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Flunarizine and cinnarizine-induced parkinsonism: a historical and clinical analysis

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Abstract

Background. Drug-Induced Parkinsonism (DIP) represents the second leading cause of Parkinsonism (PK) in several countries. Flunarizine and cinnarizine are some of the most common drugs that cause DIP. This paper reviews the first description of Flunarizine and Cinnarizine-Induced Parkinsonism (FCIP), as well as the subsequent literature, emphasizing epidemiological, clinical and diagnostic aspects. *Methods*. We reviewed the literature on the subject, with special emphasis on the first description and the later definition of the clinical syndrome that results from chronic use of flunarizine and cinnarizine. *Results*. In 1984, De Melo-Souza reported the first description of flunarizine-induced PK in five patients. Other reports followed on FCIP, emphasizing the clinical features, which are symmetrical parkinsonism, and depression, affecting mainly elderly women. *Conclusions*. Eighteen years after the original description, FCIP is a recognized condition with specific clinical features, and is the second most common cause of parkinsonism in many countries.

Keywords: Parkinsonism; Flunarizine; Cinnarizine

1. Introduction

Parkinsonism (PK) can be defined as a clinical syndrome in which two of the four cardinal features—tremor, muscle rigidity, bradykinesia and postural instability can be found in any combination [1,2]. The most common cause of PK worldwide is Idiopathic Parkinson's Disease (IPD) [1,2]. Among the causes of secondary PK, drug-induced PK (DIP), particularly due to flunarizine or cinnarizine (FCIP), is the second most common cause of PK [3–5]. This paper reviews the original reports of FCIP, discussing the evolving and most recent knowledge concerning this clinical entity.

2. Methods

All the major literature on FCIP published between 1984 and 2001, researched by Index Medicus and Internet (Medline-Pubmed) was reviewed and a critical analysis was then performed.

3. Results

The significant studies that we analyzed included the original description of De Melo-Souza and the articles of Chouza et al., Micheli et al., Negrotti and Calzetti, Marti-Massó and Poza, Gimenéz-Roldàn and Mateo and Bezerra. These studies demonstrated the historical aspects about FCIP and some of them suggest the main clinical tools for the diagnosis of this syndrome, particularly symmetrical PK symptoms, depression affecting mainly old women.

Other important articles that evaluated DIP were the studies of Llau et al,. Kuzuhara, Errea-Abad et al. and Cardoso et al.

4. Discussion

Both cinnarizine and flunarizine are calcium channel blocking drugs, but flunarizine is 2.5–15 times stronger than cinnarizine. Flunarizine is actually derived from cinnarizine, and differs from it by the fact that it has a piperazine radical in its molecule, which can also be found in neuroleptics and antihistamine drugs [6–10]. The chronic

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use of these drugs, especially in elderly patients often leads to common side effects such as drowsiness, sedation, weakness and depression [6–13].

Both flunarizine and cinnarizine have been used for some years as the main therapy for vestibular disorders as well as a treatment option for cerebrovascular disease regardless of cause [6–16]. More recently, they have also been use as prophylactic therapy for migraine and as adjunctive treatment for epilepsy.

Flunarizine-induced PK was first described in Brazil in 1984 by De Melo-Souza during the IX Brazilian Congress of Neurology. He presented five elderly female patients who had previously used flunarizine and had both PK and depression [11]. A few years later, in 1989, De Melo-Souza and Ragazzo presented a larger series at the annual meeting of the American Academy of Neurology [12]. In that series, all of the 28 patients (25 females and three males, with a mean age of 66 years) had used flunarizine 10 mg daily for at least 20 days (mean time of 6 months). Side effects included depression in 85%, insomnia in 40%, anxiety in 35%, weakness in 53% and impaired motor coordination in 50%. Neurological examination disclosed signs of PK in 27 patients, bradykinesia in 96%, muscle rigidity in 75%, tremor in 60%, reduced deep tendon reflexes in 53% and facial hypomimia in 46%. Only one patient presented with bucolingual dyskinesia and six patients had akathisia. The authors concluded that the use of flunarizine in elderly patients, especially if they are females, could lead to development of PK as a side effect [12].

In 1985, Marti-Masso et al. reported a case of a patient with PK that they thought was due to cinnarizine [13].

In 1986, Chouza et al. published the first report of PK due to flunarizine [6]. In that study they reported 12 patients who in addition to PK, had tardive dyskinesia (four patients), akathisia (one patient) and depression (11 patients)

In 1986, another study published by Micheli et al. evaluated 15 patients who used either flunarizine or cinnarizine and who developed extrapyramidal symptoms; of those, 11 had PK while the others had akathisia, dystonia and facial tremor [7].

Gimenéz-Roldàn et al. reported in 1991 that older age and essential tremor were the risk factors for cinnarizine-induced PK [10].

Bezerra, in 1993, studied 47 patients with FCIP [14]. The author concluded that, in comparison to PK induced by antipsychotic drugs, FCIP had an older age of onset, a longer time between taking the drug and the onset of PK symptoms, delayed recovery time, more frequent resting and postural tremor, a higher incidence of depression and lack of therapeutic response to anticholinergics or levodopa. The syndrome occurred mainly in women and akathisia was also observed [14].

In 1997, Negrotti and Calzetti published a series of 13 female patients with FCIP who had been followed for 7 years. In that group the long-term outcome, even after the drugs had been discontinued, was not as good as expected as none of the patients had a complete remission of their PK [8].

Based on this, one should always question whether a patient previously diagnosed with persistent or recurrent FCIP has latent IPD that emerged as a result of chronic use of calcium channel blockers.

On the other hand, in 1998, Martí-Massó and Poza published their results after following a group of patients who had PK induced by cinnarizine for 10 years [9]. This group of 74 patients, in itself a subgroup of a larger series of 172 DIP patients, had a complete recovery between one and 16 months after cinnarizine had been discontinued. As in other series, the majority of patients (89%) were female. Five patients also had tardive dyskinesia, 53% of all patients had concomitant depression and 11 later developed classic IPD.

The conflicting results of Negrotti and Calzetti and of Martin-Massó elicited many questions concerning the design of those studies, clinical criteria for diagnosis, outcome of patients with FCIP and the onset of IPD in patients who had been previously diagnosed with FCIP [8–10].

The pathological mechanism responsible for FCIP is still not completely understood, but some authors believe that it is due to pre-synaptic factors (loss of tyrosine hydroxylase in monoaminergic and serotonergic neurons leading to dopamine depletion) as well as post-synaptic ones (blocking striatal dopaminergic receptors) [8–10]. Mena et al. studied the effects of calcium antagonists on the dopaminergic system both in vivo and in vitro [15]. Not only did they discover that calcium channel blockers (flunarizine, cinnarizine and Diltiazem) reduce the viability of dopaminergic neuroblastoma cells, but also that these drugs diminish neurotransmission in the dopaminergic circuits of rats.

FCIP is more commonly found in female patients (2:1 up to 3:1) and persons older than 60 years of age are also more prone to developing PK [6–9,11–13].

FCIP often presents as a symmetrical akinetic-rigid syndrome, with resting and/or postural tremor, depression and sometimes acathisia and dyskinesia, but it can be hard to make a clear distinction between FCIP and IPD based solely on clinical criteria [6–13].

Eighteen years after the initial description of FCIP by De Melo and Souza and after reviewing several series, particularly from Negrotti and Calzetti and Marti-Massó and Poza, one can make use of their clinical tools for the diagnosis of FCIP (Table 1) [6–13].

In a series published in 1998, Cardoso et al. after studying 338 patients with PK, from the Movement Disorders Clinic Federal University of Minas Gerais, (Belo Horizonte, Brazil) reported that 68.9% of those patients had IPD and that in 13.3% PK was due to DIP [16]. PK resulting from DIP proved to be more common than PK secondary to cerebrovascular disease, PK Plus and

Table 1
Clinical tools for the diagnosis of FCIP

Previous treatment with either flunarizine or cinnarizine
Parkinsonism diagnosed after therapy with either flunarizine or cinnarizine (at least two of the cardinal signs of parkinsonism: bradykinesia, rigidity, postural instability and resting tremor)
Clinical features are indistinguishable from idiopathic Parkinson's disease; with a rigidity-akinetic syndrome, resting and postural tremor, usually begins bilateral, with symmetrical findings and associated depressive disorder
Predominantly affects elderly patients, particularly females
Remission of parkinsonian symptoms after discontinuation of flunarizine or cinnarizine
Other causes of parkinsonism (including drugs that can cause movement disorder) excluded by clinical history and neurological examination

Modified from Negrotti A, Calzetti S and Marti-Massó J, Poza JJ.

heredodegenerative PK. The drugs responsible for DIP in the Cardoso series were flunarizine, cinnarizine and neuroleptics [16].

Similar results were found at the Movement Disorders Unit of the Hospital de Clínicas of Federal University of Paraná (Curitiba, Brazil), where Herdoiza (personal communication) studied 312 patients with PK. 72.4% had IPD (including those with early-onset IPD), 19.6% had secondary PK, 6.1% had PK Plus and only 1.9% heredodegenerative PK. In these series, 58.1% of the patients with secondary PK had DIP and 24.3% had vascular PK. In the subset of DIP, 62.2% was due to the previous use of either flunarizine or cinnarizine whereas 32.4% was due to neuroleptics. Of the 23 patients who had FCIP, 67.6% were females with a mean age at onset of symptoms of 66.7 years; 43.5% also had concomitant depression. The parkinsonian findings on neurological examination were found to be bilateral and symmetrical. Thus, FCIP is an important cause of PK, a fact not always known to the general practitioner or general neurologist.

These data emphasize the epidemiological importance of DIP, particularly due to flunarizine and cinnarizine, in Brazil as well as in other countries [3–5,16,17].

In Europe, (e.g. France and Spain), as well as in Asia (Japan), DIP, particularly FCIP, is currently the second leading cause of PK [3–5].

These data are quite different from other series such as the Stacy and Jankovic report (Movement Disorders Service of the Baylor College of Medicine, TX, USA), in which the authors found that 77% of the patients with PK had IPD, 12.2% had PK Plus and only 8.2% had secondary PK. DIP was only found in 4% of the patients in that series and the drugs most commonly found were anti-psychotic drugs, anti-emetics, and dopamine depleting agents [1].

5. Conclusion

Many reports support the fact that FCIP is one of the main causes of PK, particularly in Brazil. The main clinical features of the disorder are parkinsonian signs associated with depression, tardive dyskinesia and akathisia, especially in older women. Since flunarizine and cinnarizine are not highly effective in the treatment of vestibular disorders and have clear causative roles in a substantial proportion of the cases of PK, their liberal use should be strongly discouraged.

References

[1] Stacy M, Jankovic J. In: Cedarbaum JM, Gancher ST, editors. Differential diagnosis of Parkinson's disease and the Parkinson's plus syndromes. Neurologic Clinics. Parkinson's Disease, vol. 10(2). Philadelphia: W.B. Saunders; 1992. p. 341–9.
[2] Riley DE. Secondary parkinsonism. In: Jankovic J, Tolosa E, editors. Parkinson's disease and movement disorders, 3rd ed. Baltimore, MD: Williams and Wilkins; 1998. p. 317–39.
[3] Llau ME, Nguyen L, Senard JM, Rascol O, Montastruc JL. Drug-induced parkinsonian syndromes: a 10-year experience at a regional center of pharmaco-vigilance. Rev Neurol 1994;50:757–62.
[4] Kuzuhara S. Drug-induced parkinsonism. Nippon Rinsho 1997;55: 112–7.
[5] Errea-Abad JM, Ara-Callizo JR, Aibar-Remon C. Drug-induced parkinsonism. Clinical aspects compared with Parkinson's disease. Rev Neurol 1998;27:35–9.
[6] Chouza C, Scaramelli A, Caamanõ JL, De Medina O, Aljanati R, Romero S. Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. Lancet 1986;1:1303–4.
[7] Micheli F, Pardal MF, Gatto M, Torres M, Paradiso G, Parera IC, Giannaula R. Flunarizine- and cinnarizine-induced extrapyramidal reactions. Neurology 1987;37:881–4.
[8] Negrotti A, Calzetti S. A long-term follow-up study of cinnarizine- and flunarizine-induced parkinsonism. Mov Disord 1997;12:107–10.
[9] Martí-Massó J, Poza JJ. Cinnarizine-induced parkinsonism: ten years later. Mov Disord 1998;13:453–6.
[10] Gimenéz-Roldàn S, Mateo D. Cinnarizine-induced parkinsonism: susceptibility related to aging and essential tremor. Clin Neuropharmacol 1991;14:156–64.
[11] De Melo-Souza SE. Flunarizina, Parkinsonismo e Depressão. XI Congresso Brasileiro de Neurologia (Resumos), Goiânia, Brasil; 1984.
[12] De Melo-Souza SE, Ragazzo PC. Neurologic side effects of flunarizine. Neurology 1989;39(Suppl 1):390.
[13] Martí-Massó JF, Carrera N, de La Puente E. Posible parkinsonismo inducido por cinaricina. Medicina Clínica (Barcelona) 1985;85:614–6.
[14] Bezerra JMF. Síndrome Parkinsoniana Induzida por Flunarizina e/ou Cinarizina. Thesis. Federal University of São Paul, São Paulo; 1993.
[15] Mena MA, Garcia de Yébenes MJ, Tabernero C, Casarejos MJ, Pardo B, Garcia de Yébenes J. Effects of calcium antagonists on the dopamine system. Clin Neuropharmacol 1995;18:410–26.
[16] Cardoso F, Camargo ST, Silva Jr GA. Etiology of parkinsonism in a Brazilian movement disorders clinic. Arq Neuropsiquiatr 1998;56: 171–5.
[17] Micheli F, Pardal MM, Giannaula R, Gatto M, Parera I, Paradiso G, Torres M, Pikielny R, Pardal J. Movement disorders and depression due to flunarizine and cinnarizine. Mov Disord 1989;4:139–46.