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ARTICLE

Piribedil and Pathological Gambling in six Parkinsonian patients

Piribedil e Jogo Patológico em seis pacientes parkinsonianos

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ABSTRACT

Impulse control disorders (ICD) in Parkinson's disease (PD) have attracted increasing interest. They are characterized by the inability to control the impulse to perform an act that can be detrimental to them or to others. Although dopamine agonists (DA), as a group, have been associated with impulse control disorders (ICD), piribedil has rarely been reported to cause them. **Method:** Case reports of six parkinsonian patients on piribedil presenting pathological gambling (PG). **Results:** All of the patients presented ICD associated with piribedil use. Two of them received this medication as first treatment and four of them who had developed ICDs secondary to other DA that reappeared with piribedil. **Conclusion:** Despite piribedil is commercially available in only a few countries, it should be considered in the differential diagnosis of PG in patients with PD.

Keywords: impulse control disorders, dopamine agonists, piribedil, pathological gambling.

RESUMO

Os distúrbios do controle do impulso (DCI) na doença de Parkinson (DP) têm atraído crescente interesse. Eles são caracterizados pela incapacidade da pessoa em controlar o impulso para realizar um ato que pode ser prejudicial a ela própria ou aos outros. Embora os agonistas dopaminérgicos (AD), como um grupo, têm sido associados com distúrbios do controle do impulso, o piribedil tem sido relatado raramente como causa dos mesmos. **Método:** Relatos de seis casos de pacientes parkinsonianos em uso de piribedil apresentando jogo patológico (JP). **Resultados:** Todos os pacientes apresentaram DCI com o uso do piribedil. Dois deles receberam piribedil como primeiro tratamento e quatro deles que haviam desenvolvido DCI devido a outro AD, reapresentaram o quadro com piribedil. **Conclusão:** Apesar de o piribedil estar disponível comercialmente apenas em alguns países, deveria ser considerado no diagnóstico diferencial de JP em pacientes com DP.

Palavras-chave: distúrbios do controle do impulso, agonistas dopaminérgicos, piribedil, jogo patológico.

Impulse control disorders (ICD) in Parkinson's disease (PD) have attracted increasing interest. Symptoms include pathological gambling (PG), compulsive eating, compulsive shopping, and hypersexuality[1]. These four major components of ICD are often associated with punding, excessive internet use and dopamine dysregulation syndrome, all revealing a compulsive behavior. The real prevalence of ICD in PD patients on dopamine agonists (DA) treatment is unknown, but it has been suggested that it could range from 2% to 13.7%[2,3,4,5,6]. Since Molina et al.[7] reported the association between the pharmacologic treatment of PD and PG for the first time in 2000, several reports have since implicated different dopaminergic drugs with ICDs, especially DA[7,8,9]. However piribedil, a non-ergot derived DA had not been associated with ICD until 2010 when Tschopp et al. reported 4 PD patients on piribedil who developed PG[10]. Piribedil is employed in Argentina and several other countries, and has an action on D2 and D3 dopaminergic receptors, α-2 adrenoreceptors antagonism and minimal interaction with serotonergic receptors. We describe six PD patients presenting on piribedil who developed PG (Clinical and demographic characteristics, Table).

CASE 1

A 67-year-old man suffering from an acineto-rigid form of PD for eight years and a long history of depression. He was initially put on low doses of pramipexole, which were eventually increased to 4.5 mg/day. After 2 years of treatment he developed PG. Pramipexole was discontinued and carbidopa/levodopa (C/L) 500 mg/day was initiated in

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Table. Clinical and demographic characteristics of cases reported.

Case	Sex/Age	Duration of PD (years)	Time lapse for ICDs to develop with Piribedil (months)	ICD Symptoms	Previous DA	Piribedil dose (mg/day)	Treatment
1	M/67	8	8	PG	Yes	150	DA suspension, Paroxetine 20 mg/d, Quetiapine 25 mg/d and Psychoterapy
2	F/48	4	4	PG, HS, CE, CS	Yes	200	DA suspensión, Paroxetine 20 mg/d, Quetiapine 25 mg/d and Psychoterapy
3	M/49	5	5	PG	No	150	DA suspension
4	M/65	9	9	PG	No	150	DA suspension
5	M/67	10	10	PG, CE	Yes	200	DA suspension, Paroxetine 30 mg/d
6	F/50	11	11	PG, HS, CE, CS	Yes	200	DA suspension

M: Male; F: Female; PD: Parkinson's disease; ICD: Impulse control disorder; PG: Pathological gambling; HS: Hypesexuality; CE: Compulsive eating; CS: Compulsive shopping; DA: Dopamine agonist.

association with paroxetine 20 mg/day and psychotherapy. As the response was poor, quetiapine 25 mg/day was added with complete control of the PG. Due to progressive worsening of the rigidity and walking difficulties, piribedil 150 mg/day was added. He presented considerable motor improvement, however he developed severe PG after 23 months of treatment, and piribedil had to be withdrawn. After discontinuation PG disappeared and C/L had to be increased up to 1,250 mg/day to control his motor symptoms.

CASE 2

A 48-year-old woman suffering from PD for 5 years was first put on pramipexol 3 mg/day. She developed compulsive shopping and eating disorders with a weight increase of 15 Kg pramipexole was discontinued and ropinirole started at 6 mg/day associated with paroxetine at 20 mg/day and psychotherapy. As there was no improvement of the ICD, ropinirole had to be stopped. He was put on piribedil 200 mg/day and quetiapine 50 mg/day. However, despite initial improvement after 3 months of treatment she developed PG and hypersexuality. Piribedil was completely stopped and C/L at 250 m/day started while quetiapine was kept at the same dose. The patient improved her ICDs.

CASE 3

A 49-year-old man with PD initially treated with piribedil at 150 mg/day developed PG after 24 months of exposure causing him severe social and familial problems. Piribedil was switched to ropinirole 8 mg/day and psychotherapy was initiated. As his PG did not improve, the DA was stopped and C/L was prescribed at a dose of 1,000 mg/day to control his motor symptoms. The patient experienced little improvement in PG, and refused to receive antidepressants, psychotherapy, or any other medication for his compulsions.

CASE 4

A 65-year-old man suffering from PD for 9 years was initially treated with piribedil at 150 mg/day for 30 months when he developed PG. Piribedil was discontinued and Stalevo 50 mg/tid was added. Stalevo was later changed for C/L at 500 mg/day resulting in good control of his motor symptoms, without PG.

CASE 5

A 67-year-old man suffering from PD for 10 years was initially treated with pramipexole 1.75 mg/day. Five years later, due to progressive worsening, pramipexole was increased to 4.5 mg/day, and Stalevo 50 mg four times/day was added. A year later, he developed irritability, compulsive eating and PG and pramipexole had to be progressively withdrawn. Paroxetine at 20 mg/day and quetiapine at 25 m/day were introduced with the resolution of his PG. As his motor function worsened, piribedil up to 200 mg/day was added with Stalevo 100 mg/tid, stalevo 50 mg/qid, levodopa/benzerazide (L/B) in the fast release formulation 100/25 mg/tid and paroxetine 20 mg/day. The patient stopped quetiapine by himself. Two years later, he developed compulsive eating and PG, piribedil was then stopped with complete resolution of the ICDs. Stalevo, L/B and paroxetine were increased due to worsening of motor symptoms and depression.

CASE 6

A 50-year-old woman suffering from tremor predominant PD for 11 years had been treated with pramipexole in low doses with progressive increases reaching 4 mg/day and L/B, up to 600 mg/day with good control of her parkinsonian symptoms, except for her right hand resting tremor. Three years after the diagnosis was made and while on pramipexole,

she developed compulsive eating and shopping disorders. Pramipexole was discontinued and she was put on piribedil at 200 mg/day, however she developed PG, along with hypersexuality, binge eating and compulsive shopping. At the time piribedil was reduced to 100 mg/day and amantadine 300 mg/day was added with no control of the ICDs. A left thalamotomy was performed for the severe right hand resting tremor. As she continued presenting ICDs, piribedil was stopped, and she was put on L/B 500 mg/day, and L/B in the fast release formulation 100/25 mg qid, with a marked improvement in the ICDs.

DISCUSSION

Four of our cases first developed ICD while on other DA, which promptly disappeared after stopping the DA but reappeared when piribedil was added. The other two cases, first manifested ICD (pathological pambling) with piribedil as a first therapy.

Patients with PD who develop ICD, particularly PG, are usually male, have younger PD age of onset, a personal or family history of alcohol abuse, or a previous history of ICD. They are generally receiving DA as PD treatment although any anti-Parkinsonian treatment is liable to trigger ICD[11]. In addition, the patient's psychological profile may have a role as a risk factor since PD patients with ICD have higher novelty-seeking trait scores as well as impaired planning on the impulsivity scale[12,13]. Depression is also considered a powerful risk factor. Low performance in cognitive tasks exploring frontal function has also been reported[4,14]. Sometimes ICD are associated with compulsive medication use, known as hedonistic homeostatic dysregulation or dopamine dysregulation syndrome, characterized by the increased use of levodopa beyond the doses required to achieve relief of motor symptoms. This is also associated with a disabling mood and behavioral changes when anti-Parkinsonian drugs are withdrawn or doses decreased[9,11]. Occasionally, patients hide taking extra doses of medication. Perhaps they misunderstand the prescription, thus the importance to check exactly what they are receiving[15]. Among the other ICD, PG is described as the most frequent compulsion, which was the case in our patients[12,16].

There are 5 different dopamine receptors and l-dopa increases the availability of dopamine in the brain without any known specificity for a dopamine receptor subtype. However, DA present high affinity for the D3 receptors, and this is the strongest theory explaining the compulsive behaviors in PD patients. D3 receptor expression is particularly rich in limbic areas modulating the physiologic and emotional experience of novelty, reward and risk assessment[16].

The most useful medical strategy in the management of patients with ICD is the removal of the causal agent. However in some infrequent cases, either changing the DA or reducing the dose can be useful. Serotonin reuptake inhibitors have a dubious benefit in ICD, but are useful in the treatment of concomitant depression. Atypical antipsychotics including clozapine and quetiapine have also been described be useful[17,18,19]. In addition amantadine has also been used but it's therapeutic effects remain controversial[20,21]. Although piribedil is commercially available in a few countries, there are only two reports[10,15] describing the association of ICD with this DA and both are from Argentina.

Piribedil is currently marketed in 24 countries including Brazil, Venezuela and Argentina in South America, in 3 European countries and the remainder in Central America and Asia.

Side effects include piribedil-induced sleep attacks in PD and non PD cases have been reported[22,23,24]. Piribedil is regarded as a useful, well tolerated, antiparkinsonian agent, which is also effective in symptoms such as apathy and depression. Curiously piribedil induced ICD have not been reported elsewhere. In the REGAIN study including four hundred and five early PD patients, surprisingly ICD was not reported as a side effect[25]. In addition another study performed in India included 515 non PD patients with memory disorders and no ICD was reported[26]. Other smaller trials in different Asian countries also failed to report these side effects[22]. Whether this is just because these studies were performed before ICD became widely known or not, remains an open question.Our cases show that piribedil might have a similar risk to cause ICD as compared with others DA. However more evidence is required to determine its prevalence.

References

1. Ávila A, Cardona X, Martín-Baranera M, Bello J, Sastre F. Impulsive and compulsive behaviors in Parkinson's disease: a one-year follow-up study. J Neurol Sci. 2011;310(1-2):197-201. http://dx.doi.org/10.1016/j.jns.2011.05.044
2. Voon V, Hassan K, Zurowski M, Duff-Canning S, Souza M, Fox S et al. Prospective prevalence of pathologic gambling and medication association in Parkinson disease. Neurology. 2006;66(11):1750-2. http://dx.doi.org/10.1212/01.wnl.0000218206.20920.4d
3. Voon V, Hassan K, Zurowski M, Souza M, Thomsen T, Fox S et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology. 2006;67(7):1254-7. http://dx.doi.org/10.1212/01.wnl.0000238503.20816.13
4. Pontone G, Williams JR, Bassett SS, Marsh L. Clinical features associated with impulse control disorders in Parkinson disease. Neurology. 2006;67(7):1258-61. http://dx.doi.org/10.1212/01.wnl.0000238401.76928.45
5. Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales Kh, Duda JE et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch Neurol. 2006;63(7):969-73. http://dx.doi.org/10.1001/archneur.63.7.969

6. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010;67(5):589-95. http://dx.doi.org/10.1001/archneurol.2010.65

7. Molina JA, Sáinz-Artiga MJ, Fraile A, Jiménez-Jiménez FJ, Villanueva C, Ortí-Pareja M et al. Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? Mov Disord. 2000;15(5):869-72. http://dx.doi.org/10.1002/1531-8257(200009)15:5<869::AID-MDS1016>3.0.CO;2-I

8. Gallagher DA, O'Sullivan SS, Evans AH, Lees AJ, Schraq A. Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation: an analysis of published case series. Mov Disord. 2007;22(12):1757-63. http://dx.doi.org/10.1002/mds.21611

9. Avanzi M, Baratti M, Cabrini S, Uber E, Brighetti G, Bonfà F. Prevalence of pathological gambling in patients with Parkinson's disease. Mov Disord. 2006;21(12):2068-72. http://dx.doi.org/10.1002/mds.21072

10. Tschopp L, Salazar Z, Gomez Botello MT, Roca CU, Micheli F et al. Impulse control disorder and piribedil: report of 5 cases. Clin Neuropharmacol. 2010;33(1):11-3. http://dx.doi.org/10.1097/WNF.0b013e3181c4ae2e

11. Voon V, Thomsen T, Miyasaki JM, Souza M, Shafro A, Fox SH et al. Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. Arch Neurol. 2007;64(2):212-6. http://dx.doi.org/10.1001/archneur.64.2.212

12. Ceravolo R, Frosini D, Rossi C, Bonuccelli U. Impulse control disorders in Parkinson's disease: definition, epidemiology, risk factors, neurobiology and management. Parkinsonism Relat Disord. 2009;15 Suppl 4:S111-5. http://dx.doi.org/10.1016/S1353-8020(09)70847-8

13. Isaias IU, Siri C, Cilia R, De Gaspari D, Pezzoli G, Antonini A. The relationship between impulsivity and impulse control disorders in Parkinson's disease. Mov Disord. 2008;23(3):411-5. http://dx.doi.org/10.1002/mds.21872

14. Santangelo G, Vitale C, Trojano L, Verde F, Grossi D, Barone P. Cognitive dysfunctions and pathological gambling in patients with Parkinson's disease. Mov Disord. 2009;24(6):899-905. http://dx.doi.org/10.1002/mds.22472

15. Giugni JC, Tschopp L, Escalante V, Micheli F. Dose-dependent impulse control disorders in piribedil overdose. Clin Neuropharmacol. 2012;35(1):49-50. http://dx.doi.org/10.1097/WNF.0b013e31823d78ab

16. Kelley BJ, Duker AP, Chiu P. Dopamine agonists and pathologic behaviors. Parkinson's disease. 2012;2012:ID603631. http://dx.doi.org/10.1155/2012/603631

17. Weiss HD, Marsh L. Impulse control disorders and compulsive behaviors associated with dopaminergic therapies in Parkinson disease. Neurol Clin Practice. 2012;2(4):267-74. http://dx.doi.org/10.1212/CPJ.0b013e318278be9b

18. Ferrara JM, Stacy M. Impulse-control disorders in Parkinson's disease. CNS Spectr. 2008;13(8):690-8.

19. Raina G, Cersosimo MG, Micheli F. Zoophilia and impulse control disorder in a patient with Parkinson disease. J Neurology. 2012;259(5):969-70. http://dx.doi.org/10.1007/s00415-011-6270-z

20. Thomas A, Bonanni L, Gambi F, Di Iorio A, Onofrj M. Pathological gambling in Parkinson disease is reduced by amantadine. Ann Neurol. 2010;68(3):400-4. http://dx.doi.org/10.1002/ana.22029

21. Weintraub D, Sohr M, Potenza MN, Siderowf AD, Stacy M, Voon V et al. Amantadine use associated with impulse control disorders in Parkinson disease in cross-sectional study. Ann Neurol. 2010;68(6):963-8. http://dx.doi.org/10.1002/ana.22164

22. Evidente VG, Esteban RP, Domingo FM, Carbajal LO, Parazo MA. Piribedil as an adjunct to levodopa in advanced Parkinson's disease: the Asian experience. Parkinsonism Relat Disord. 2003;10(2):117-21. http://dx.doi.org/10.1016/S1353-8020(03)00096-8

23. Gouraud A, Millaret A, Descotes J, Vial T, French Association of Regional Pharmacovigilance Centres. Piribedil-induced sleep attacks in patients without Parkinson disease: a case series. Clin neuropharmacol. 2011;34(3):104-7. http://dx.doi.org/10.1097/WNF.0b013e31821f0d8b

24. Tan EK. Piribedil-induced sleep attacks in Parkinson's disease. Fundam Clin Pharmacol. 2003;17(1):117-9. http://dx.doi.org/10.1046/j.1472-8206.2003.00122.x

25. Rascol O, Dubois B, Caldas AC, Senn S, Del Signore S, Lees A. Early piribedil monotherapy of Parkinson's disease: a planned seven-month report of the REGAIN study. Mov Disord. 2006;21(12):2110-5. http://dx.doi.org/10.1002/mds.21122

26. Hastak SM. Treatment of memory impairment, vertigo and tinnitus in the elderly with piribedil in an Indian general practice setting. J Indian Med Assoc. 2003;101(8):500-1.