Acta Neurol Scand 2003: 107: 202–206
Printed in UK. All rights reserved

ACTA NEUROLOGICA
SCANDINAVICA
ISSN 0001-6314

Piribedil and bromocriptine in Parkinson's disease: a single-blind crossover study

E. K. Tan[1,2], P. Ratnagopal[1], S. Y. Han[1], M. C. Wong[1]

[1]Department of Neurology, Singapore General Hospital, [2]National Neuroscience Institute Sing Health, Singapore

Tan EK, Ratnagopal P, Han SY, Wong MC. Piribedil and bromocriptine in Parkinson's disease: a single-blind crossover study. Acta Neurol Scand 2003: 107: 202–206. © Blackwell Munksgaard 2003.

Introduction – Clinicians switch from one dopamine agonist to another for various reasons. However, each change may inadvertently result in certain potential risks such as decreased medication efficacy or new side-effects. *Objective* – We evaluated the tolerability of a switch of bromocriptine to piribedil using two conversion ratios as a primary outcome measure, with motor function as a secondary outcome measure, in patients with mild to moderate Parkinson's disease (PD). *Methods* – Twenty consecutive patients with mild to moderate PD (Hoehn and Yahr, stage II–III) on treatment with stable doses of bromocriptine and levodopa were randomized to two groups of 10 patients each, to receive piribedil based on 1:5 or 1:10 conversion ratios. Blinded evaluations were performed: 1) United Parkinson's Diseased Rating Scale (UPDRS) scores both in 'on' and 'off', 2) Open-ended interviews for adverse events, 3) Epworth Sleepiness Scale, 4) Purdue Pegboard assessment during 'on' and 'off', 5) Hand-arm movement test during 'on' and 'off', and 6) Walking test during 'on' and 'off'. *Results* – Major adverse events included 'sleep attacks' in one patient and minor side-effects included giddiness, nausea, hallucinations, sleepiness and lethargy. However, these were mild and 19 (95%) of the 20 patients completed the study. There was a significant improvement in both the UPDRS 'off' total and motor scores at 1 month compared with baseline for the group on 1:10 ratio. The walking times during the 'off' state at 1 and 2 months were significantly better compared with baseline in the 1:5 group. There were otherwise no significant differences in the rating tests during both 'off' and 'on' states before and after the bromocriptine switch. *Conclusions* – We demonstrated that patients with mild to moderate PD who were on relatively low doses of bromocriptine can be safely switched to piribedil based on a conversion ratio of either 1:5 or 1:10. However, the higher conversion ratio has to be carried out with caution in patients with daytime somnolence.

Key words: bromocriptine; piribedil; Parkinson's disease; adverse events

Eng-King Tan, Parkinson's Disease and Movement Disorder Programme, Department of Neurology, Singapore General Hospital, Outram Road, Singapore 169608
Tel.: 65 3265003
Fax: 65 2203321
e-mail: gnrtek@sgh.com.sg

Accepted for publication July 3, 2002

Dopamine agonists (DA) are effective as monotherapy in early Parkinson's disease (PD) and as adjunctive treatment to levodopa in advanced PD (1–3). A number of DA are currently available for the treatment of PD: bromocriptine, pergolide, lisuride, cabergoline, piribedil, ropinirole, pramipexole and apomorphine. Despite suggestions that some DA may be more effective than others, comparative trials of different DA (4–17) lack conclusive evidence.

Clinicians switch from one DA to another for various reasons including allergic reactions, cost, perceived or intolerable side-effects, suboptimal response and patient preference. However, change may inadvertently result in unwanted outcomes such as decreased medication efficacy or new unwanted side-effects. There is a need for studies to explore such common situations which clinicians routinely face. Three recent studies demonstrated that a rapid or gradual switchover of an older DA (bromocriptine, pergolide) to a newer DA (ropinirole, pramipexole) could be carried out safely with no loss of efficacy (5, 6, 12). However, the newer DA such as ropinirole and pramipexole are not available in many countries. Piribedil is similar to pramipexole as a non-ergot DA with both D2 and

D3 agonist action and has demonstrated efficacy for treatment of PD (18). Bromocriptine is an older ergot DA, widely used in many countries, including ours. To our knowledge, the tolerability of switching bromocriptine, an ergot DA to piribedil at 1:5 and 1:10 conversion ratios has not been evaluated in a clinical study.

We evaluated the tolerability of a switch of bromocriptine to piribedil using two conversion ratios as a primary outcome measure, with motor function as a secondary outcome measure, in patients with mild to moderate PD.

Methods

Twenty consecutive PD patients evaluated at our Movement Disorder Clinic participated. The inclusion criteria for those who reported no significant side-effects at the time of this study entry included: 1) On stable doses of bromocriptine, levodopa formulations and other anti-parkinsonian medications, 2) Mild to moderate PD (Hoehn and Yahr, stage II–III), 3) Not taken piribedil previously and 4) Given written consent for the study. Approval was obtained from our institution's ethics committee.

The recommended daily upper end dose of bromocriptine is about 50 mg, and for piribedil (Trivastal Retard, controlled release formulation) about 250 mg. This is equivalent to a bromocriptine to piribedil conversion ratio 1:5. The majority of our local PD patients were on 10–15 mg of bromocriptine per day. This allowed us to study a higher conversion ratio (1:10). Ten patients were randomized to a bromocriptine:piribedil conversion ratio of 1:5 and 10 other patients to a ratio of 1:10. The study patients were required to stop taking bromocriptine after the evening dose of the day and commence taking piribedil therapy the following day at a dose in accordance with conversion ratios. Patients on 1:10 ratio were instructed to step up to the required piribedil dose over 1–2 weeks if they were assigned to take 200 mg or more per day. Other anti-parkinsonian medications (e.g. levodopa) were kept constant to minimize confounding variables.

Baseline evaluation was carried out on the last day of bromocriptine ingestion. Patients were evaluated together with non-study patients in the clinic by two observers blinded to the objectives and design of the study. The following evaluations were performed: 1) United Parkinson's Diseased Rating Scale (UPDRS) scores both in 'on' and 'off' states, 2) Open-ended interviews for adverse events, 3) Epworth Sleepiness Scale, 4) Purdue Pegboard (Lafayette Instruments, Lafayette, IN, USA) assessment during 'on' and 'off', 5) Hand-arm movement test during 'on' and 'off' and 6) Walking test during 'on' and 'off'. All patients were examined at about the same time of day throughout the study. All study subjects were contacted fortnightly to ascertain potential adverse events. They were examined at baseline and at 1 and 2 months after commencement of piribedil.

'off' was defined as patient's clinical state when all PD medications were taken off overnight for 12 h.

'on' was defined as the clinical state where functional benefits were maximal, as agreed by patient and investigators. This was usually about 1–2 h after ingestion of anti-parkinsonian medications.

Purdue Pegboard (Lafayette Instruments)

Each patient was instructed to put 10 pegs into the respective holes. If a peg dropped during the process, the test was repeated. Each arm was tested twice. The mean time taken to complete each task was calculated.

Hand-arm movement test

With hands outstretched, patients were instructed to alternate between two fixed points, 30 cm apart, for a period of 20 s. Each hand was tested twice and the mean number of alternations recorded.

Walking test

Patients were instructed to walk as fast as possible for 7 m to and fro, including turning. The test was repeated twice and the mean time ascertained. Freezing episodes when present, were recorded.

Epworth Sleepiness Scale

This scale (19) consisted of eight self-administered questions to assess the likelihood of dozing in different situations. Each answer was graded from 0 = would never doze to grade 3 = high chance of dozing. The maximal score was 24. A score above 11 was interpreted as abnormal.

Statistical analysis

Wilcoxon signed ranks test was utilized to compare the median values of the various rating tests. In addition, student test and chi-squared test were used to compare the continuous and categorical variables. Statistical significance was defined at $P < 0.05$.

Results

Amongst the 1:5 (bromocriptine:piribedil) conversion ratio group, there were eight (80%) males, with mean age of 62.0 ± 9.3 (47–74) years. Amongst the 1:10 conversion ratio group, there were 10 males (100%) with mean age of 59.6 ± 8.1 (47–72) years. Mean bromocriptine dose was 15.8 ± 9.9 (7.5–40) and 11.5 ± 7.1 (5–30) mg/day, respectively (Table 1).

Following conversion to piribedil, 19 (95%) of the 20 patients completed the study. The one patient who dropped out was on 1:10 conversion ratio. He reported 'sleep attacks' as a major adverse effect. All the other patients reported mild and tolerable adverse effects and completed the study. These adverse effects included giddiness, nausea, hallucinations, sleepiness and lethargy (Table 2). For the 1:5 ratio group, four (40%) patients experienced minor adverse effects. Only one patient chose to stop piribedil after completion of the study because of persistent lethargy and reverted back to bromocriptine. For the 1:10 ratio group, five (50%) reported side-effects. However, four of these five patients continued on piribedil. One patient stopped piribedil after the study was completed.

There was a significant improvement in both the UPDRS 'off' total and motor scores at 1 month compared with baseline for the 1:10 conversion ratio. The walking times during the 'off' state at 1 and 2 months were significantly better compared with baseline in the 1:5 group. There were otherwise no significant differences in the rating scores during both 'off' and 'on' states before and after bromocriptine conversion (Tables 3–8).

Table 1 Demographics

Bromocriptine:piribedil ratio	1:5	1:10
Number of patients	10	10
Mean age (years) (range)	62.0 ± 9.3 (47–74)	59.6 ± 8.1 (47–72)
Gender		
Males	8	10
Females	2	
Mean bromocriptine dose (mg/day)	15.8 ± 9.9 (7.5–40)	11.5 ± 7.1 (5–30)

Table 2 Adverse events*

Adverse events	Number of patients†
Major	
Sleep attacks	1
Minor	
Giddiness	3
Nausea	3
Hallucinations	2
Sleepiness	2
Lethargy	1

* Only one patient did not complete trial because of adverse events.

† Some patients reported more than one adverse event.

Table 3 Pegboard test

	Baseline (s)	One month (s)	Two months (s)
Ratio 1:5			
Left 'off'	30.3 (26–47.5)	28.0 (23–77.5)	28 (22–90.5)
Left 'on'	29.5 (22–58)	26.5 (25.5–27)	25 (22–61.5)
Right 'off'	34.5 (24.5–43)	30.8 (26–52.5)	29 (27–45)
Right 'on'	30.5 (26–52)	29.5 (26.8–44)	29 (25–41)
Ratio 1:10			
Left 'off'	40.5 (32–102.5)	36.5 (27–112.5)	35.8 (29–60)
Left 'on'	33.3 (27.5–79)	36.3 (28.5–110)	35.3 (28–55.5)
Right 'off'	34.5 (27–100.5)	31 (24–121)	31.5 (28–55.5)
Right 'on'	29 (22.5–69.5)	30 (23–70.5)	29 (24–50)

Values are given as median (range).

Table 4 Hand-arm movement test

	Baseline (s)	One month (s)	Two months (s)
Ratio 1:5			
Left 'off'	40.5 (17–49.5)	42.1 (20–48)	40.8 (20.5–47.5)
Left 'on'	33.5 (17–42.5)	38 (17–44.5)	39.5 (16.5–45.5)
Right 'off'	40 (13.5–50)	40.8 (22.5–52.5)	38 (21–48)
Right 'on'	38.5 (16–46)	40 (15.5–48)	35.5 (18–45.5)
Ratio 1:10			
Left 'off'	30.5 (27–49.5)	31 (21.5–41.5)	37 (17–38.5)
Left 'on'	24.5 (20–37.5)	29 (23–51)	25 (18–48.5)
Right 'off'	35.5 (22–64.5)	34 (23–54.5)	40.5 (12.5–58)
Right 'on'	30 (22.5–57.5)	35 (12.5–39.5)	30.5 (18–50.5)

Values are given as median (range).

Table 5 Walking test

	Baseline (s)	One month (s)	Two months (s)
Ratio 1:5			
'off'	18* (8.5–37)	14.0* (7.5–18)	16.5* (8–25)
'on'	13 (9.5–28)	11.5 (8–18.5)	15 (9–26)
Ratio 1:10			
'off'	13 (8–108.5)	14 (9–63)	11.5 (9–90.5)
'on'	12 (9–108)	12 (10–55)	12 (9–42)

Values are given as median (range). * $P < 0.05$.

Table 6 UPDRS (total score)

	Baseline (s)	One month (s)	Two months (s)
Ratio 1:5			
'off'	44.5 (30–71)	44.5 (30–57)	48 (29–67)
'on'	22 (5–32)	16 (5–34)	21 (15–35)
Ratio 1:10			
'off'	62* (28–69)	46* (27–65)	53 (20–70)
'on'	11 (5–34)	11 (3–36)	14 (3–38)

Values are given as median (range). * $P < 0.05$.

Table 7 UPDRS (motor score)

	Baseline (s)	One month (s)	Two months (s)
Ratio 1:5			
'off'	31 (22–59)	34 (22–71)	36 (26–67)
'on'	16.5 (4–26)	19.5 (4–26)	19 (11–35)
Ratio 1:10			
'off'	40* (19–56)	33* (14–53)	39 (15–68)
'on'	10 (3–27)	8 (1–29)	12 (3–32)

Values are given as median (range). * $P < 0.05$.

Table 8 Epworth Sleepiness Scale score

	Baseline (s)	One month (s)	Two months (s)
Ratio 1:5	8 (0–15)	7 (1–10)	6 (3–11)
Ratio 1:10	7 (2–19)	5 (1–12)	7 (1–13)

Values are given as median (range).

Discussion

Our study showed that almost all of the mild to moderate PD patients who were on stable doses of bromocriptine (D2 agonist and weak D1 antagonist), could be switched to piribedil (D2 and D3 agonist) at conversion ratios of 1:5 or 1:10 with tolerable side-effects. Whilst the switch of DA appeared to exacerbate some of the adverse effects generally associated with DA, only one patient did not complete the study. This patient dropped out of the study after 1 month at a piribedil dose of 100 mg/day, because of excessive daytime somnolence. He reported almost falling asleep numerous times whilst driving a motor vehicle. These symptoms appeared similar to 'sleep attacks' described by various authors (20–23). This patient's baseline Epworth score (a measure of tendency to sleepiness) was 14 (relatively high), together with a relatively higher bromocriptine:piribedil conversion ratio (1:10) may have exacerbated this pre-existing tendency. Cessation of piribedil led to complete resolution of his somnolence state. He had previously not complained of such 'sleep attacks' while on bromocriptine. Other than this patient, minor side-effects such as giddiness, nausea, lethargy, hallucination and sleepiness, which did not warrant stopping of piribedil during the study were observed in 40% each of the two groups with different conversion ratios. There was no significant increase in the Epworth scores in our study subjects.

Based on blinded evaluations using the UPDRS ratings, Purdue Pegboard test, hand-arm movement test, and walking test during 'off' and 'on' states, we did not detect any significant deterioration in the motor function of our patients as a result of the switch of DA. For the group on 1:10 conversion ratio, there was significant improvement of both the UPDRS total and motor scores during the 'off' state at 1 month after the DA switch, but this was not sustained. This could be the result of an actual initial benefit of increased drug potency or an initial placebo effect. Study of the 1:10 ratio was possible because the majority of our study patients were on relatively low doses of bromocriptine (about 10–15 mg), and hence the recommended upper end dose of piribedil (250–300 mg/day) was not exceeded.

Three studies have previously demonstrated that pergolide or bromocriptine can be rapidly or gradually switched to pramipexole or ropinirole (5, 6, 12) without significant change in adverse events. Hanna et al. (12) in an open label study evaluated 25 patients who were converted from pergolide to pramipexole and did not find any differences in their efficacy. Goetz et al. (5) compared rapid- vs slow-titration for initiating pramipexole in patients already on bromocriptine or pergolide using a conversion of 1:1 for pergolide dose and 10:1 for bromocriptine dose. In the rapid-titration group, the mean time to reach a UPDRS score that was better than baseline without increased adverse events was significantly shorter. The switchover to pramipexole resulted in improved motor function compared with baseline disability on the other DA. Canesi et al. (6) reported better UPDRS activities of daily living score at 4 weeks after an overnight switch from pergolide or bromocriptine to ropinirole (conversion ratio 1:6 and 10:6, respectively). Other studies have shown that when patient's benefit to a DA has waned, switching it to another DA may result in renewed efficacy (14, 15). The exact mechanism of this phenomenon has not been clarified, although differential stimulation of the various dopamine receptors may play a role.

We provided patient tolerability and efficacy data for clinicians contemplating switching DA therapy. While the need for a switch from bromocriptine to piribedil can be argued, the latter drug may be the only non-ergot DA available for PD in a number of countries, and hence our findings will be useful. Our study was not designed for a head-to-head comparison between the two DA. However, we performed comprehensive blinded clinical evaluations designed to examine the tolerability and motor function following the conversion. Furthermore, patients assigned to either conversion ratio were matched in age, gender, stage of disease, and doses of bromocriptine, allowing a

more accurate comparison between the two groups of patients.

In conclusion, we demonstrated that patients with mild to moderate PD on relatively low doses of bromocriptine can be switched to piribedil based on a conversion ratio of either 1:5 or 1:10, with tolerable adverse effects. There was also no loss in medication efficacy following the switch. However, the higher conversion ratio has to be carried out with caution in patients who are high-risk of daytime somnolence. A baseline Epworth score may be useful to stratify the risk of 'sleep attacks' in these patients.

Acknowledgements

We thank Stephanie Fook-Cheong and staff of Department of Neurology, Singapore General Hospital for their assistance and Servier (S) Pte Ltd for contributions to our Movement Disorders Research Fund.

References

1. Brooks DJ. Dopamine agonists: their role in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 2000;**68**:685–9.
2. Tan EK, Jankovic J. Choosing dopamine agonists in Parkinson's disease. Clin Neuropharmacol 2001;**24**:247–53.
3. Montastruc JL, Rascol O, Senard JM. Treatment of Parkinson's disease should begin with a dopamine agonist. Mov Disord 1999;**14**:725–30.
4. Korczyn AD, Brunt ER, Larsen JP et al. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. Neurology 1999;**53**:364–70.
5. Goetz CG, Blasucci L, Stebbins GT. Switching dopamine agonists in advanced Parkinson's disease: is fast titration preferable to slow? Neurology 1999;**52**:1227–9.
6. Canesi M, Antonini A, Mariani CB et al. An overnight switch to ropinirole therapy in patients with Parkinson's disease. J Neural Transm 1999;**106**:925–9.
7. Korczyn AD, Brooks DJ, Brunt ER, Poewe WH, Rascol O, Stocchi F. Ropinirole versus bromocriptine in the treatment of early Parkinson's disease: a 6-month interim report of a 3-year study. 053 Study Group. Mov Disord 1998;**13**:46–51.
8. Guttman M. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. International Pramipexole-Bromocriptine Study Group. Neurology 1997;**49**:1060–5.
9. Inzelberg R, Nisipeanu P, Rabey JM et al. Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. Neurology 1996;**47**:785–8.
10. Mizuno Y, Kondo T, Narabayashi H. Pergolide in the treatment of Parkinson's disease. Neurology 1995;**45**:S13–21.
11. Pezzoli G, Martignoni E, Pacchetti C et al. Pergolide compared with bromocriptine in Parkinson's disease: a multicenter, crossover, controlled study. Mov Disord 1994;**9**:431–6.
12. Hanna PA, Ratkos L, Ondo WG, Jankovic J. A comparison of the therapeutic efficacy of pergolide and pramipexole in Parkinson's disease. J Neural Transm 2001;**108**:63–70.
13. Laihinen A, Rinne UK, Suchy I. Comparison of lisuride and bromocriptine in the treatment of advanced Parkinson's disease. Acta Neurol Scand 1992;**86**:593–5.
14. Goetz CG, Shannon KM, Tanner CM, Carroll VS, Klawans HL. Agonist substitution in advanced Parkinson's disease. Neurology 1989;**39**:1121–2.
15. Goetz CG, Tanner CM, Glantz RH, Klawans HL. Chronic agonist therapy for Parkinson's disease: a 5-year study of bromocriptine and pergolide. Neurology 1985;**35**:749–51.
16. LeWitt PA, Ward CD, Larsen TA et al. Comparison of pergolide and bromocriptine therapy in parkinsonism. Neurology 1983;**33**:1009–14.
17. LeWitt PA, Gopinathan G, Ward CD et al. Lisuride versus bromocriptine treatment in Parkinson's disease: a double-blind study. Neurology 1982;**32**:69–72.
18. Rondot P, Ziegler M. Activity and acceptability of piribedil in Parkinson's disease: a multicentre study. J Neurol 1992;**239**:S28–34.
19. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;**14**:540–5.
20. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;**52**:1908–10.
21. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson's disease treatment. Lancet 2000;**355**:1333–4.
22. Tan EK, Lum SY, Fook-Chong SM et al. Evaluation of somnolence in Parkinson's disease: comparison with age and sex matched controls. Neurology 2002;**58**:465–8.
23. Tan EK. Piribedil-induced sleep attacks in Parkinson's disease. Fundam Clin Pharmacol (in press).