Movement Disorders
Vol. 13, No. 3, 1998, pp. 453–456

Cinnarizine-Induced Parkinsonism: Ten Years Later

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Summary: A retrospective study was carried out to investigate the evolution of patients diagnosed with cinnarizine-induced parkinsonism (CIP) over the past 15 years. A total of 74 cases of CIP were found among 172 patients with drug-induced parkinsonism (DIP). Both CIP and other DIP were significantly more frequent in women. No clinical differences between CIP and other DIP were found. Most of the patients (66 of 74) completely recovered after cinnarizine withdrawal in 1–16 months. Eleven patients later developed Parkinson's disease; four of them had previously recovered. Five patients had tardive dyskinesia. CIP accounts for a high proportion of DIP referred to neurologists in populations in which cinnarizine is widely prescribed. The symptoms typically resolve after drug withdrawal, although complete recovery may take more than 1 year. **Key Words:** Drug-induced parkinsonism—Cinnarizine—Clinical characteristics—Evolution.

Cinnarizine, and its derivative flunarizine, represents one of the most common causes of drug-induced parkinsonism (DIP) in countries where these compounds are widely prescribed, especially in Spain and South America.[1] The first case was described in 1985.[2] A survey conducted that same year estimated that approximately 5–7% of all individuals over age 60 in the Spanish population were treated with cinnarizine.[3] The excessive use of cinnarizine in Spain was the result of a triple conceptual error of general practitioners: (1) they thought most cases of "dizziness" were of cerebral ischemic origin; (2) that cinnarizine was useful for the treatment of vertebro-basilar insufficiency, and (3) that this drug should be used as lifelong treatment to prevent vertebro-basilar insufficiency. A large number of elderly individuals were begun on long-term treatment with cinnarizine after an episode of benign positional vertigo or some other peripheral cause of vertigo, or as a prophylactic treatment for vascular dementia. Subsequent parkinsonian symptoms were thought to be a manifestation of further cerebrovascular insufficiency. Considering this dramatic figure, the number of cases of cinnarizine-induced parkinsonism (CIP) detected in large populations has remained disproportionately low, which suggests that additional factors may play a critical role in the development of this side effect. The most important factors seem to be advanced age, the sex of the patient, and a background of genetically determined essential tremor.[4]

We present our experience with cinnarizine-induced parkinsonism, analyzing the clinical characteristics and evolution of the disorder in the 10 years since the first description of this side effect.

PATIENTS AND METHODS

A review of the patients with parkinsonism seen in a general consultation of neurology between January 1979 and December 1994 was carried out. All the patients were examined by one of us (JFMM). The criteria used for the diagnosis of CIP were: (a) treatment with cinnarizine; (b) presence of at least two cardinal signs of parkinsonism (tremor at rest, rigidity, bradykinesia, and postural instability); (c) onset of the symptoms of parkinsonism after the initiation of cinnarizine therapy; and (d) improvement of the symptoms after the withdrawal of cinnarizine.

RESULTS

A total of 306 patients with parkinsonian syndromes were reviewed. A diagnosis of DIP was made in 172 of them. The drug most frequently implicated was cinnarizine, which was present in 74 cases (43% of DIP). The other offending drugs and the number of patients who

Received March 17, 1997; revisions received October 16 and December 22, 1997. Accepted January 13, 1998.

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were taking them are listed in Table 1. In 45 patients with DIP, cinnarizine was the only offending agent; however, 29 patients were simultaneously taking other drugs capable of producing parkinsonism (26 were taking cinnarizine and another drug, and three were taking cinnarizine and two other drugs; Table 2).

CIP was detected more frequently in women than in men (55 women versus 19 men). A similar proportion was found when considering exclusively the 45 patients who were taking only cinnarizine (34 women and 11 men). This higher number of women affected was also seen in other DIP (71 women versus 27 men), and no significant differences in the gender predisposition between CIP and other DIP were found (Chi-square, Fisher's exact probability, $0.64 > p > 0.49$).

The probability of having CIP increased with age (Table 3). No differences in age distribution between sexes were observed. Patients with CIP were significantly older than patients with other DIP (75 ± 7 yrs in CIP versus 70 ± 11 yrs in DIP; Student's t test, $p > 0.001$). The same difference was found when considering exclusively the 45 patients who were only taking cinnarizine (mean age, 74 yrs; standard deviation [SD], 7 yrs).

The patients had been taking cinnarizine for an average of 33 months (range, 1–120 months). The reasons for cinnarizine prescription included vertigo and dizziness (45%), mental deterioration (11%), gait disturbances (apraxia; 7%), and others (27%). In eight patients, the reason for the prescription was unknown.

Fifty-seven patients (77%) sought consultation because of parkinsonian symptoms. In five (7%), depression was the reason for the consultation. Clinically, rigidity and akinesia were the most frequent signs, being present in 46% of the cases. Bilateral tremor was detected in 37% of the patients, and 13% presented exclusively with unilateral tremor. In 5% of the patients, rigidity, akinesia, and unilateral tremor were present simultaneously. No clinical differences between CIP and other DIP were found (51% of DIP presented with rigidity and akinesia, 27% with bilateral tremor, 19% with unilateral tremor, and 3% simultaneously with rigidity, akinesia, and unilateral tremor). Clinical characteristics were not influenced by the age of onset of CIP. Only eight patients with CIP had a history of postural tremor.

Postural tremor was present at the time of diagnosis in 51% of CIP and 23% presented perioral tremor. In five patients (7%), orobuccolingual dyskinesias were evident; two were only taking cinnarizine, two were taking reserpine simultaneously, and one was taking perphenazine. Depression was present in 39 cases (53%); however, only five of them came to us because of this symptom. These percentages were similar in the other DIP (47% with postural tremor, 20% with perioral tremor, 63% with depression, and 8% with dyskinesias).

Three patients were erroneously diagnosed as having

TABLE 1. *Offending drugs in all patients with drug-induced parkinsonism*

Drug	No. of patients
Cinnarizine	74
Sulpiride	39
Flupentixhol	20
Flunarizine	18
Amiodarone	15
Reserpine	12
Thioridazine	11
Haloperidol	8
Clebopride	8
Perphenazine	4
Levopromazine	4
Piperazine	3
Eskazine	2
Veralipride	2
Metochlopramide	2
Etumine	1
Diltiazem	1
Verapamil	1
Alpha-methyl-dopa	1
Fluoxetine	1

TABLE 2. *Other drugs capable of inducing parkinsonism which were taken simultaneously by 29 patients who had cinnarizine-induced parkinsonism*

Drug	No. of patients
Sulpiride	9
Flunarizine	5
Amiodarone	5
Reserpine	3
Flupentixhol	3
Haloperidol	2
Perphenazine	1
Thioridazine	1
Levopromazine	1
Clebopride	1
Tietilperazine	1

TABLE 3. *Distribution by age of patients with cinnarizine-induced parkinsonism (CIP) and drug-induced parkinsonism (DIP)*

Age	% of patients with CIP	% of patients taking cinnarizine exclusively	% of patients with DIP
<50	0	0	4
50–59	3	4	11
60–69	19	20	26
70–79	51	53	40
80–89	27	23	19

Parkinson's disease. Two of them improved when treated with levodopa.

Sixty-six patients (89%) completely recovered after cinnarizine withdrawal. Recovery time ranged from 1–16 months (mean, 5 months). In the eight patients not recovering, the follow up ranged from 9–96 months. The possibility of recovering was not influenced by the age of onset of CIP. The proportion of patients completely recovering after CIP (89%) was significantly higher than after other DIP considered as a whole (76%; Chi-square, $p < 0.05$).

Eleven patients later developed progressive features suggestive of a diagnosis of Parkinson's disease. Four of them had previously completely recovered between 3 and 12 months after cinnarizine withdrawal (mean, 6.5 months). However, between 12 and 72 months after recovery (mean, 48 months), parkinsonian symptoms reappeared. Seven of the eight patients whose parkinsonism did not resolve completely after cinnarizine withdrawal later demonstrated evidence of progressive parkinsonism.

Five patients with CIP (6.76%) demonstrated features of persistent tardive dyskinesia with an orobuccolingual distribution. The time of follow up in these patients ranged from 7 months to 3 years (mean, 40.2 months). Three of them were only taking cinnarizine and the other two were taking other drugs simultaneously (1 sulpiride and 1 reserpine). In all cases, the symptoms were mild, and the exact time of onset was difficult to determine. Two patients already had evidence of dyskinesia at the time of presentation with CIP. Eleven patients with DIP who were taking other drugs different from cinnarizine (11.22%) had tardive dyskinesia. The frequency of tardive dyskinesia was not statistically different in both groups—CIP and other DIP (Fisher's exact test, $p = 0.43$).

DISCUSSION

Our series confirms the high frequency of DIP among parkinsonian syndromes. However, our data probably reflect an overestimated prevalence biased by our special interest in this field. The most striking result is the large proportion of CIP detected.

In 1985, the potential for this drug to induce parkinsonism was reported,[2] and a year later its ability to aggravate Parkinson's disease was demonstrated.[5] Several subsequent studies have confirmed these findings.[1,4,6] The mechanisms by which these drugs induce parkinsonism is uncertain. Because other calcium channel blockers such as dihydropiridines (that is, nifedipine) usually do not induce this side effect, it is unlikely that parkinsonism is mediated by its calcium antagonist activity. A different affinity for calcium receptors and/or diverse degrees of passage through the blood–brain barrier partially may account for its ability to induce parkinsonism.[4] Some studies have demonstrated that old mice treated with cinnarizine have a reduced number of D1 and D2 receptors in different brain areas compared with young control mice. Further studies have confirmed the capacity of cinnarizine to block postsynaptic striatal dopamine receptors.[7–11] Systemic injections of flunarizine (a difluorinated derivative of cinnarizine) in mice can induce a transient loss of tyrosine hydroxylase immunoreactive nigrostriatal neurons without cell loss.[12] A possible toxic effect on monoamine and serotonin neurons has also been postulated.[6] Thus, both presynaptic dopamine depletion and postsynaptic dopamine receptor blockade may contribute to the development of CIP.

The question of whether this parkinsonism was reversible remained unanswered. A prospective follow-up study involving 32 patients found that 18 months after cinnarizine withdrawal, 44% of patients had depression, 88% had tremor, and 33% still had criteria of parkinsonism.[13] Our series is more optimistic. Eighty-nine percent of our patients completely recovered over a period ranging from 1–16 months. Only a few of these (4 of 66) later developed evidence of Parkinson's disease, suggesting that they were in a presymptomatic phase when they had the CIP. Given the long duration of follow up, we think it is possible to assert that CIP is reversible in most of the cases, and that CIP does not predispose to later development of Parkinson's disease. However, the time for recovery may be longer than 1 year after cinnarizine withdrawal.

In the past 4 years, the frequency of referred cases of CIP has decreased. We believe this is the result of a true decline in the prevalence of CIP. The wide diffusion of knowledge of this important side effect has resulted in a more restrictive use of cinnarizine and a higher sensibility of general practitioners about this problem with a reduction in prescription of other drugs, such as substituted benzamides (that is, metoclopramide) with obvious capacity to induce parkinsonism.

The clinical association between tardive dyskinesia and neuroleptic-induced parkinsonism has been widely reported.[14–16] The possibility that other drugs with less evident antidopaminergic activity could induce tardive dyskinesia has not been studied extensively. Chouza et al. described two cases of tardive dyskinesia in patients with flunarizine-induced parkinsonism.[17] Five of our patients with CIP had tardive dyskinesia, and in three of them, cinnarizine was the only drug implicated. Although it would seem the association with tardive dyskinesia is not as frequent as in cases of neuroleptic-

induced parkinsonism,[5,18] cinnarizine must still be considered a potential cause of tardive dyskinesia. In our series, tardive dyskinesia tended to be more frequent in DIP induced by other drugs different from cinnarizine than in CIP even if the difference did not reach statistical significance.

The story of CIP provides some important lessons. First, the prolonged use of apparently harmless drugs can induce important side effects. Physicians must be extremely cautious when prescribing prolonged treatment for patients, especially the elderly, and particularly when the indication for the drug is not clear. Second, CIP seems to be reversible in most patients. Those whose parkinsonism fails to resolve completely may have been in a presymptomatic phase of idiopathic Parkinson's disease.

Acknowledgment: The author thanks Anthony E. Lang for critical comments to the manuscript.

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