Antiparkinsonian drug-induced sleepiness: a double-blind placebo-controlled study of L-dopa, bromocriptine and pramipexole in healthy subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Dopamine agonists used in Parkinson's disease patients are associated with excessive daytime sleepiness and sleep attacks occurring without prior warning.
- Parkinson's disease accounts in itself for a variety of sleep disorders. It is therefore important to study the drug-induced sleepiness in healthy volunteers.
- In healthy subjects, pramipexole has proved to decrease alertness and ropinirole to reduce sleep latency.

WHAT THIS STUDY ADDS

- Results from our study show that pramipexole reduces the mean sleep latency as measured by the Multiple Sleep Latency Test in healthy volunteers, hence providing an objective measure of increased sleepiness.
- Furthermore, the reduction in sleep latency was not associated with a subjective impression of increased sleepiness.
- Such dissociation may underlie the occurrence of sleep attacks without prior warning.

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AIMS

To assess the sleepiness induced by pramipexole, a D2/D3-dopamine receptor agonist commonly used in Parkinson's disease and restless legs syndrome, without the problem of the confounding factors related to the disease.

METHODS

Placebo, bromocriptine (2.5 mg), L-dopa (100 mg) and pramipexole (0.5 mg) were administered in a single oral dose on four separate days, with at least a 2-week wash-out period in a randomized cross-over design. Induced somnolence was assessed using Multiple Sleep Latency Test (MSLT) and subjective scaling of vigilance. Twelve male subjects (26.3 ± 5.5 years old) without anxiety, mood, sleep or sedation disorders were enrolled.

RESULTS

Pramipexole significantly reduced mean sleep latency compared with placebo 3 h 30 min [-6.1 min ($-9.8, -2.4$), $P = 0.002$] and 5 h 30 min [-5.6 min ($-7.7, -3.5$), $P = 0.003$] after administration. In addition, the total duration of sleep during the tests was higher with pramipexole than with placebo [$+6.0$ min ($2.3, 9.7$), $P < 0.001$]. These differences were not observed with L-dopa and bromocriptine in comparison with placebo. The induced sleepiness was not associated with an increase in subjective somnolence scaling, indicating that this adverse event may occur without prior warning.

CONCLUSIONS

These results show that a single oral dose of pramipexole induces sleepiness as assessed by MSLT in healthy young subjects, independent of disease-related sleep dysfunction.

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease caused by loss of dopaminergic neurons within the substantia nigra. It is characterized by tremor, rigidity and akinesia. Although sleep disorders have been observed since the first description of the disease [1], they have only recently been acknowledged as a disabling feature. Frucht *et al.* first reported the occurrence of sudden and irresistible sleep attacks with subsequent automobile accidents on PD patients treated with pramipexole or ropinirole, two non-ergot dopamine D2/D3-receptor agonists [2]. This observation has been confirmed by further case reports and one retrospective chart review [3, 4]. Since then, sleep attacks as well as excessive daytime sleepiness have also been observed in patients taking ergot dopamine agonists such as bromocriptine [5], lisuride [5], cabergoline [6], pergolide [7, 8] and priribedil [9]. In addition to the well-known sedative effect of apomorphine [10] and reports of sleep attacks in patients on levodopa monotherapy [11–13], these reports together suggest that sleep attacks and excessive daytime sleepiness are a class effect of dopaminergic agents [14, 15].

However, the study of the sedative effects of drugs on PD patients remains biased by many confounding factors. Indeed, excessive daytime sleepiness is a frequent and early feature of this disease [16] and could be a preclinical marker [17]. Moreover, various surveys have estimated the prevalence of sleep disorders in these patients to be as high as 66–98% [18]. Night-time sleep disturbances that frequently occur during the course of the disease include among others sleep fragmentation, motor symptoms such as restless legs syndrome, rapid eye movement sleep, behavioural disorders (which represent common features of all synucleinopathies) and obstructive sleep-breathing disorders [1, 18]. In addition to being disturbing *per se*, they may also contribute to excessive daytime sleepiness. Surprisingly, altered night-time sleep is overall not associated with greater sleepiness in PD patients, suggestive of hypersomnia of central origin [1]. Thus, it seems more likely that this excessive sleepiness is the consequence of a variety of changes arising in this condition such as dopaminergic denervation itself, mood disorders and, of course, the treatment. Owing to these confounding factors, the role of the treatment is difficult to establish. Therefore, several studies have been aimed at characterizing the sedative effects of dopamine agonists in healthy subjects. Andreu *et al.* found that acute administration of 200 mg L-dopa produced a sedative effect with weak tolerance phenomena [19]. Some of their results have been confirmed in a similar study conducted in our department [20]. More recently, Ferreira *et al.* have investigated the sedative effects of ropinirole in a placebo-controlled, randomized, double-blind study of 20 healthy adults using the Multiple Sleep Latency Test (MSLT) [21]. The administration of ropinirole induced a significantly lower mean sleep latency compared with

placebo, suggesting a sedative effect independent of other disease-related dysfunction. Pramipexole has recently gained further interest through its efficacy in restless legs syndrome (RLS) [22, 23]. The aim of this study was therefore to compare the sedative effects of this drug with those of L-dopa and bromocriptine all administered at the doses recommended in RLS [23] in a double-blind, placebo-controlled trial.

Materials and methods

Subjects

Twelve male subjects aged 18–45 years (mean 26.3 ± 5.5 years) participated. None of the subjects was overweight as determined by their body mass index (mean BMI = 22.5 ± 2.3 , range 19.4–26.0). All were in good physical health and underwent a complete medical assessment, including a medical history questionnaire, physical examination, laboratory profile (haematological and biochemical analysis, breath alcohol quantification) and electrocardiogram. Urinary tests were performed so as to eliminate individuals under psychoactive drugs (barbiturate, benzodiazepines, cannabinoid, cocaine, opioids).

All subjects smoked <10 cigarettes day⁻¹ and were able to refrain from smoking during test days. No spontaneous adverse events that may be related to withdrawal were reported by the subjects.

Subjects who had taken drugs acting on dopaminergic or vigilance systems or substances with psychotropic effects within the last 4 weeks were excluded. None was regularly consuming >2 cups/glasses of tea, coffee or drinks containing caffeine. All subjects were right-handed and had normal or corrected-to-normal visual acuity.

None had excessive somnolence or had a diagnosis of sleep disorder or any subjective sleep complaint. To be included in the study, subjects had to be judged as not anxious (based on clinical interview and Hamilton Anxiety Scale Rating Score) [24], good sleepers (with a maximum score of 6/21 on Pittsburgh Sleep Quality Index) [25], without any tendency to fall asleep during everyday situations (score in Epworth Sleepiness Scale <8/21) [26]. Subjects with excessive morning (score >69/89) and excessive evening (score <31/89) chronotypes as defined by the Horne-Ostberg Morningness-Eveningness Questionnaire were excluded [27]. This study was conducted in accordance with the principles of the declaration of Helsinki. Approval was obtained from the local Ethics Committee (CCPPRB Marseille). All subjects were registered on the French National File and gave written informed consent before entering the study.

Study design

The study was a randomized, double-blind, balanced trial with four sessions separated by a 2-week wash-out interval. Subjects were randomly assigned and given a single

oral dose of either 100 mg levodopa, 0.5 mg pramipexole or 2.5 mg bromocriptine or placebo (lactose) in a cross-over design. These drugs were selected because of their different profiles among dopaminergic receptors. Bromocriptine is an ergot-derived dopamine agonist that acts as a partial antagonist for the D1-receptor and has a high affinity for the D2-receptor. The time to attain peak concentration is estimated between 1 and 2 h, the plasma elimination half-life is about 3–8 h [28]. Pramipexole is a full intrinsic activity non-ergot dopamine agonist with high selectivity for interacting with D2 subfamily receptors and with a preferential affinity for D3-receptors. Maximum plasma concentration is attained between 1 and 3 h and its plasma elimination half-life in healthy adults is 8 h [28].

The doses used in the study were chosen based on published articles [29–32] in order to limit adverse events in healthy subjects (such as vomiting, postural hypotension) that may interact with the measures. In addition, the doses are those commonly used in patients suffering from RLS [23].

All treatments were supplied as indistinguishable capsules administered with tap water. Subjects received domperidone (60 mg day⁻¹ orally: two tablets three times a day for 3 days before each session and through the test day) to prevent adverse dopaminergic effects such as nausea, vomiting and hypotension [33].

Tests

Assessment of the sedative effects of treatments was performed using objective and subjective measures.

- The MSLT: for this test, subjects were given the opportunity to fall asleep during a 20-min period five times a day while they were monitored electroencephalographically [34]. Five test sessions were performed at 2-h intervals throughout the day, beginning 1 h 30 min after the treatment administration (hereafter referred to as T1h30, T3h30, T5h30, T7h30 and T9h30). Subjects were asked to lie quietly in a darkened room and to try to fall asleep. Sleep onset and stages were scored by the same investigator (MR) using standardized international criteria [34]. For each test, sleep latency (defined as the time between the start of the test, lights out and the first period of any sleep stage) and duration of each sleep stage were measured. The MSLT was recorded on an ambulatory EEG device (Brain-spy; Micromed, Saint-Etienne des Oullières, France), with 12 leads including C3-A2, EOG, EMG for sleep evaluation. Even though patients were not allowed to sleep between MSLT sessions, they were recorded during the entire session day, which allowed us to know whether or not they had slept between the MSLT sessions (assessment of duration of total sleep between MSLT sessions). At the end of each MSLT session the subject evaluated his sleep/wake state during the test between four states, awake–drowsy–sleep–dream. Mean sleep latency across

the first four and all five tests were calculated (MSLT4 and MSLT5, respectively).

- The Thayer's scale: a subjective activation auto-evaluation scale, the Thayer's Activation-Deactivation Adjective Checklist, was used 5 min before each MSLT. It consists of 20 self-descriptive adjectives rated on a four-point scale [35]. Vigilance was calculated as the ratio between two domains of the scale (General Activation/Deactivation-Sleep, GA/DS).
- Hindmarch's visual analogue rating scales (VAS): 10-cm horizontal line visual analogue scales, translated into French, were used to assess subjects' subjective state [36]. Six of these scales assessed complementary aspects of sedation (drowsy, woozy, clumsy, fine, energetic and tired) and five assessed different aspects of mood (anxious, happy, relaxed, sad and depressed).
- Autonomic function: supine and standing blood pressure and heart rate were measured in a standardized manner. Blood pressure (SBP, DBP) was measured using an automatic oscillomanometer after 10 min in supine position and after 2 min in standing position. Five measurements were monitored 10 min before each MSLT in order to detect orthostatic hypotension.

Study procedure

Healthy subjects were admitted to the Centre for Clinical Pharmacology and Therapeutics two consecutive days before each assessment session in order to control bed-time and wake-up time (lights were turned off before 23.00 h and turned on at 06.30 h) and to perform nocturnal polysomnographies with the same ambulatory device (Brain-spy; Micromed) scored according to standardized criteria [37]. For each session, the two nights (including the adaptation night) were recorded in the same room of the Centre. Subjects had their breakfast at 07.00 h and treatment (levodopa, bromocriptine, pramipexole or placebo) was administered at 08.00 h (T0). MSLT was performed at 09.30, 11.30, 13.30, 15.30, 17.30 (T1h30, T3h30, T5h30, T7h30 and T9h30, respectively). Thayer's scale was rated 5 min before each MSLT. VAS were completed at T2h, T4h, T6h and T8h.

No concomitant treatment was allowed for the duration of the study, except domperidone.

Alcohol, tobacco, tea, coffee or other substances containing caffeine were prohibited on study days. After each session, subjects were transported home with instructions not to drive a motor vehicle until the next morning.

Statistical analysis

Data analysis was performed using the SAS-PC computer program (version 8.2; SAS Inc., Cary, NC, USA). The two-tailed level of significance was equal to 0.05 unless otherwise specified.

Comparability of nocturnal polysomnography measures observed during the night before each treatment

Table 1Polysomnographical parameters (mean $\pm$ SD) the night before each treatment administration

	L-dopa	Placebo	Treatments Bromocriptine	Pramipexole
Sleep latency	37.2 $\pm$ 42.3	29.8 $\pm$ 26.1	25.4 $\pm$ 23.3	23.5 $\pm$ 10.9
Stage 1	28.1 $\pm$ 20.4	24.7 $\pm$ 19.4	23.4 $\pm$ 8.5	16.8 $\pm$ 4.1
Stage 2	171.0 $\pm$ 32.9	188.4 $\pm$ 37.6	195.1 $\pm$ 27.8	201.0 $\pm$ 29.1
Stage 3	35.4 $\pm$ 13.8	33.5 $\pm$ 12.5	31.3 $\pm$ 7.2	27.7 $\pm$ 10.2
Stage 4	71.2 $\pm$ 20.8	54.5 $\pm$ 19.5	71.1 $\pm$ 32.7	70.6 $\pm$ 15.2
REM sleep	80.1 $\pm$ 27.2	87.2 $\pm$ 25.0	92.2 $\pm$ 25.2	89.4 $\pm$ 25.2
Total sleep time	437.0 $\pm$ 39.2	436.1 $\pm$ 25.8	455.8 $\pm$ 35.5	451.7 $\pm$ 24.2
Awakenings	51.3 $\pm$ 46.5	47.6 $\pm$ 37.3	42.8 $\pm$ 20.8	46.2 $\pm$ 49.0
REM latency	77.0 $\pm$ 32.3	88.7 $\pm$ 58.6	69.9 $\pm$ 10.5	89.8 $\pm$ 64.6

Data are expressed in minutes and shown as mean values $\pm$ SD.

administration was established using two-way analysis of variance (ANOVA) (treatment, period and treatment $\times$ period).

Sleep latency and BP parameters were compared between treatment groups across the five MSLT sessions using repeated measures ANOVA (treatment, period and treatment $\times$ period). Mean sleep latency over the first four and all five MSLT sessions (MSLT4 and MSLT5, respectively) were compared between treatment groups using two-way ANOVA (treatment, period and treatment $\times$ period). If a significant treatment effect was observed, pairwise comparisons between pramipexole and others treatments were performed using Dunnett's multiple comparisons test.

Duration of total sleep, VAS sedation and Thayer's scores were compared between treatment groups using nonparametric ANOVA (Kruskal–Wallis' test) for each MSLT session. Pairwise comparisons with pramipexole were performed using Wilcoxon's rank test. Level of significance for nonparametric tests was adjusted by the Bonferroni correction. Means and the 95% confidence intervals are presented in the text.

Results

Nocturnal polysomnography measures revealed normal sleep efficiency for all subjects. No differences in sleep duration and sleep architecture were observed during the night before each treatment administration (Table 1).

Significantly reduced sleep latency was observed at T3h30 with pramipexole compared with placebo [−6.1 min (−9.8, −2.4), $P = 0.002$] and bromocriptine [−8.3 min (−12.5, −4.1), $P < 0.001$]. At T5h30 a significant difference between pramipexole and placebo was found [−5.6 min (−7.7, −3.5), $P = 0.003$] (Figure 1). At T1h30, T7h30 and T9h30, no significant difference of sleep latency was observed between the four compounds (Figure 1).

Mean sleep latency over the first four MSLT sessions (MSLT4) was lower under pramipexole than under placebo,

Figure 1

Comparative time course of sleep latency on Multiple Sleep Latency Test (MSLT) for the four treatments. Data are expressed in minutes and shown as mean values $\pm$ SD of each MSLT session for each treatment (* $P < 0.01$). L-dopa (◆); Placebo (■); Bromocriptine (▲); Pramipexole (●)

levodopa and bromocriptine [respectively, −5.6 min (−8.7, −2.6); −3.6 min (−6.5, −0.8); −4.6 min (−8.0, −1.2); $P < 0.005$]. However, the difference in mean sleep latency over all five MSLT sessions (MSLT5) did not reach statistical significance.

Comparative results between treatment groups and total sleep during the MSLT session showed a significant difference at T3h30 (second test). The duration of total sleep time with pramipexole was significantly higher compared with placebo [+6.0 min (2.3, 9.7), $P < 0.001$] and with bromocriptine [7.6 min (3.3, 11.9), $P < 0.001$].

Even though none of the subjects were overweight (mean BMI = 22.5 $\pm$ 2.3, range 19.4–26.0), we sought to determine whether weight or BMI could influence the propensity of subjects to show sedation after dopaminergic drug administration. No correlation was found between

the BMI or weight and sleep latency at any time point or for the mean sleep latency across the first four and all five tests (MSLT4 and MSLT5). Furthermore, adding the BMI as a covariate into the ANOVA (ANCOVA) did not change the above results.

Neither the Thayer's scale rated 5 min before each MSLT nor the Hindmarch's scale performed 10 min after the end of MSLT showed any significant difference between treatments among the different items, in particular items drowsy and woozy (Figure 2).

Overall, three subjects reported nausea during one session each (three occurrences out of 48 sessions). One patient reported mild nausea 2 h after bromocriptine administration, two patients reported moderate nausea 1 h 20 min and 2 h 10 min after L-dopa and pramipexole administration, respectively. The adverse event lasted for 1–5 h. None of the subjects experienced vomiting. There is good evidence to suggest that this figure would have been much higher if the subjects had not received domperidone concomitantly [38]. No significant change in mean supine and standing BP or heart rate was observed under treatments during each time of evaluation.

Discussion

This study was designed to investigate antiparkinsonian drug-induced sleepiness using the MSLT as main criterion.

Main results

The main finding of this study is that pramipexole induces sleepiness when administered to healthy volunteers.

The MSLT, which measures sleep latency during four to five daytime nap opportunities using polysomnography, is widely accepted as the 'gold standard' for quantifying daytime sleepiness [34]. Pramipexole-induced daytime sleepiness was significant at 3 h 30 min and 5 h 30 min after drug administration. These results are concordant with the pharmacokinetic and pharmacodynamic profile of pramipexole. Indeed, Schilling *et al.* have investigated the neuroendocrine profile of pramipexole in healthy subjects and have shown that pramipexole decreased serum prolactin levels in a dose-dependant manner with a maximum effect after 2–4 h [39]. The absence of significant difference in mean sleep latency over the five MSLT sessions (MSLT5) compared with that calculated over the four first MSLT sessions (MSLT4) further suggests the disappearance of any effect of pramipexole on sleep during the last session.

Special care was given to factors that might influence the results on MSLT, such as the excessive morning or evening chronotype (explaining the non-inclusion criteria defined by the Horne-Ostberg Morningness-Eveningness Questionnaire) [27] and chronic sleep deprivation. The

Figure 2

Subjective assessment of vigilance levels for each treatment using the Thayer's and Hindmarch's scales. Mean visual analogue scaling scores for items 'woozy' (A) and 'drowsy' (B) of Hindmarch's scale and mean self-alertness ratio (GA/DS) calculated from items of the Thayer's scale (C). Results are shown for each treatment and each assessment time. Error bars (SD) are indicated. L-dopa (X); Placebo (■); Bromocriptine (◇); Pramipexole (▲).

quality of sleep, the night before each administration, was monitored and was not significantly different between treatments. Moreover, the mean sleep latency was in the range normally observed in healthy humans (10–20 min) [34].

The concomitant intake of domperidone in association with pramipexole is unlikely to account for the observed effect. Indeed, a double-blind, placebo-controlled cross-over study of pharmacokinetic interactions between pramipexole and domperidone in 12 volunteers has revealed that domperidone did not alter the pharmacokinetics in human (unpublished data, Upjohn Technical Report, 1995). Furthermore, a pharmacodynamic interaction with domperidone is unlikely since it minimally crosses the blood–brain barrier [40]. It is worth mentioning, however, that the concept of exclusive peripheral action of domperidone has recently been challenged in a study suggesting that it may have access to some dopamine receptors when administered at higher doses [41]. Nonetheless, these authors observed a reliable sedative effect of pramipexole (administered to healthy subjects at the same single dose as in our study) maintained in the presence of domperidone even though the latter may antagonize some of its central effects [41].

Finally, it has been suggested that autonomic failure could play a major role in the increased sleepiness in PD [14]. In the present study, we have monitored supine and standing BP and heart rate before each MSLT session and did not observe any change at any time.

It is interesting to note that neither Thayer's nor Hindmarch's scales were able to detect vigilance reductions in subjects treated with pramipexole, although they experienced increased sleepiness. This finding is particularly striking with Thayer's scale, which was performed 5 min before each MSLT session, whereas Hindmarch's scale was performed 10 min after each MSLT and hence potentially after a sleep period. This result is consistent with the absence of warning preceding the sleep attacks in patients treated with dopamine agonists [2]. However, one cannot exclude the possibility that reduced sleep latency more accurately reflects sleepiness than subjective language-based appraisal tools such as scales.

Mechanisms of dopamine agonists-induced sleep attacks

It is known that several substances that enhance dopaminergic transmission, such as amphetamine [42] and even pure dopamine agonists [43], increase cortical activity assessed by electroencephalogram as well as behavioural excitation in nonparkinsonian animals. Several dopaminergic structures located in the vicinity of the substantia nigra, such as the ventral tegmental area or ventral periaqueductal grey matter, feature diffuse ascending cortical projections suggestive of a wake-promoting network [44]. It has been suggested that the sedative effects of dopamine agonists depend on the stimulation of a dopamine presyn-

aptic autoreceptor. Indeed, administration of low doses of various agonists increased sleep in rats, whereas high doses increased wakefulness [43]. Nevertheless, these results suggesting a biphasic effect are not in accordance with the clinical observation that patients treated with high doses of agonists experience more severe sleep attack episodes than those treated with lower doses [13, 14]. In this regard, the doses administered in our study were deliberately lower than those producing a significant effect in Parkinsonian patients in order to minimize the deleterious effects of dopaminergic drugs (digestive discomfort). In spite of this, a single administration of pramipexole significantly decreased the mean sleep latency compared with placebo. The lower doses administered could also account for the absence of drowsiness in subjects treated with L-dopa, contrary to a previous study [19]. On the other hand, the more pronounced sedative effect of pramipexole may be related to a higher selectivity on dopamine receptors than other parkinsonian drugs [45].

One should be cautious when extrapolating these results to PD patients, for several reasons: (i) the administered doses were chosen in order to avoid side-effects as much as possible and were not equivalent to each other. However, it should be borne in mind that the dose equivalence is based upon empirical observations of clinical efficacy and does not reflect in any way the receptor occupancy [46]; (ii) the sedative effects of dopaminergic drugs is likely to be exaggerated in PD patients compared with healthy subjects in relation to the underlying disease process and dopamine neuronal loss, as suggested by Chaudhri *et al.* [47] and Rye and Jankovic [15]; (iii) it is also likely that the acute and chronic effects of dopaminergic drugs are different, as suggested by the results of clinical studies such as Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease, showing that pramipexole-induced sedation occurred mostly during titration [48].

In conclusion, pramipexole administered in a single and low dose (0.5 mg, similar to that used in RLS) in healthy subjects reduced sleep latency assessed by MSLT 3h30 and 5h30 after administration without any significant effect on subjective vigilance assessment using Thayer's and Hindmarch's scales. Since these results have been found in young healthy subjects after a single oral dose, other investigations may be performed in long-term treated PD and RLS patients.

Competing interests

Nothing to declare.

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