 100% | >50% | <50% | 0% |
| Week 0 | 74.1 | 18.5 | 3.7 | 3.7 | 73.1 | 19.2 | 3.8 | 7.7 |
| Week 1 | 96.2 | 3.8 | 0 | 0 | 100 | 0 | 0 | 0 |
| Week 3 | 96.0 | 0 | 4.0 | 0 | 100 | 0 | 0 | 0 |

### Plasma Piribedil Concentrations

Figure 1 shows plasma levels of piribedil. There was a high degree of consistency in plasma piribedil levels using the transdermal route of administration, in contrast to oral dosing[16] where there are marked interindividual variations. Increases in plasma levels between Week 1 and Week 3 of 68% in the 1 PP group and 19% in the 2 PP group were also observed, indicating that absorption was saturated at the study dose.

## DISCUSSION

The main reason for developing a transdermal patch for piribedil was pharmacokinetic. The aims were not only to avoid the hepatic first-pass effect observed after oral dosing and hence improve the bioavailability of piribedil, but also to achieve stable plasma levels over 24 hours. This is especially important in a condition such as Parkinson's disease, in which it is well-recognized that the fluctuations in activity seen on long-term L-dopa therapy can be partially improved by multiple divided dosing or by using sustained-release formulations.[22–24] These symptoms can also be reduced by co-administration of drugs acting directly on the dopaminergic receptor and with a long half-life, or by drugs in a dosage form giving highly stable plasma levels.[25]

The present study was performed in a relatively small number of patients. No pharmacologic effect was demonstrated in any score whether for motor function, postural or rest tremor, mental state, behavior and mood, rigidity, or dopaminergic status.

The most frequent adverse events were nausea, vomiting, and malaise, that is, those already encountered in

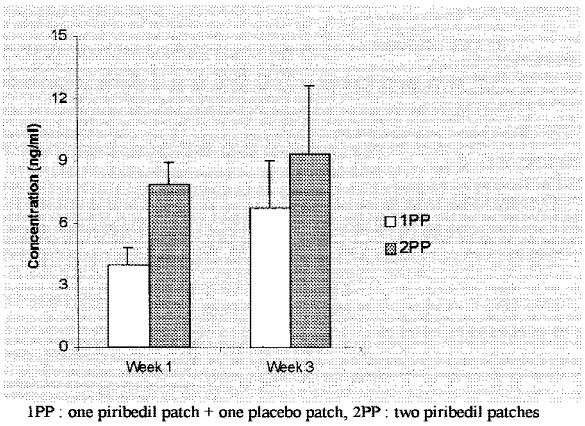


**FIG. 1.** Plasma piribedil concentrations.

clinical trials with piribedil, in particular the gastrointestinal events which are the most frequent.[15,16]

The clinical inefficacy of the patch in this study may be explained first by a too-short treatment course (3 weeks) for an advanced stage of disease (complete Parkinson's disease in 81.5% of patients), and secondly and more importantly by insufficient plasma piribedil concentrations. Plasma piribedil levels at Week 1 were below 10 ng/mL. A pharmacodynamic study in patients with Parkinson's disease receiving intravenous piribedil showed that a pharmacologic effect, in particular against tremor, needs a plasma concentration range between 10 and 30 ng/mL.[16]

Although this dosage form has several advantages (local tolerance, good patch adhesion, and low interindividual variability in plasma piribedil concentrations), its development has been stopped. The improved bioavailability of patch-delivered piribedil would require an increase in adhesive area (currently 30 $cm^2$), which would be difficult to put into practice. However, the use of patches to deliver drugs in Parkinson's disease remains an exciting prospect. Pharmaceutical research in this area is also concentrating on the development of new dopaminergic drugs as well as drugs acting on non-dopaminergic pathways. It is also experimenting with new delivery forms for older treatments providing sustained release of the active substance, for example, intraduodenal, intravenous, or intracerebroventricular infusion, together with transcutaneous administration.[25,26]

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