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Pramipexole Combined with Levodopa Improves Motor Function but Reduces Dyskinesia in MPTP-Treated Common Marmosets

Kayhan A. Tayarani-Binazir, BSc,[1] Michael J. Jackson, BSc,[1] Sarah Rose, PhD,[1] C. Warren Olanow, MD,[2] and Peter Jenner, DSc[1]*

[1]*Neurodegenerative Diseases Research Centre, School of Health and Biomedical Sciences, King's College London, London, United Kingdom*
[2]*Department of Neurology, Mount Sinai School of Medicine, New York, New York, USA*

Abstract: Reduced expression of dyskinesia is observed in levodopa-primed MPTP-treated common marmosets when dopamine agonists are used to replace levodopa. We now investigate whether a combination of the D-2/D-3 agonist pramipexole and levodopa also reduces dyskinesia intensity while maintaining the reversal of motor disability. Drug naïve, non-dyskinetic MPTP-treated common marmosets were treated daily for up to 62 days with levodopa (12.5 mg/kg plus carbidopa 12.5 mg/kg p.o. BID) or pramipexole (0.04–0.3 mg/kg BID) producing equivalent reversal of motor disability and increases in locomotor activity. Levodopa alone resulted in marked dyskinesia induction but little or no dyskinesia resulted from the administration of pramipexole. From day 36, some animals were treated with a combination of levodopa (3.125–6.25 mg/kg plus carbidopa 12.5 mg/kg p.o. BID) and pramipexole (0.1–0.2 mg/kg p.o. SID). This improved motor disability to a greater extent than occurred with levodopa alone. Importantly, while dyskinesia was greater than that produced by pramipexole alone, the combination resulted in less intense dyskinesia than produced by levodopa alone. These results suggest that pramipexole could be administered with a reduced dose of levodopa to minimize dyskinesia in Parkinson's disease while maintaining therapeutic efficacy. © 2010 Movement Disorder Society

Key words: pramipexole; L-dopa; motor disability; dyskinesia; MPTP; primate; Parkinson's disease

Levodopa (L-dopa) and dopamine agonists are the mainstay of the treatment of Parkinson's disease (PD) through dopamine replacement therapy.[1–5] L-dopa use is, however, associated with a high incidence of motor complications including dyskinesia.[1,6–8] As a consequence, dopamine agonists, predominantly pramipexole and ropinirole, are used in the early treatment of PD to provide relief from motor symptoms and to delay the appearance of motor complications.[5,9,10] This has been attributed to the longer duration of effect of the dopamine agonists providing a more physiological and continuous stimulation of striatal dopamine receptors.[2,11] Continuous dopaminergic stimulation is a useful clinical concept for explaining the differences that exist between the side-effect profile of dopamine agonists and L-dopa. However, it does not explain differences between different agonist drugs and clearly some dopamine agonists, such as pramipexole and ropinirole, have an inherently lower ability to induce dyskinesia than other compounds.[3,10,12–16]

Dopamine agonists are also used as an adjunct therapy to L-dopa. They provide a more prolonged reversal of motor deficits through their longer duration of action in individuals with PD who experience motor fluctuations in the form of a shortening of the duration of effect of each L-dopa dose ("wearing off") and unpredictable swings in motor response ("on off").[6,7] However, in those patients who exhibit dyskinesia in response to L-dopa, the addition of a dopamine agonist can lead to a worsening of involuntary movements and these can become treatment limiting.[17,18]

*Correspondence to: P. Jenner, NDRG, School of Biomedical Health and Sciences, King's College London, London SE1 1UL, United Kingdom. E-mail: peter.jenner@kcl.ac.uk

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There is good evidence to suggest that dyskinesia seen in mid to late stage PD can be diminished in intensity by the introduction of more continuous dopaminergic therapy. This has been shown after the use of subcutaneous infusions of apomorphine and more recently after the continuous intrajejunal infusion of L-dopa.[2,12,19–21] What this suggests is that there is a role for longer acting dopamine agonist drugs in the treatment of the later stages of PD to reduce dyskinesia while providing efficacy against motor disability. Indeed, in studies in MPTP-treated primates, we have previously demonstrated that switching from repeated L-dopa treatment that has induced dyskinesia to monotherapy with a dopamine agonist, maintains efficacy but leads to an immediate reduction in dyskinesia intensity.[16,22,23] Interestingly, there is evidence that switching patients with late stage PD to high-dose pergolide treatment can have the same effect.[12,18]

Switching to high-dose agonist therapy is not, however, a viable clinical strategy because of the risk of inducing psychosis in older patients with PD and because of the lower efficacy of dopamine agonist drugs compared with L-dopa.[24–26] An alternative approach would be to reduce the dose of L-dopa and to combine it with a moderate dose of a dopamine agonist to maintain efficacy and to determine whether this would lead to reduced dyskinesia expression through the longer duration of effect exerted by the agonist. This has not been previously explored clinically or even in the MPTP-treated primate model of PD.

For this reason, we have examined the effect of L-dopa and pramipexole treatment of previously drug naïve MPTP-treated common marmosets initially as monotherapy and subsequently in a lower dose combination. As expected, L-dopa induced marked dyskinesia, whereas pramipexole did not. Importantly, continuing to treat the animals with a lower L-dopa dose in combination with pramipexole led to maintenance of the control of motor function, but to a lower expression of dyskinesia.

METHODS AND MATERIALS

Animals

Adult common marmosets (*Callithrix jacchus*) of either sex (n = 18, n = 6 per group, 9 male and 9 female, aged 2–7 years; weight 320–420 g) were used in the study. Animals were housed singly or in pairs, in a room maintained at constant temperature (25°C ± 1°C), 50% relative humidity, and with a 12-hour light/dark cycle. All animals were fed fresh fruit once daily, and had ad libitum access to food pellets (Mini Marex (E), Special Diet Services, UK) and fresh water. All of the animals were drug naïve before commencing this study. All experiments were performed in accordance with the Animals (Scientific Procedures) Act 1986 under project licence number 70/6345.

MPTP Administration

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride; Sigma Chemical Co, UK) was dissolved in 0.9% sterile saline solution and administered at 2.0 mg/kg daily for 5 consecutive days.[27,28] For the following 8–10 weeks, animals were hand fed on a high protein/carbohydrate liquid diet (Marmoset jelly, Special Diet Services, UK and Complan, Complan Foods, UK) until they had recovered from the acute effects of MPTP treatment. All of the animals exhibited persistent motor deficits including akinesia, bradykinesia, rigidity, impaired balance/coordination, and intention tremor resulting in a mean (n = 18) motor disability score of 15.4 ± 0.3 SEM out of a maximum of 18 indicating a marked to severe degree of motor disability. Basal locomotor activity was assessed before the start of the drug administration phases and animals were assigned to three treatment groups of equivalent locomotor activity (n = 6 per group).

Drugs

L-3,4-dihydroxyphenylalanine (L-dopa) methyl ester (10–12.5 mg/kg or 3.125–6.25 mg/kg free amino acid p.o.; Sigma Chemical Co, UK) was dissolved in 10% sucrose solution and administered by oral gavage in a volume of 2 mL/kg. A pretreatment of carbidopa (12.5 mg/kg p.o.; Sigma Chemical Co, UK) prepared as a suspension in a 10% sucrose solution, was given 1 hour before L-dopa at a volume of 2 mL/kg. Pramipexole HCl (0.04–0.3 mg/kg; Boehringer Ingelheim, Germany) was dissolved in a 10% sucrose solution and administered orally in a volume of 2.0 mL/kg. Domperidone (2 mg/kg p.o. in a volume of 2 mL/kg) was administered to prevent vomiting/retching following administration of pramipexole. On test days, domperidone was given as a pretreatment 1 hour before the first of the twice daily pramipexole treatments and in combination with the second pramipexole dose.

Treatment

All animals were assessed for basal activity, motor disability, and dyskinesia before the start of treatment. Animals were then treated on a daily basis and locomotor activity, motor disability, and dyskinesia was

assessed on days 1, 3, 5, 7 and then once-a-week until day 35 (PHASE I), and on days 36, 38, 40, 42 and then once-a-week until day 63 (PHASE II).

Group 1 (L-dopa alone): L-dopa (10–12.5 mg/kg, BID) was administered orally from day 1–63 with modifications to the doses to moderate dyskinesia levels.

Group 2 (pramipexole plus L-dopa): Animals were treated orally with pramipexole (0.04–0.3 mg/kg, BID) alone from day 1–35 and then pramipexole (0.04–0.3 mg/kg SID plus L-dopa, 3.125–6.25 mg/kg, BID) from day 36–63.

Group 3 (pramipexole alone): Pramipexole (0.04–0.3 mg/kg BID) alone was administered orally between days 1–35 followed by pramipexole (0.04–0.3 mg/kg SID) dosing from day 36–63.

It was necessary to adjust the dose regime of pramipexole (Group 3) during PHASE I and for the animals receiving L-dopa plus pramipexole (Group 2) during PHASE II, to maintain locomotor equivalence with animals receiving L-dopa alone, BID. To moderate the degree of dyskinesia during PHASE II, the dose of L-dopa was reduced to 10 mg/kg in Group 1 for 4 animals receiving L-dopa, BID, alone and to 3.125 mg/kg in 1 animal from the Group 2 receiving L-dopa, BID plus pramipexole, SID.

Behavioral Assessments

Animals were assessed for locomotor activity, motor disability, and dyskinesia for up to 8 hours after drug administration by trained observers in a blinded manner as described below.

Locomotor Activity

Animals were acclimatized to the automated activity (test) units for 60 min following pretreatment with carbidopa (12.5 mg/kg) or domperidone (2.0 mg/kg). Each test unit was fitted with eight photoelectric beams arranged to detect floor, perch and climbing activity, interruption of a beam being automatically recorded as a single locomotor count. During this time, baseline locomotor activity was determined according to previously described studies.[29] Pramipexole and/or L-dopa treatment was then administered at time = 60 and 300 min. Locomotor activity was monitored for up to 8 hours after the 1st dose.

Rating of Motor Disability

Motor disability was assessed simultaneously with assessment of locomotor activity through a one-way mirror by experienced observers blinded to treatment. Basal disability was assessed during the 1-hour acclimatization period and once every 30 min after drug administration for up to 8 hours using an established motor disability rating scale; alertness (normal 0, reduced 1, sleepy 2); checking movements (present 0, reduced 1, absent 2); 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); reaction (normal 0, reduced 1, slow 2, absent 3); vocalization (normal 0, reduced 1, absent 2); motility (normal 0, bradykinesia 1, akinesia 2).[30,31]

Rating of Dyskinesia

Dyskinesia was assessed simultaneously with motor disability using an established dyskinesia rating scale.[32] Chorea: rapid random flicking movements of the fore and hind limbs; Athetosis: sinuous writhing limb movements; Dystonia: sustained abnormal posturing. Dyskinesia was scored as follows: 0 = absent; 1= mild, fleeting, and rare dyskinetic postures and movements; 2 = moderate: more prominent abnormal movements, but not significantly affecting normal behavior; 3 = marked, frequent and at times continuous dyskinesia affecting the normal pattern of activity; and 4 = severe, virtually continuous dyskinetic activity, disabling to the animal and replacing normal behavior.

Statistical Analysis

All data was treated as non-Gaussian. Locomotor activity counts, motor disability scores, and dyskinesia scores were calculated as total locomotor activity counts, motor disability, and dyskinesia scores and presented as median and range. Total locomotor activity counts, motor disability, and dyskinesia scores were determined by area under the curve (GraphPad Prism 4®). Differences in area under the curve for locomotor activity, motor disability and dyskinesia and peak dyskinesia were determined by nonparametric ANOVA (Kruskal Wallis or Friedman test) followed by a nonparametric post-hoc test (Mann Whitney or Wilcoxon test) where appropriate (GraphPad Prism®). Treatment groups for both PHASE I and II were compared with basal levels. In PHASE II of the study, treatment groups were compared with each other. Statistical significance was set at $P < 0.05$.

RESULTS

There was a significant and comparable increase in locomotor activity during PHASE I in animals receiv-

ing L-dopa (Group 1) or pramipexole (Groups 2 and 3) compared with their basal locomotor activity in these MPTP-treated common marmosets before the start of the study (Fig. 1a). During PHASE I in both groups (1 and 2), receiving L-dopa or pramipexole treatments motor disability was significantly reversed compared with untreated MPTP-treated common marmosets (Fig. 1b). The administration of pramipexole alone (Group 2) during PHASE I did not produce a significant increase in dyskinesia compared with basal dyskinesia levels, however, L-dopa (Group 1) administration did produce a highly significant increase in dyskinesia during this phase (Fig. 2a). Peak dyskinesia was also significantly increased following L-dopa administration (Group 1) compared with basal dyskinesia levels for the animals before any drug administration (Fig. 2b). The peak dyskinesia induced by pramipexole administration (Group 2) was not significantly different compared with basal levels and when it was observed it was primarily mild and fleeting (Fig. 2b).

During PHASE II, the group receiving L-dopa (Group 1) produced similar levels of locomotor activity as seen in PHASE I as did the animals receiving pramipexole alone (Group 2) and L-dopa plus pramipexole (Group 3) (Fig. 1a). The reversal of motor disability seen during PHASE I with both Groups 1 and 2 was sustained in PHASE II (Fig. 1b). However, L-dopa plus pramipexole (Group 3) significantly improved the reversal of motor disability compared with L-dopa alone (Group 1) (Fig. 1b). This combination of pramipexole and L-dopa (Group 3) produced a maximal reversal of motor disability within 150 min after drug administration which was sustained until the end of the test day during the nonassessed observation period including when animals had been placed back into home cages (Data not shown).

During PHASE II, L-dopa (Group 1) continued to produce similar dyskinesia levels as seen in PHASE I and animals treated with pramipexole alone (Group 2) expressed dyskinesia that was not significantly different compared with basal (Fig. 2a). In addition, in PHASE II, the administration of pramipexole plus L-dopa (Group 3) produced a significant increase in dyskinesia severity compared with pramipexole alone (Group 2) (Fig. 2a).

In PHASE II, the L-dopa-induced peak dyskinesia seen in Group 1 was similar to that seen in PHASE I (Fig. 2b). Peak dyskinesia induced by pramipexole alone (Group 2) for PHASE II was not different to that produced by pramipexole alone in PHASE I (Fig. 2b). During PHASE II, pramipexole plus L-dopa (Group 3) produced significantly increased peak dyskinesia levels compared with pramipexole alone (Group 2) but these were still moderate in severity (score of 2) (Fig. 2b).

DISCUSSION

The classical roles for dopamine agonist drugs in the treatment of PD are either as early monotherapy for the avoidance of motor complications or as an adjunct to L-dopa in late stage PD to deal with the onset of significant "wearing off."[6,20,33] Both of these uses are based on their longer duration of action compared with L-dopa. More continuous dopaminergic stimulation produced by dopamine agonists, such as pramipexole and ropinirole, delays the onset of dyskinesia, whereas a longer duration of action smoothes out "off" periods by increasing "on" time in those showing a reduced duration of action to each dose of L-dopa.[6,34] At later time points, the usual problem is that adding further dopaminergic medication exacerbates established involuntary movements which can then become treatment limiting. Interestingly, there has been little investigation into whether adding a dopamine agonist to therapy while reducing L-dopa intake at this point in the illness can maintain efficacy but reduce dyskinesia intensity.

The first part of this study confirmed the differences that are known to exist between the ability of L-dopa and dopamine agonist drugs in inducing dyskinesia in MPTP-treated primates.[23,29,35] Despite producing equivalent improvements in motor function by dose titration in the early stages of the study, there was the rapid development of marked involuntary movements in response to L-dopa that appeared with every dose administered but only mild dyskinesia in response to pramipexole treatment. This difference may relate solely to difference in the duration of action of L-dopa and pramipexole with the former resulting in pulsatile nonphysiological stimulation of striatal dopamine receptors, whereas the latter produces a more tonic physiological stimulation as suggested by the concept of continuous dopaminergic stimulation.[2,11,36] However, since there is no correlation between the ability of dopamine agonists to induce dyskinesia and their biological half-lives, another concept is that there are inherent differences between dopamine agonists that lead to low dyskinesia induction by some molecules.[37]

Whether the difference between dopamine agonists and L-dopa relates to the process of dyskinesia induction ("priming") or whether it has more to do with the ability to express dyskinesia is not well established. However, in previous studies, we have treated animals with ropinirole, piribedil, or rotigotine resulting in mild dyskinesia and shown that switching to an equi-effective antiparkinsonian dose of L-dopa leads to the

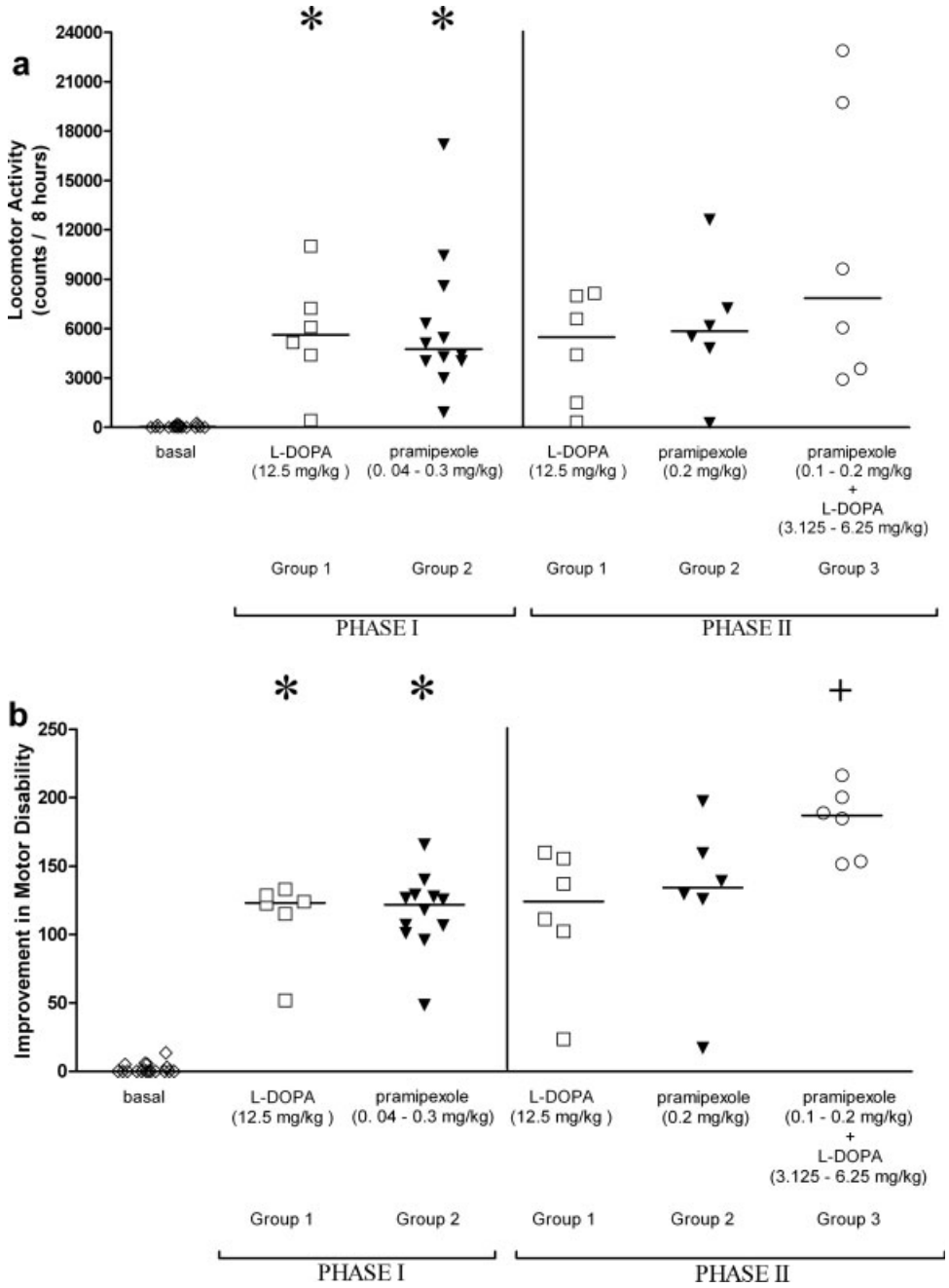

FIG. 1. (**a**) Total locomotor activity counts for PHASES I and II: Data (n = 6) are median (range) for PHASE I (days 7–35) and PHASE II (days 42–63). * $P < 0.05$ compared with basal locomotor activity (PHASE I) (Kruskal Wallis $P < 0.0001$, Dunn's multiple comparison post-hoc test $P < 0.05$, df = 15 and KW = 26.31). (**b**) For PHASE I and II. Data (n = 6) are median (range) for PHASE I (days 7–35) and PHASE II (days 42–63). * $P < 0.05$ compared with basal scores (Kruskal Wallis $P < 0.0001$, multiple comparison post-hoc test, $P < 0.05$, df = 15 and KW = 27.28), + $P < 0.05$ compared with levodopa alone (PHASE II) (Kruskal Wallis $P < 0.0001$, Mann Whitney, $P < 0.05$, df = 15 and KW = 6.117).

immediate expression of intense involuntary movements.[22,23,29] This suggests that agonists do prime but do not express dyskinesia. For this reason, the primary objective of this study was to determine whether this could be applied in a beneficial manner in a paradigm related to the late stage treatment of PD in individuals with established dyskinesia where improved control of motor function was required.

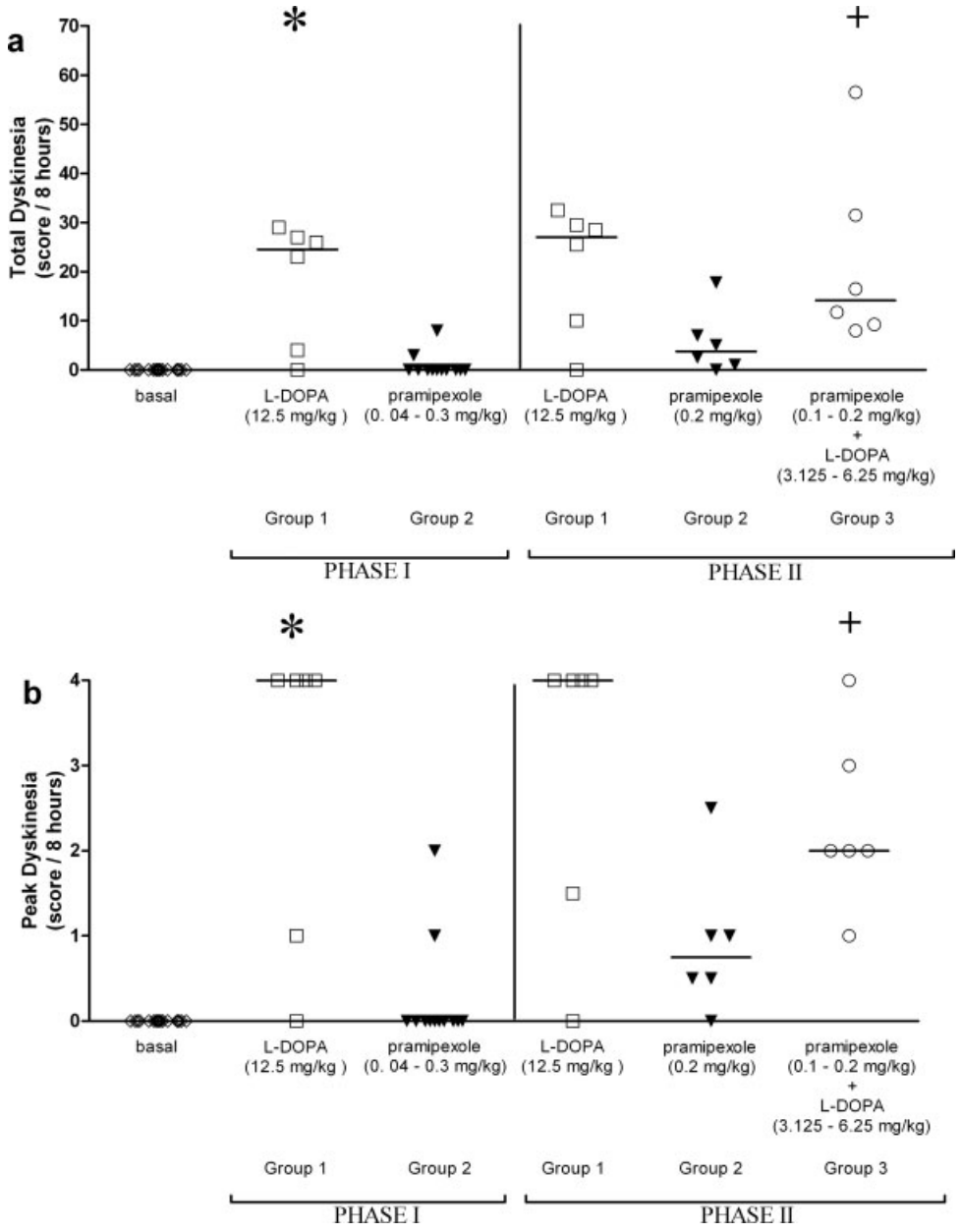

FIG. 2. (**a**) Dyskinesia scores for PHASE I and II. Data (n = 6) median (range) for PHASE I (days 7–35) and PHASE II (days 42–63). *$P <$ 0.05 compared with basal scores (Kruskal Wallis $P < 0.0001$, Mann Whitney $P < 0.05$, df = 15 and KW = 18.34), + $P < 0.05$ compared with pramipexole alone (PHASE II) (Kruskal Wallis, Mann Whitney $P < 0.05$, df = 15 and KW = 5.711). (**b**) Peak dyskinesia scores for PHASES I and II. Data (n = 6) are median and range for PHASE I (days 7–35) and PHASE II (days 42–63). * $P < 0.05$ compared with basal (Kruskal Wallis $P < 0.0001$, Mann Whitney $P < 0.05$, df = 15 and KW = 18.16), + $P < 0.05$ compared with pramipexole alone (PHASE II) (Kruskal Wallis, KW = 5.652, Mann Whitney $P < 0.05$, df = 15) (Mann Whitney).

The results of the second part of the study showed that a reduction in L-dopa dosage concomitant with the introduction of pramipexole treatment did not result in any reduction of the control of motor disability. Importantly, however, dyskinesia diminished to a level that was ranked between that seen with treatment with L-dopa alone and pramipexole alone. This suggests that the concept of using a combination of L-dopa and pramipexole in late stage disease may have therapeutic benefit. Precisely, how the reduction in dyskinesia occurs is not certain. It could be the lowered ability of the agonist to express dyskinesia in L-dopa primed

animals or alternatively, since the study basically incorporated an L-dopa "sparing" strategy, it could simply reflect the lowering of the L-dopa dosage.

The present data add to and support previous preclinical and clinical observations in this area. Our group has previously shown that treating otherwise drug naïve MPTP-treated common marmosets with combinations of L-dopa and ropinirole could alter dyskinesia induction.[29] The use of an agonist dominant combination provided efficacy but levels of dyskinesia were not different from that produced by ropinirole alone, whereas an L-dopa dominant combination resulted in the expected marked dyskinesia seen with L-dopa alone. We have also shown that in MPTP-treated common marmosets treated with L-dopa to induce marked dyskinesia, switching to an equivalent antiparkinsonian dose of ropinirole or piribedil led to an immediate reduction in dyskinesia intensity while the control of motor function was maintained. Lastly, we showed that in animals that had been treated with ropinirole and had modest dyskinesia, the addition of pulsatile L-dopa treatment rapidly led to intense dyskinesia expression, whereas the more continuous administration of L-dopa plus entacapone did not worsen dyskinesia over that produced by ropinirole treatment.[22] All of these studies suggest that there is a role for dopamine agonists in the treatment of the later stages of PD both alone and in combination with L-dopa.

The clinical value of dopamine agonists in the later stages of the treatment of PD has also been demonstrated. Subcutaneous or intravenous infusions of apomorphine and lisuride[2,19,20,38–40] reduce dyskinesia intensity in some patients with advanced PD who were also receiving L-dopa therapy. Similar results can be obtained using continuous intrajejunal infusion of L-dopa[36] suggesting that it is the continuous nature of drug delivery that can lead to the reversal of the expression of dyskinesia to dopaminergic medication. There is also evidence that switching from L-dopa to high-dose pergolide treatment in late PD can also lead to a reduction in dyskinesia in those able to tolerate the drug.[41]

We conclude that consideration should be given to a clinical investigation involving the reduction of L-dopa dose in the later stages of PD to determine whether replacement by pramipexole maintains control of motor function but lessens dyskinesia intensity.

Author Roles: Kayhan Tayarani-Binazir—execution of research project; execution of statistical analysis; writing of 1st draft of manuscript. Michael Jackson—organization and execution of research project; review and critique of statistical analysis; review and critique of manuscript. Sarah Rose—conception and organization of research project; review and critique of statistical analysis; review and critique of manuscript. Warren Olanow—conception of research project; review and critique of statistical analysis; review and critique of manuscript. Peter Jenner—conception of research project; review and critique of statistical analysis; review and critique of manuscript.

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