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Piribedil: sleep attacks, also in patients without Parkinson's disease

● **Piribedil is a dopamine agonist used in Parkinson's disease and a variety of other clinical situations although its efficacy has not been demonstrated.**

● **A study based on the French national pharmacovigilance database identified and analysed 7 reports of sleep attacks attributed to *piribedil* in patients without Parkinson's disease. The case reports are detailed and indicate that *piribedil* has a direct role in the onset of sleep attacks.**

● **To spare patients unnecessary exposure to the adverse effects of *piribedil*, it is better to avoid using *piribedil* and to choose drugs with demonstrated efficacy instead.**

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Piribedil is a dopamine agonist used to treat Parkinson's disease, but its efficacy is less well evaluated than that of other dopamine agonists (1,2). It is also authorised in France as a "vasodilator" to treat certain types of chronic cognitive and neurosensory deficits in elderly patients, intermittent claudication caused by chronic peripheral artery occlusive disease, and in ophthalmology, although its efficacy in these indications has not been demonstrated (2-5).

Piribedil exposes patients to the adverse effects of dopamine agonists, including sudden sleep attacks, most of which have been reported in patients with Parkinson's disease (a)(1,6). Does this adverse effect also occur when *piribedil* is used for other disorders, by patients without Parkinson's disease? A case series published in 2011 provides some answers to this question.

Sudden sleep attacks, from the first few days of treatment. A group from the Lyon Regional Pharmacovigilance Centre searched the French national pharmacovigilance database for reports of sleep attacks attributed to *piribedil* in patients without Parkinson's disease, recorded between January 1988 and December 2008 (7).

According to the definition adopted in this study, sleep attacks are "events of overwhelming sleepiness that occur without warning or with a prodrome sufficiently short or overpowering to prevent protective measures" (7).

The French pharmacovigilance database contained 7 reports of sleep attacks that met this definition in patients without Parkinson's disease who were taking *piribedil*. The average age of these 7 patients was 69 years. The daily dose ranged from 20 mg to 150 mg (median: 50 mg). Six patients were using *piribedil* for a variety of vascular disorders, and the other patient was taking it for essential tremor. In 6 cases, *piribedil* was the only drug implicated (7).

In 5 cases, the sleep attacks began within 3 days of taking the first dose. In one woman who had taken *piribedil* for 10 years with 2 interruptions, the sleep attacks stopped after each discontinuation and recurred each time the drug was reintroduced (7).

Road traffic accidents, falls. Four patients experienced sleep attacks while working or driving. One 56-year-old man was admitted to hospital following sleep attacks that occurred two hours after his second dose of *piribedil*. One 75-year-old man had an initial sleep attack while he was driving, one hour after taking his first dose of *piribedil*. He felt the need to stop for a 10-minute nap. He had two more attacks after resuming his journey, the second of which caused a road traffic accident. One 86-year-old man taking *piribedil* for peripheral vascular disorders had two falls caused by sleep attacks. The patients described these sleep attacks as intense and sudden. In all cases, the sleep disorders resolved after discontinuation of *piribedil* (7).

A direct role for *piribedil*. Sleep attacks are a known adverse effect of dopamine agonists. As most of the data came from patients with Parkinson's disease, uncertainty remained over the role of the disease in these sleep disorders (6). These case reports, in patients taking *piribedil* but who did not have Parkinson's disease, are consistent with this

drug having a direct role in sleep attacks, and probably a similar role to that of other dopamine agonists.

In practice: *piribedil* has little value. *Piribedil* has not been shown to be an effective treatment for vascular disorders. It is not the first-choice dopamine agonist in Parkinson's disease, and its value is unclear (1,3,8). Unnecessary exposure of patients to the adverse effects of *piribedil* is not justified. It is better to use drugs with demonstrated efficacy instead.

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a- The main adverse effects of dopamine agonists are: gastrointestinal disorders; hypotension, particularly orthostatic hypotension; and mental disorders (confusion, hallucinations, delusions, psychomotor agitation, pathological gambling and hypersexuality) (ref 1).

Selected references from Prescrire's literature search.

- 1- Prescrire Rédaction "12-4-4. Patients sous agoniste dopaminergique" *Rev Prescrire* 2012; **32** (350 suppl. interactions médicamenteuses).
- 2- ANSM "RCP-Trivastal 50 mg LP + 20 mg comprimés" 21 December 2011: 10 pages.
- 3- Prescrire Rédaction "Les indications des médicaments dits "vasoactifs" en ophtalmologie. Le flou organisé" *Rev Prescrire* 2002; **22** (228): 330-331.
- 4- Prescrire Rédaction "Vasodilatateurs toujours remboursables" *Rev Prescrire* 2005; **25** (258): 99.
- 5- ANSM "Commission d'AMM du 12 juillet 2012. Verbatim" 10 October 2012: 45 pages.
- 6- Prescrire Rédaction "Accès soudains de sommeil et antiparkinsoniens" *Rev Prescrire* 2004; **24** (256): 834-835.
- 7- Gouraud A et al. "Piribedil-induced sleep attacks in patients without Parkinson disease: a case series" *Clin Neuropharmacol* 2011; **34** (3): 104-107.
- 8- Prescrire Rédaction "Traitement de la maladie de Parkinson. Première partie: d'abord une monothérapie par lévodopa ou agoniste dopaminergique" *Rev Prescrire* 2011; **31** (329): 200-205.