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JOURNAL OF NEUROLOGY AND NEUROSCIENCE

2013
Vol. 4 No. 1:4
doi: 10.3823/331

Lack of absorption of extended-release pramipexole in a patient with early parkinson´s disease

Alberto Villarejo[1], Gema Lizcano[2], Álvaro Sánchez-Ferro[3], Eduardo de Pablo-Fernández[4]

1 Department of Neurology. Hospital Universitario "12 de Octubre", Madrid, Spain.
2 Centro de Salud Vicente Soldevilla. Madrid, Spain.
3 Department of Neurology. Hospital Universitario "12 de Octubre", Madrid, Spain.
4 King's College Hospital. London, UK.

Corresponding author:

avgalende@yahoo.es

Dr. Alberto Villarejo, Servicio de Neurología, Hospital Universitario Doce de Octubre. C/ Andalucía, Km 5,4. E-28041 Madrid, Spain.

Fax: 0034 913908600

This article is available from:
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Pramipexole is a nonergot dopamine agonist indicated for treating Parkinson's disease (PD) and restless legs syndrome. Pramipexole extended release (ER) is a recently developed once-daily formulation which has demonstrated noninferiority compared with pramipexole immediate release (IR) in the treatment of early [1] and advanced PD [2]. Compared with the immediate release (IR) formulation, the ER formulation offers some advantages, including the potential for improved compliance owing to its simple once-daily dosing regimen and steadier plasma levels over 24 h [3]. According to data from clinical trials, both formulations have a similar digestive absorption with a bioavailability of more than 90%, and the overnight switch from pramipexole IR three times a day to pramipexole ER once daily at unchanged dosage in PD patients has been shown to be successful in more than 80% of patients, with minor adjustments needed in the other patients [4]. Here we report the case of a patient with mild PD, unsuccessfully treated with pramipexole ER due to lack of digestive absorption of the drug.

Case report

A 67-year-old man with hypertension presented with one-year history of right hand tremor and progressive slowness and clumsiness for most of his movements. His treatment included atenolol, valsartan, hidroclorotiazide, manidipine and aliskiren. Detailed clinical examination revealed resting tremor (of a pill-rolling character) of the upper extremity, hypomimia, right arm cogwheel rigidity and asymmetric bilateral bradykinesia on rapid alternating movements, predominantly on the right side. Diagnosis of Parkinson's disease was made according to BB criteria, and treatment with rasagiline 1 mg once daily was started, without improvement. Two months later, Pramipexole ER was added, with increasing doses until 1,05 mg (base) once daily. On his third visit, he reported mild progression of his symptoms and Pramipexole ER was increased to 2,1 mg once daily. Two months later, the patient and his son, a physician, reported no improvement of the symptoms, and expressed concern about the lack of digestive absorption of the drug, since undigested pills could sometimes be seen in the faeces. Pramipexol ER was gradually switched to the same dosage of pramipexol IR (0,7 mg tid), with a marked improvement of all parkinsonian symptoms. During the previous months, there were no changes in his diet, concomitant medications or bowel movements (one defecation per day). He denied constipation, abdominal pain, diarrhoea or other gastrointestinal symptoms. He has been treated with stable doses of rasagiline and pramipexole IR over the last six months with good control of PD symptoms.

Discussion

In the pharmacokinetic studies performed in healthy male volunteers and in clinical trials in PD patients, once-daily ER pramipexole formulation resembled the IR formulation given

3 times daily in terms of both pharmacokinetics and tolerability [5]. Pramipexole ER – a matrix single-unit prolonged release tablet – releases pramipexole dihydrochloride monohydrate, which is dispersed homogenously throughout the matrix, by two different mechanisms of diffusion and erosion [3]. Following oral administration, gastrointestinal fluids penetrate the matrix and dissolve the active substance. The erosion mechanism directly separates the matrix surface from the core and thus leads to direct release of the active substance [3]. In our patient, the problem with absorption seems related to altered diffusion and / or erosion, since the pills appeared undigested in stool, but we could not find an explanation and cannot provide a reason for this problem. In previous studies, food intake decreases the rate but not the extent of absorption. Interaction with other medications seems unlikely, and a generalized malabsorption was reasonably ruled out, as the patient did not have other GI symptoms and routine/extensive blood tests were normal. To our knowledge, this lack of absorption with the use of pramipexole ER has not been previously reported. Although it may be a rare phenomenon, we consider that treating physicians should be aware of this possibility, especially in patients with advanced Parkinson´s disease and complicated medication schedules, whose lack of improvement, fluctuations or worsening of the symptoms when switching pramipexole IR to ER may be wrongly attributed to other factors.

Acknowledgements

We are very grateful to the patient and his family.

Conflict of interest

None.

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