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An Appraisal of the Antiparkinsonian Activity of Piribedil in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-Treated Common Marmosets

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Summary: The D2 dopamine agonist piribedil is not widely used in the treatment of Parkinson's disease because it was thought to be effective mainly on parkinsonian tremor and to produce a high incidence of peripheral side effects, particular nausea. In this study, we used 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates to reevaluate the antiparkinsonian ability of piribedil after its oral administration in the presence or absence of domperidone pretreatment. Adult common marmosets (*Callithrix jacchus*) were treated with the nigral toxin MPTP to induce a parkinsonian syndrome characterised primarily by bradykinesia and other motor deficits. Oral administration of a solution of piribedil [1-(3,4-methylenedioxybenzyl)-4-(2-pyrimidinyl)piperazine] produced a dose-related reversal of all MPTP locomotor and behavioural deficits. However, this effect was short lived and associated with unwanted effects, particular nausea and retching, which clearly hindered locomotion. In contrast, after pretreatment with the peripheral dopamine antagonist domperidone, administration of piribedil did not induce nausea or retching in MPTP-treated marmosets. In these animals, piribedil caused a more marked and longer lasting enhancement of locomotor activity and a further reduction in behavioural deficits than that observed after administration of piribedil alone. In addition, piribedil induced increased vigilance and awareness. These data show that piribedil can reverse akinesia and rigidity in MPTP-treated primates. In addition, they show the drug to be effective without peripheral side effects when used in conjunction with domperidone. These data indicate that piribedil should be an effective monotherapy for Parkinson's disease. **Key Words:** Piribedil—Parkinson's disease—1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine—Common marmosets—Locomotor activity—Behavioural deficits.

Piribedil [1-(3,4-methylenedioxybenzyl)-4-(2-pyrimidinyl)piperazine; Trivastal) is a centrally acting dopamine agonist that is structurally distinct from other classes of dopamine-agonist drugs (1–3). The nature of the interaction of piribedil with D1- and D2-like dopamine receptors has remained a matter of debate. Piribedil displaces ligands that identify D2-like receptors from striatal membranes (4). Piribedil itself does not stimulate striatal adenylate cyclase activity, although its catechol metabolite S 584 is effective in this respect (5). So its actions may reflect both D1- and D2-like receptor stimulation. As expected, in normal rats, piribedil induces dose-dependent stereotyped behaviour characterised by sniffing, abnormal head and limb movements, gnawing, and biting, together with an increase in locomotor activity (6,7). Similarly, in rats with an unilateral 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal pathway, piribedil induces contralateral rotation indicative of a direct dopamine-agonist action (6–9). In addition, in primates with an unilateral radiofrequency lesion of the ventromedial tegmental area causing tremor and hypokinesia of the contralateral extremities, piribedil mimicked the actions of L-Dopa in the relief of tremor and in producing dyskinesias (1). Consequently, it was concluded that piribedil would be useful in the treatment of Parkinson's disease (1,6).

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Early studies showed piribedil to improve several features of idiopathic Parkinson's disease, but in most investigations, improvement in tremor was the most marked effect observed (10–12). In addition, the incidence of adverse effects, such as nausea, confusion, and drowsiness was high. In conjunction with L-Dopa, piribedil produced an improvement of total parkinsonian disability, which was significantly greater than that with piribedil alone (13); again there was a high incidence of adverse effects (12). Consequently, piribedil received limited acceptance either as a monotherapy or as adjunct therapy for the treatment of Parkinson's disease.

The limited effect of piribedil in Parkinson's disease was surprising considering its pharmacologic actions. However, the drug was assessed clinically in an era before the introduction of domperidone to control peripheral side effects of dopamine agonists. A more recent study in humans has shown that administration of piribedil with domperidone was markedly effective against tremor but less so against other symptoms of the disease (20). Consequently, we set out to reassess the antiparkinsonian activity of piribedil. We used the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmoset, a model of Parkinson's disease, not available when the drug was being developed, and which is so far entirely predictive of therapeutic action in humans. The antiparkinsonian activity of piribedil has been assessed with and without pretreatment with domperidone.

METHODS

Animals

Four common marmosets (weighing 350–400 g, aged 3–5 years, and of either sex) were used in the studies. Animals were housed alone under standard conditions at a temperature of 25–27°C and 50% relative humidity, using a 12-h light–dark cycle (light on from 8.00–20.00 h). Animals had free access to food and water. During MPTP treatment and throughout the following weeks, the animals were hand-fed with Mazuri marmoset jelly and fresh fruit puree until they were able to maintain themselves.

Administration of MPTP

Animals were treated with MPTP in doses of 2 mg/kg subcutaneously daily for 5 days or until obvious parkinsonism developed. The cumulative doses administered ranged between 8 and 12 mg/kg. After MPTP treatment, the animals made a gradual recovery from the acute effects of MPTP over some weeks. However, before behavioural testing, ~6–8 weeks after MPTP administration, all animals showed a marked reduction in basal locomotor activity, poor coordination, reduced checking movements of the head, and abnormal posture of trunk and limbs.

Behavioural Observations: Rating of Disability

In addition to the automated recording of locomotor activity, the animals were observed and scored through a one-way mirror by experienced observers who were blinded to the treatments received by the monkeys. Immediately before drug treatments and for the duration of the experiment, the disability of each animal was rated in 10-min intervals as follows; alertness (normal, 0; reduced, 1; sleepy, 2); reaction to stimuli (normal, 0; reduced, 1; slow, 2; absent, 3); checking movements (present, 0; reduced, 1; absent, 2); attention and eye movements (normal, 0; abnormal, 1); posture (normal, 0; abnormal trunk, 1; abnormal limbs, 1; abnormal tail, 1; or grossly abnormal, 4); balance/coordination (normal, 0; impaired, 1; unstable, 2; spontaneous falls, 3); vocalisation (normal, 0; reduced, 1; absent, 2). The maximum score possible was 17, where an animal was showing marked motor and behavioural deficits. In addition, motor behaviour was rated qualitatively to determine the presence or absence of grooming, stereotyped activity, oral movements, head twitches, wet-dog shakes, or other obvious motor signs.

Measurement of Locomotor Activity

Locomotor activity was measured simultaneously for four individual animals each in a metal cage (50 cm wide × 60 long × 70 high) with transparent plastic doors (50 cm wide × 70 high), similar to the home cages but fitted with eight horizontally orientated infrared photocells. Three beams were located at floor level across the cage, and one along each of the two perches. Other beams were directed from front to back of the cage at floor level and above each perch. Locomotor counts were measured as the number of light-beam interruptions that occurred as the animals moved about. These movement counts were accumulated in 10-min intervals and recorded for 120 min. Recordings were made using a Commodore CBM 4032 computer. Before administration of vehicle or drug, animals were allowed a 60-min period of acclimatisation in the test cages.

Preparation and Administration of Drug Solutions

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride; Research Biochemicals, Inc., Natick, MA, U.S.A.) was dissolved in sterile 0.9% saline. Domperidone (Janssen, Belgium) was suspended in a few drops of 70% ethanol and diluted to volume (2 ml/kg body weight) with 10% sucrose solution and administered orally by gavage 30 min before piribedil at a dose of 2.0 mg/kg. Piribedil monomethane sulphonate (Servier, France) was dissolved in a minimal amount of 10% tartaric/lactic acids and made up to volume with 10% sucrose solution. It was administered orally by gavage at doses of 1.25, 5.0 or 12.5 mg/kg. Domperidone vehicle was administered on each experimental day for comparison with drug treatments. In the first study, piribedil was administered in the presence of domperidone vehicle pretreatment to each animal with a 1-week period of recovery between treatments by using an incomplete Latin-square design.

In the second study, which commenced some 8 weeks after the end of the first, piribedil was administered to the same animals in the presence of domperidone pretreatment. As in the previous study, a 1-week period of recovery was allowed between treatments.

Data Analysis

The mean ± SEM was calculated for time courses and accumulated locomotor counts for the different treatment groups. Dose–response data for total locomotor counts or disability scores were subjected to one-way analysis of variance (ANOVA) for repeated measures to test overall significance. Student's *t* test for paired samples was employed to assess differences in total locomotor counts or total disability scores between treatments.

RESULTS

Effect of Piribedil Administration on Locomotor Activity and Disability Scores

Administration of piribedil vehicle produced a small but transient increase in locomotor activity that was equal to that produced by handling the animals (Fig. 1A). Piribedil produced a dose-related increase in locomotor activity with a duration of action of some 120 min at 12.5mg/kg, the highest dose employed (Fig. 1A). An increase in locomotor activity was seen within 2–10 min of administration, depending on the dose of the drug. There was an immediate and pronounced phase of locomotor activity lasting for ~40 min, which was followed by a phase of lower activity that exceeded vehicle treatment and lasted for up to 60 min. Peak activity occurred ~10–20 min after drug administration for all dosage levels. The dose-related effect of piribedil was most obvious in terms of total locomotor counts, but there were no statistically significant differences (one-way ANOVA and Student's *t* test) between treatments (Fig. 1B).

Piribedil also produced a dose-related reduction in disability scores (Fig. 2A, B). The reduction in disability scores paralleled the pattern observed with changes in locomotor activity and was most marked over the first 20 min of drug administration, with effects greater than those seen with vehicle treatment, and that lasted throughout the period of observation (Fig. 2A). Improvements in behavioural disability were most obvious as an increase in vigilance and a greater awareness of the environment. The drug-induced reduction in disability scores, although clearly dose related, showed no statistically significant differences (one-way ANOVA and Student's *t* test) between treatments (Fig. 2B). Piribedil also induced a variety of stereotyped activities such as rearing, climbing, gnawing of perch, and grooming. These activities became more pronounced with increasing doses of the drug and were most marked during the first 20–30 min of drug administration.

Nausea and retching were commonly observed with all doses of the compound, and these had marked effects not only on the amount of locomotor activity produced but also on the disability scores, in that the animals spent much time cleaning themselves and were stationary during these periods. Nausea and retching occurred within 2–10 min of piribedil administration. Nausea and retching were observed in all animals that had received the highest 12.5-mg/kg dose of piribedil, in three of four animals receiving the 5.0-mg/kg dose, and two of four of those receiving 1.25 mg/kg.

Effect of Piribedil Administration on Locomotor Activity and Disability Scores After Pretreatment with Domperidone

Pretreatment with domperidone enhanced the ability of piribedil to reverse MPTP-induced motor and behavioural deficits, and the dose–response effect of the drug was clearly maintained (Fig. 3A, B). For all doses of piribedil, an increase in locomotor activity was seen within 10 min of administration,

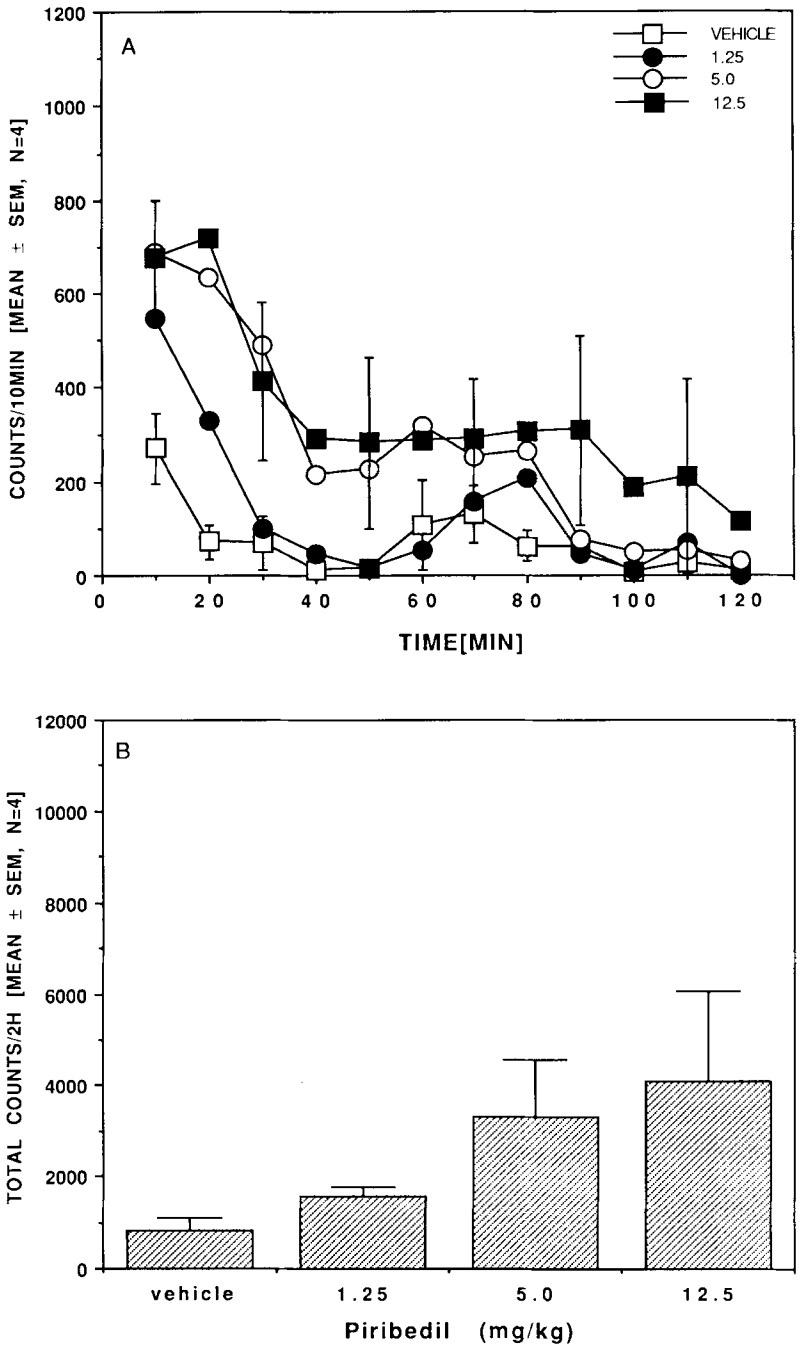

FIG. 1. The effect of piribedil on locomotor activity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets. A: Mean cumulative locomotor counts accumulated in 10-min intervals over 2 h (±SEM) after oral administration of vehicle, 1.25, 5.0, or 12.5 mg/kg piribedil. Error bars for the lower doses of piribedil are omitted for clarity but were in the same range as those shown for the highest dose of the drug. B: Mean total locomotor counts over 2 h (±SEM) for the data shown in A. There was a dose-related increase in locomotor activity as the dose of piribedil was increased (one-way analysis of variance and Student's *t* test showed no overall significance between treatments).

with peak activities seen some 20–30 min after drug administration (Fig. 3A). Pretreatment with domperidone prolonged the period of locomotor activity for all doses of piribedil but especially for the two lower doses (1.25 and 5.0 mg/kg) when compared with no domperidone pretreatment. For total locomotor counts, domperidone pretreatment caused statistically significant (one-way ANOVA and Student's *t* test) increases between vehicle treatment and the two highest doses of piribedil (Fig. 3B). Well-controlled bouts of locomotion, during which the animals developed a more vigilant interest in their environment, were observed with all doses of piribedil.

Pretreatment with domperidone enhanced the reduction in disability scores produced by piribedil (1.25–12.5 mg/kg) in a dose-dependent manner (Fig. 4A, B). The reduction in disability scores was more

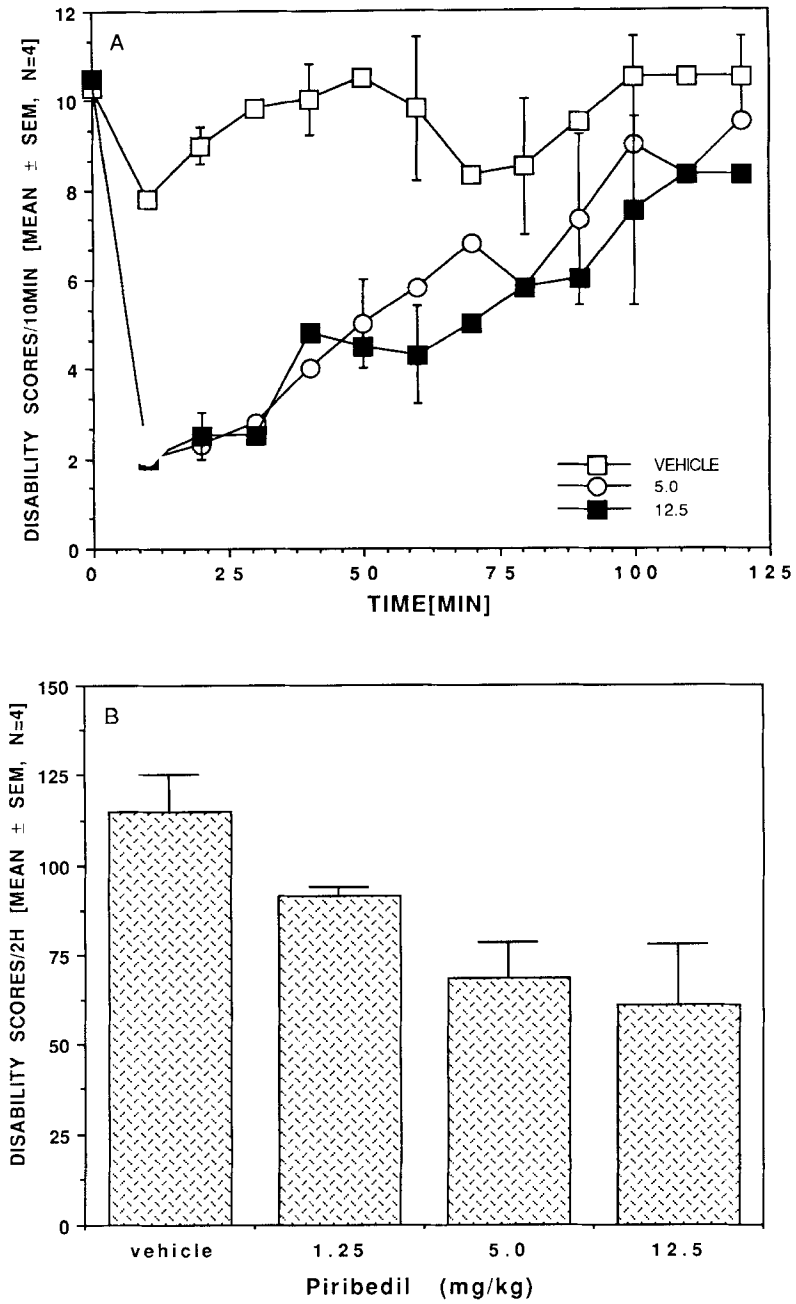

FIG. 2. The effect of piribedil on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced behavioural and motor deficits (represented as disability) in the common marmoset. **A**: Mean disability scores assessed at 10-min intervals over 2 h (±SEM) after oral administration of vehicle, 5.0 or 12.5 mg/kg piribedil. Error bars for the lower dose of piribedil are omitted for clarity but were in the same range as those shown for the highest dose of the drug. **B**: Mean total disability scores over 2 h (±SEM) for the data shown in A. There was a dose-related reduction in total disability scores from vehicle treatment with increasing dose of piribedil (one-way analysis of variance and Student's *t* test showed no overall significance between treatments).

pronounced than the drug-induced increase in locomotor activity, and the increase in awareness and vigilance lasted throughout the period of experiment for the two highest doses of piribedil, 5.0 or 12.5 mg/kg (Fig. 4A). Indeed, the animals became fully active and alert, characterised by a greater interest in their surroundings, within 10 min of drug administration. A statistically significant decrease (one-way ANOVA and Student's *t* test) in disability scores between vehicle treatment and the highest dose of piribedil was produced (Fig. 4B). Piribedil-induced stereotyped behaviours were enhanced after domperidone pretreatment. Rearing, climbing, gnawing of perch, and grooming again appeared to be dose related. At times these activities became quite intense after administration of the highest dose of piribedil.

Pretreatment with domperidone effectively abolished the nausea and retching seen when piribedil was administered alone. In fact, apart from one an-

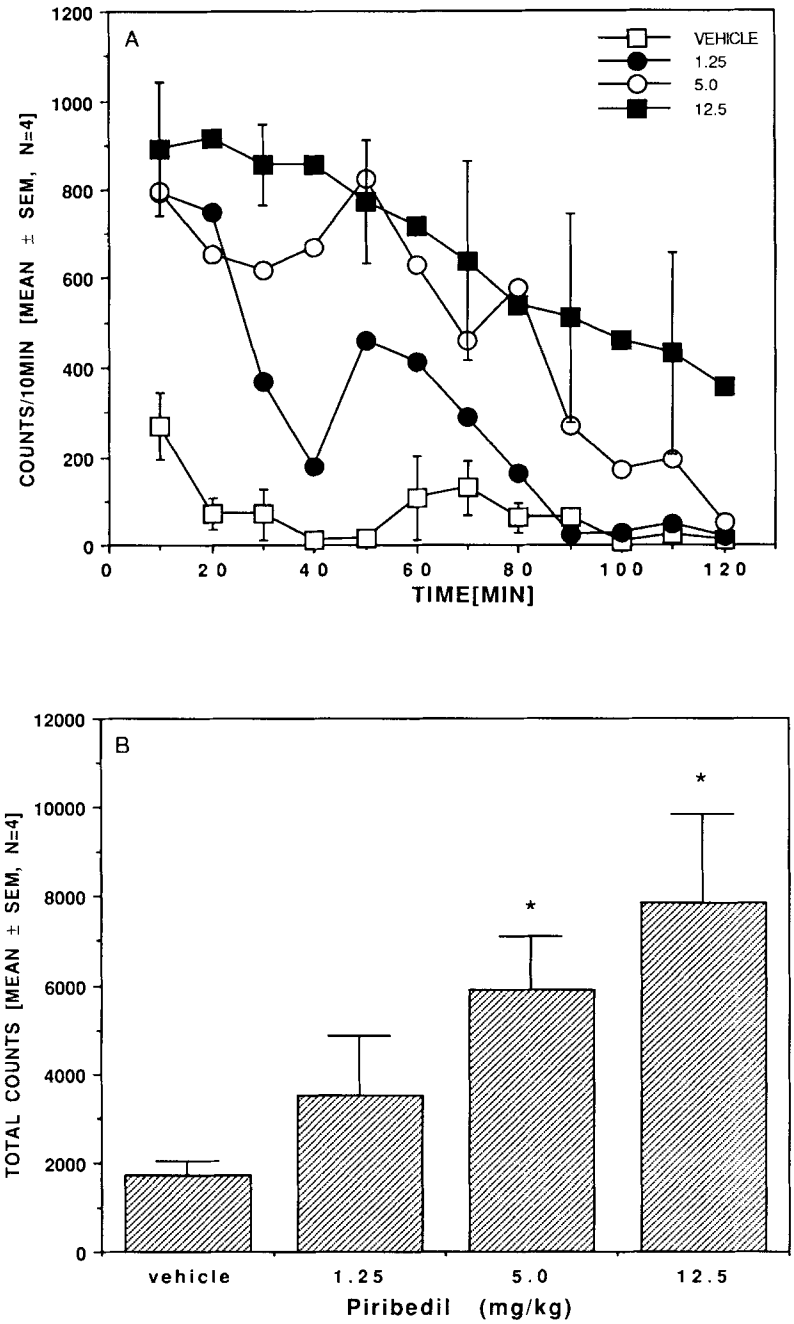

FIG. 3. The effect of piribedil on locomotor activity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets. A: Mean cumulative locomotor counts accumulated in 10-min intervals over 2 h (±SEM) after pretreatment with domperidone (2 mg/kg, orally) 30 min before the oral administration of vehicle, 1.25, 5.0, or 12.5 mg/kg piribedil. Error bars for the lower doses of piribedil are omitted for clarity. B: Mean total locomotor counts over 2 h (±SEM) for the data shown in A. There was a dose-dependent increase in locomotor activity as the dose of piribedil was increased (one-way analysis of variance; $*p < 0.05$, Student's t test).

imal that had a short bout of retching after receiving the highest dose, no other signs of discomfort were observed after administration of piribedil with domperidone.

Comparison of Locomotor and Disability Scores After Administration of Domperidone Versus Piribedil Alone

These results are a pooling of the data from the first (piribedil without domperidone) and second (piribedil with domperidone) study. Pretreatment with domperidone enhanced locomotor activity induced by all doses of piribedil (Fig. 5B). With the highest dose of piribedil, there was an increase in the magnitude and duration of action after domperidone pretreatment. The duration of marked locomotor activity lasted for >60 min with domperidone pretreatment as compared with 20–30 min in the absence of domperidone (Fig. 5A). However, these differences were not statistically significant (one-

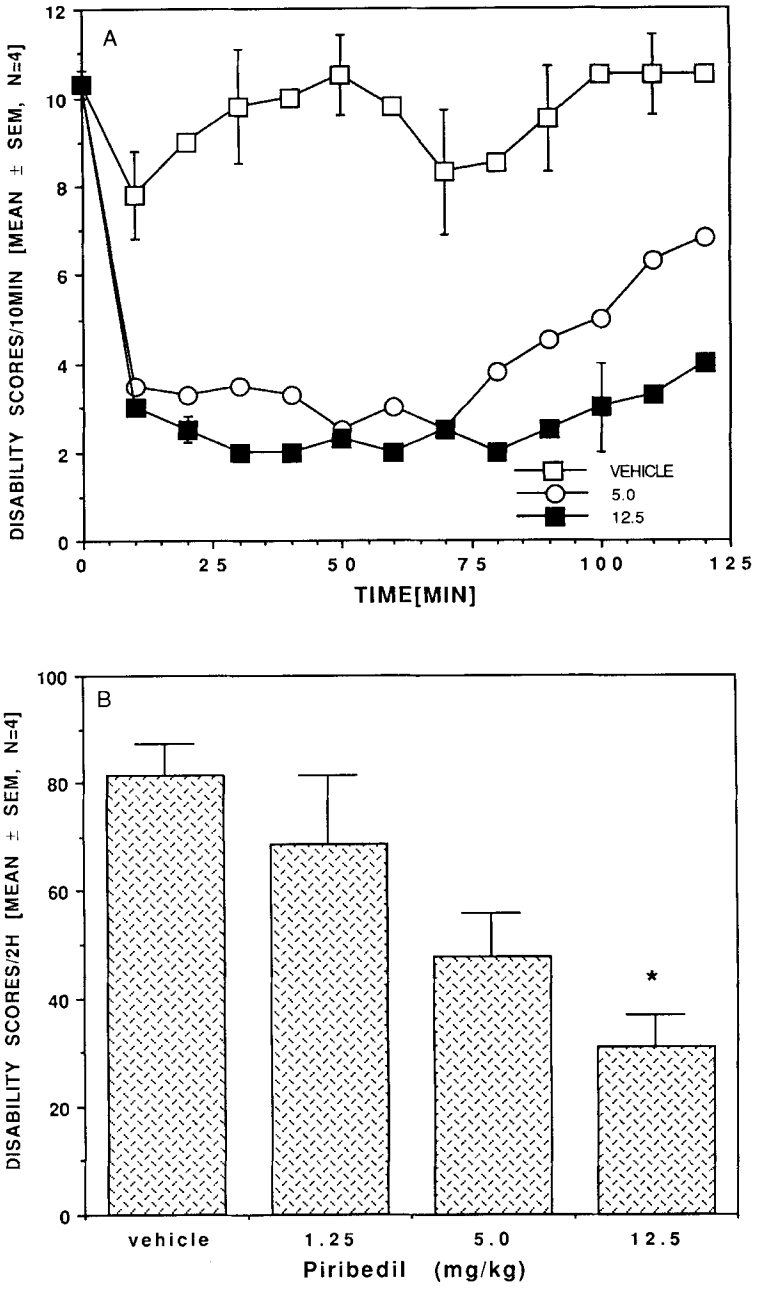

FIG. 4. The effect of piribedil on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced behavioural and motor deficits (represented as disability scores) in the common marmoset. A: Mean disability scores assessed at 10-min intervals over 2 h (±SEM) after pretreatment with domperidone (2 mg/kg, orally) 30 min before the oral administration of vehicle, 5.0 or 12.5 mg/kg piribedil. Error bars for the lower doses of piribedil are omitted for clarity. B: Mean total disability scores over 2 h (±SEM) for the data shown in A. There was a dose-dependent reduction in disability scores as the dose of piribedil was increased (one-way analysis of variance; $*p < 0.05$, Student's t test).

way ANOVA and Student's t test). The domperidone-enhancing effect on locomotor activity was seen at all doses of piribedil, with total locomotor counts being effectively doubled (Fig. 5B). When the effects of piribedil-induced changes in disability scores in the presence or absence of domperidone pretreatment were compared, it was clear that domperidone had an important enhancing effect (Fig. 6A, B).

DISCUSSION

The reported clinical effects of piribedil in Parkinson's disease have led to the belief that the drug is effective mainly against tremor. This is surprising when the pharmacologic profile of piribedil is considered, because it induces stereotyped behaviour and rotational activity in 6-OHDA–lesioned rats, which is associated with postsynaptic dopamine-receptor activation (6,7).

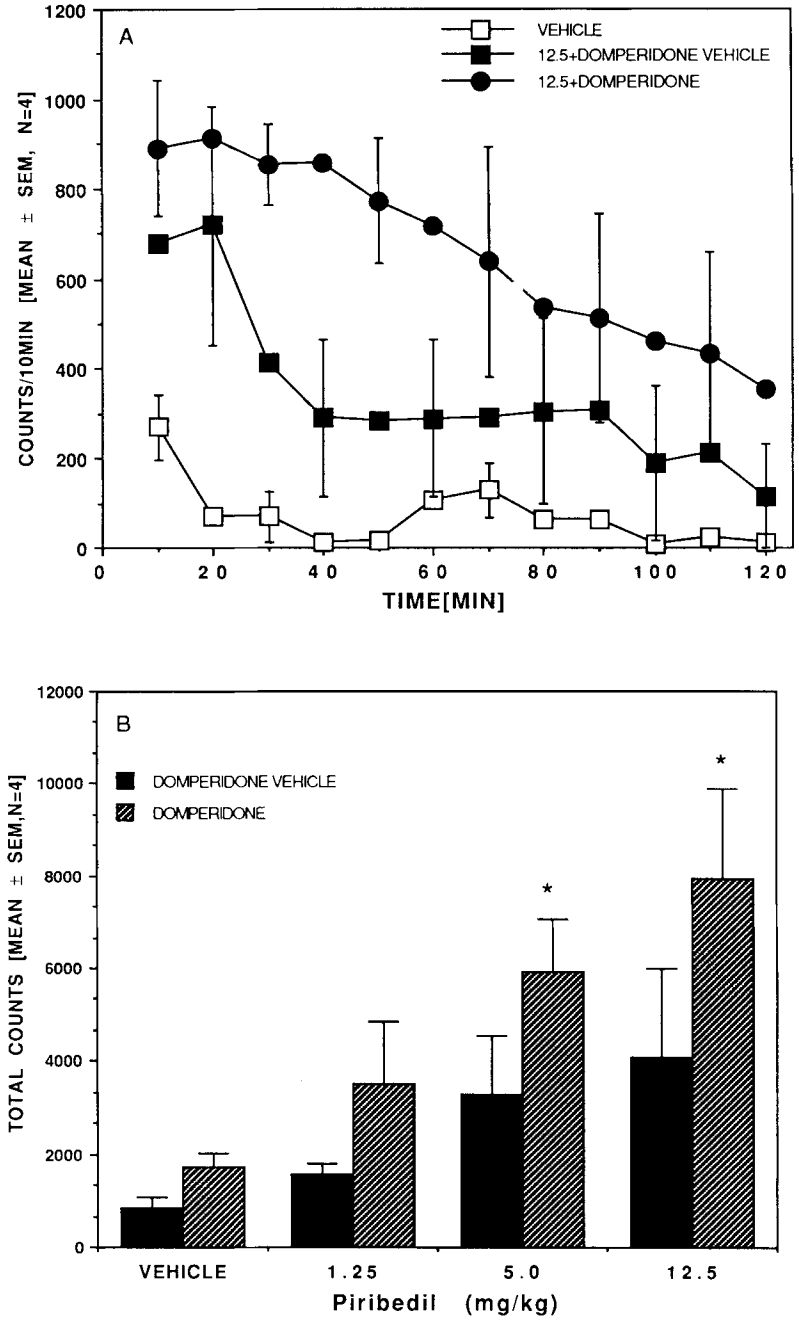

FIG. 5. Comparison of the effects of piribedil-induced locomotor activity in the presence or absence of domperidone pretreatment in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets. A: Mean cumulative locomotor counts accumulated in 10-min intervals over 2 h (±SEM) after pretreatment with domperidone vehicle or domperidone (2 mg/kg, orally) 30 min before the oral administration of 12.5 mg/kg piribedil. B: Mean total locomotor counts over 2 h (±SEM) for the data (with additions) shown in A. Pretreatment with domperidone enhanced piribedil-induced locomotor activity for the two higher doses of piribedil (one-way analysis of variance; $*p < 0.05$ compared with vehicle treatment, Student's t test).

The actions of piribedil have not previously been examined in the MPTP-treated primate model of Parkinson's disease. The development of the drug was undertaken in an era before the discovery of MPTP. Because the model appears to be highly predictive of drug action in humans, it was important to assess whether or not piribedil had a major effect on MPTP-induced motor deficits (14). In the MPTP-treated common marmoset, rest tremor characteristic of Parkinson's disease is seldom observed, allowing assessment of drug action on other motor symptoms shown by these animals, particularly akinesia, rigidity, postural abnormalities, and loss of vocalisation.

The results of this investigation show that piribedil causes a rapid reversal of all motor symptoms in MPTP-treated common marmosets. These effects were dose related and obvious from both an in-

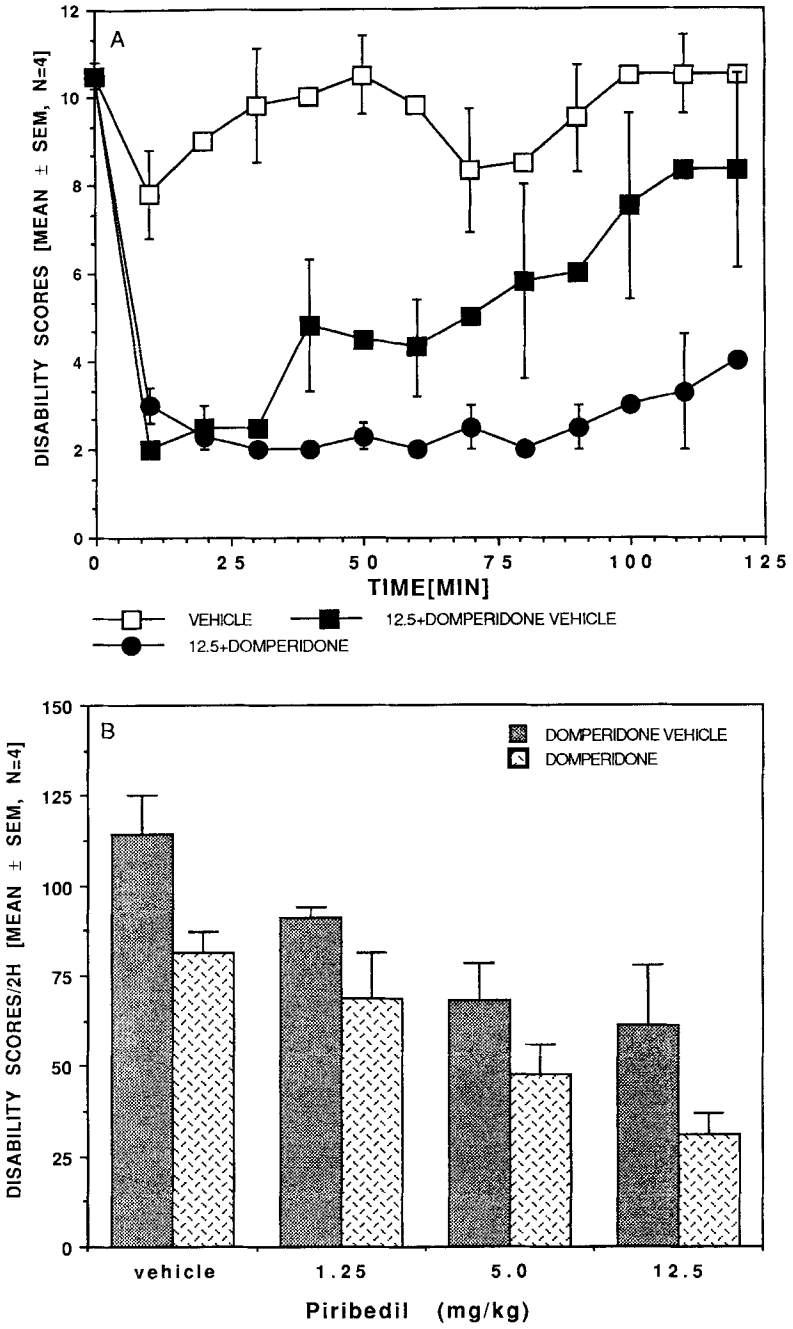

FIG. 6. Comparison of the effects of piribedil-induced changes in behavioural and motor deficits (represented as disability scores) in the presence or absence of domperidone pretreatment in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets. A: Mean cumulative disability scores assessed at 10-min intervals over 2 h (±SEM) after pretreatment with domperidone vehicle or domperidone (2 mg/kg, orally) 30 min before the oral administration of 12.5 mg/kg piribedil. B: Mean total disability scores over 2 h (±SEM) for the data (with additions) shown in A. Pretreatment with domperidone produced a dose-related and greater reduction in disability scores by piribedil when compared with domperidone vehicle pretreatment (one-way analysis of variance and Student's *t* test showed no overall significance between vehicle and domperidone pretreatment).

crease in overall locomotor activity and a decrease in disability scores. These findings emphasise that the pharmacology of piribedil in rodents is confirmed in a primate model of Parkinson's disease, and thus the drug is effective on all motor abnormalities produced as a result of MPTP treatment. Why this has not been reflected in the early clinical trials of piribedil is not clear. However, it may be that too rapid an increase in dosage produced a high level of side effects that were also apparent in these experiments.

Nausea and vomiting are common early side effects of therapy with L-Dopa and dopamine agonist drugs in Parkinson's disease (15–17). The use of domperidone, a peripherally acting dopamine antagonist, allows alleviation of these unwanted actions of dopamine-replacement therapy. In humans, administration of piribedil with domperidone was

shown to be markedly effective against tremor but much less so against rigidity and akinesia (20). In our experiments, the administration of piribedil alone produced nausea and retching, particularly at high drug-dosage levels. This led to a disruption of the animals' behavioural pattern and probably was a major contributor to the apparent short duration of action of piribedil. Pretreatment with domperidone was highly effective in preventing nausea and retching induced by piribedil in the MPTP-treated common marmoset. The animals pretreated with domperidone showed a high degree of activity of longer duration than was observed after administration of piribedil alone. This may reflect the abolition of nausea or the prevention of gastrointestinal disruption, which might have impaired the absorption of piribedil.

The effects of piribedil on the behaviour of MPTP-treated common marmosets were notable for the quality of movement produced. Most D2 agonists we have examined in this model produce a hyperactivity syndrome in which the animals show continuous, repetitive movement and stereotypies (18). In contrast, piribedil produced balanced and well-coordinated movements that closely resembled the pattern of normal movements in naive common marmosets. In particular, the animals showed bursts of activity, and the nature of the movement was not repetitive. The animals also looked more normal than is observed with other dopamine agonists. Some stereotyped behaviour was observed with piribedil, but this was only marked at the highest dose employed. Piribedil is one of few dopamine-agonist drugs we have studied that produce this pattern of response. In addition, piribedil also caused an increase in awareness and vigilance in the marmoset in the manner in which they interacted with their environment and with external stimuli. Again, we have not observed this type of response with other dopamine agonists, suggesting that there is something different about the manner in which piribedil interacts with brain dopamine receptors.

The available evidence suggests that piribedil can displace [^{3}H]-spiperone and [^{3}H]-sulpiride from their binding sites on striatal membranes, indicating D2-agonist activity (19). Piribedil does not stimulate cyclic adenosine monophosphate (AMP) production in rat striatal tissue, but its catechol metabolite S 584 is an effective and potent stimulant (5). This would suggest both D1- and D2-receptor actions of piribedil as important components of its actions. However, because the onset of activity of the drug in MPTP-treated common marmosets is rapid, this would argue against metabolite involvement.

There is some evidence to suggest that piribedil does not interact with all dopamine-receptor populations in brain. Thus after intravenous administration of [^{3}H]-piribedil to rats, a specific accumulation of radioactivity occurred in the substantia nigra, tuberculum olfactorium, and nucleus accumbens but not in the striatum (4). In contrast, administration of [^{3}H]-*N*, *n*-propylnorapomorphine (NPA) led to a specific accumulation of radioactivity in all these brain regions, but unlabeled piribedil could only prevent this occurring in the substantia nigra, tuberculum olfactorium, and nucleus accumbens, but not in the striatum (4). So there may be fundamental differences in the areas of brain affected by piribedil compared with other dopamine agonists. In particular, the selective interaction of piribedil with limbic brain regions may explain the ability of the drug to cause increased awareness and vigilance. In contrast, the lack of interaction with striatal dopamine receptors may explain why the drug does not induce continuous repetitive movements as do other D2-agonist compounds.

This study has demonstrated that piribedil is effective against all motor deficits in MPTP-induced parkinsonism in the common marmoset. The data indicate how the side effects of piribedil can influence its antiparkinsonian ability and why the drug may not have gained general acceptance in an era when domperidone was not available. These studies also emphasise that piribedil may have major advantages over other antiparkinsonian drugs in the quality of movement produced and because of its ability to increase vigilance and awareness. These results are in agreement with those from a recent study that showed that in patients not previously treated with L-Dopa, piribedil monotherapy was effective against the major features of Parkinson's disease, including akinesia and rigidity (21).

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