ORIGINAL ARTICLE

Piribedil-induced sleep attacks in Parkinson's disease

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ABSTRACT

'Sleep attacks', episodes of sudden onset of sleep without any prodromal symptoms, were initially described in patients with Parkinson's disease (PD) taking the newer dopamine agonists pramipexole and ropinirole. Piribedil, a nonergot agonist with both D2 and D3 agonist action, is an effective antiparkinsonian medication. However, there are very few reports of Piribedil-induced sleep attacks in PD. Among 50 PD patients seen at our Movement Disorder Clinic who had recently taken Piribedil, we identified three (6%) who satisfied the clinical description of sleep attacks. Here we provide details of the clinical characteristics of Piribedil-induced sleep attacks in these PD patients.

INTRODUCTION

Hypersomnolence is a common clinical problem in patients with Parkinson's disease (PD) [1], and can be secondary to the disease and/or related to the use of antiparkinsonian medications or sedatives [1–11]. Frucht et al. recently coined the term 'sleep attacks' to refer to episodes of sudden onset of sleep without any prodromal symptoms in PD patients who were on the newer dopamine agonists pramipexole and ropinirole [3]. While the definition of sleep attacks has been debated, it is increasingly recognized that such sleep episodes pose real hazards to PD patients who drive or operate heavy machinery. Although the original report only implicated the newer nonergot dopamine agonists, subsequent studies have demonstrated sleep attacks also to be associated with the use of various different ergot dopamine agonists and levodopa [4–13].

Piribedil (Trivastal; Servier, France), a nonergot agonist with both D2 and D3 agonist action, is an effective antiparkinsonian medication [14]. It is has been marketed in Europe and Asia for the treatment of PD for many years. However, there are very few reports of piribedil-induced sleep attacks in PD [6]. Here we provide details of the clinical characteristics of piribedil-induced sleep attacks in three PD patients.

METHODS

Among 50 PD patients seen at our Movement Disorder Clinic who had taken piribedil, we identified three (6%) who satisfied the clinical description of sleep attacks as employed by Frucht et al. [3]. We routinely enquired about the presence of sleep attacks in all the 50 patients who were newly prescribed piribedil. A sleep attack is defined as 'an event of sudden, irresistible, and overwhelming sleepiness that occurs without warning and not preceded by feeling sleepy'. These three patients have been personally followed up by the author for between 6 months and 2 years.

CASE ONE

A 51-year-old hypertensive Chinese man presented with a 6-month history of slowness and stiffness of his limbs. He was diagnosed with PD based on clinical evidence of rest tremor, bradykinesia, rigidity, and postural instability. He was initially treated with bromocriptine with little improvement. Subsequently, levodopa was added. Over the course of about 1 year, his symptoms were optimized with bromocriptine at 10 mg/day, and levodopa/carbidopa at 600 mg/day. He did not complain of any significant adverse drug reactions with these two medications.

He later agreed to participate in an open clinical trial which involved an overnight switching of his bromocriptine at 10 mg/day to piribedil at 100 mg/day, while maintaining his levodopa dose [15]. Unfortunately, he dropped out of this trial after taking Piribedil for less than 2 weeks. Without us asking leading questions, he volunteered the following information. He described 'an intense urge to fall asleep without warning' within a few days of starting to take piribedil. This sensation usually occurred within 1–2 h of taking the medication, and had no relation to time of the day. His sleep attacks were first noticed when he was driving to work. He felt the urge to fall asleep was so 'irresistible' that his head would slump onto the driving wheel at the traffic junction. He had great difficulty anticipating and preventing these episodes voluntarily. There was no previous experience of such episodes when he was on bromocriptine or levodopa. He ceased driving shortly thereafter. Upon stopping Piribedil, these episodes resolved.

However, as subjectively he felt his stiffness and tremor were much improved while he was on Piribedil, he restarted piribedil himself without our knowledge. He experimented with the drug at different times of day, and came to his own conclusion that taking a 50-mg tablet of the drug at night helped him sleep better, with very few episodes of sleep attack during the daytime. While off work, he experimented with a 50-mg tablet three times a day and experienced more than 10 episodes of sleep attack compared to one or two per day if he took only a nighttime dose. He insisted on continuing with Piribedil, taking one or two 50-mg tablets per day, as he felt better on it. However, he has not started driving again.

CASE TWO

A 53-year-old previously well Malay man was diagnosed with PD characterized by rest tremor, rigidity, and bradykinesia. As he was relatively young, with mild to moderate parkinsonian symptoms, we started him on Piribedil at 50 mg once a day and slowly increased to 50 mg twice a day. Within 1–2 days of taking piribedil at 100 mg/day, he complained of an 'irresistible urge to fall asleep', of sleepiness that 'came on suddenly' and of 'difficulty controlling the sleep sensation'. This was much worse when the dose of piribedil was increased to 50 mg three times a day. He experienced such episodes during his daily activities such as 'watching television', 'reading the newspaper' and being 'on a bus'. He was afraid to drive because of the fear of these sleep attacks. However, as there were both subjective and objective improvements of his tremor, rigidity and bradykinesia with piribedil, he insisted on carrying on with the drug, but at a reduced dose at which such episodes were infrequent. He declined a switch to another dopamine agonist.

CASE THREE

A 63-year-old Chinese man presented with a 3-month history of gait difficulty, slowness of movement and intermittent limb tremor. He was diagnosed as having PD and started on levodopa. His symptoms were much improved on 300 mg of levodopa per day. After 4 months on this dose of levodopa, piribedil (100 mg/day) was gradually added over 1 week. Within 1 week on the 100 mg/day dose, the patient complained of excessive sleepiness. He would 'fall asleep suddenly without warning' while engaged in daily activities such as reading newspapers, watching television, and eating meals. These episodes occurred many times a day. The patient did not seek medical attention, but reduced the dose of piribedil to 50 mg/day, which led to significant improvement in the frequency of these sleep episodes. Subsequently, he consulted us at the outpatient clinic and was advised to stop Piribedil completely. The dose of the levodopa was not changed. After complete cessation of piribedil, the sleep episodes resolved.

DISCUSSION

In this report we have described three patients with distinct piribedil-induced sudden onset of sleep episodes similar to the clinical description of sleep attack as reported by Frucht et al. [3] and other authors [4–13]. It is possible that levodopa could be a contributory cause of sleep attacks. However, both patients 1 and 3 were on relatively low and constant doses (300 and 600 mg/day) of levodopa, and patient 2 was not on any levodopa at all. None of the three patients were prescribed any other antiparkinsonian medications or sedatives. Furthermore, the sleep attacks occurred within 1 week after piribedil was first taken, and markedly improved or resolved on reducing the dose or stopping the drug. Hence piribedil was the most likely major cause of the sleep attacks in our patients.

These three cases illustrate some of the clinical characteristics of piribedil-induced sleep attacks: first, the occurrence and frequency of sleep attacks appear to be dose-dependent; secondly, sleep attacks can occur in both levodopa-naïve patients and those exposed to levodopa,

and, thirdly, prolonged usage despite sleep attacks may lead to tolerance to this side-effect. The first two observations do not appear to be unique to piribedil. Previous reports have suggested that sleep attacks induced by other dopamine agonists may be also be dose-dependent [1,2]. The PD patients who experienced sleep attacks in the Frucht et al. [1] and Hauser et al. [2] series took pramipexole at doses of about 3 and 4 mg/day. In several instances, the sleep attacks resolved after the dose of pramipexole was reduced. Other studies also suggest that there may be a threshold effect of sedation for pramipexole [16]. We have previously demonstrated that a higher dose of levodopa predicts sleep attacks in PD [8].

It is interesting that patients 1 and 2 chose to continue with piribedil but at a lower dose, despite the occurrence of sleep attacks. They claimed to be getting used to the sleep attack episodes and found them tolerable at a lower dose. However, there may be potential problems if the dose of levodopa needs to be increased in the future. Details of piribedil-induced sleep attacks are rarely available in the literature. One such case involved a 69-year-old man with PD who was treated with 250 mg of levodopa per day, and 150 mg of piribedil per day. His wife highlighted his sleep problems, and the patient apparently fell asleep while driving.

While the notion of sleep attacks remains controversial, the clinical problem of such sleep episodes induced by dopamine agonists with a background of increased somnolence in PD patients is a real one. Blanket regulations restricting driving privileges for PD patients who are on certain agonists may be premature at this point. However, we should recognize this as a clinical problem in some of our PD patients and institute preventive measures [17]. A number of studies have highlighted some predictive factors of sleep attacks in PD such as advanced age, longer duration of disease, and higher dose of levodopa [7,8]. The Epworth Sleepiness Scale [18] or other validated sleep scale may also be useful to stratify the risk of sleep attacks. Prospective epidemiologic studies examining the risk of sleep attack associated with the different dopamine agonists will provide clinically useful information.

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