Movement Disorders
Vol. 12, No. 1, 1997, pp. 107–110

Brief Report

A Long-Term Follow-Up Study of Cinnarizine- and Flunarizine-Induced Parkinsonism

A. Negrotti and S. Calzetti

Istituto di Neurologia, Università di Parma, Parma, Italy

Summary: The natural course of calcium-entry blocker–induced parkinsonism was evaluated in 13 elderly patients previously exposed to cinnarizine or flunarizine or both for a median period of 7 months. Clinical assessments were carried out before drug discontinuation and twice thereafter over a period lasting ≤7 years. None of the patients showed a full recovery of extrapyramidal signs, indicating that the long-term prognosis of the parkinsonism is less benign than previously reported. Two main patterns of clinical outcome were recognized (i.e., "remittent" and "persistent and not progressive" parkinsonism), whereas the development of a progressive disorder was observed only in one patient. No significant correlation was found between the patterns of outcome and some clinical variables, such as total duration of exposure to cinnarizine and flunarizine, cumulative drug dosages, and age at onset of parkinsonism. There was no significant difference in terms of family history of essential tremor or parkinsonism or both among the patients with the two main patterns of clinical course. **Key Words:** Parkinsonism—Drug-induced—Cinnarizine—Flunarizine—Long-term outcome.

Drug-induced parkinsonism (DIP) is a well-recognized clinical condition, but its natural course remains poorly defined, as the syndrome occurs mainly in psychotic patients after chronic exposure to neuroleptics, thus making unfeasible a prolonged discontinuation of the offending drug(s). Although most of the previous short-term studies (1,2) showed that parkinsonism induced by calcium channel–entry blockers cinnarizine (CNZ) or flunarizine (FNZ) or both is completely reversible after withdrawal of the involved drug, this conclusion was recently questioned after the results of a prolonged follow-up (3). This issue has relevant clinical implications, because the long-term prognosis of DIP may not be benign, expecially in the elderly, in which brain compensatory processes are known to be inadequate to restore nigrostriatal function (4). A better knowledge of the clinical outcome of these patients could also prove of value in the understanding of the basic pathogenetic mechanism of Parkinson's disease.

Received January 3, 1995, and in revised form March 13, 1996. Accepted March 12, 1996.

Address correspondence and reprint requests to Dr. S. Calzetti, Istituto di Neurologia, Via del Quartiere No. 4, 43100 Parma, Italy.

The aim of this study was to evaluate the long-term prognosis of parkinsonism induced by CNZ or FNZ or both in elderly nonpsychotic patients after discontinuation of the responsible drug and better to characterize the clinical picture of this drug-induced disorder.

PATIENTS AND METHODS

Thirteen consecutive outpatients with parkinsonism resulting from long-term treatment with CNZ or FNZ or both, who were attending the Extrapyramidal Disorders Clinic at the Institute of Neurology, University of Parma, were included in the study. In these patients, the calcium channel–entry blockers had been prescribed for treating vertigo or peripheral circulatory disturbances. Inclusion criteria were (a) onset of symptoms during prolonged treatment with CNZ or FNZ or both; (b) diagnosis of parkinsonism and baseline clinical assessment made when the patients were still taking CNZ or FNZ or both, or not >3 months after their discontinuation; (c) absence of personal history of other movement disorders; (d) lack of previous or concurrent exposure to other drugs capable of inducing extrapyramidal syndromes; and (e) absence of other possible causes of parkinsonism by history

and on clinical examination. Table 1 shows the clinical features of the patients included. The diagnosis of parkinsonism was established by the presence of at least two of the cardinal motor signs (i.e., resting tremor, rigidity, and bradykinesia). At the time of inclusion, two patients were taking anticholinergics, which were discontinued just after baseline assessment. During the follow-up period, none of the drugs known to induce extrapyramidal side effects was allowed, and all the patients were maintained free of antiparkinsonian drugs, unless required because of subjective or objective worsening (or both) of the clinical status. The detection at subsequent assessments of additional neurologic signs indicative of organic brain damage or their presence in the history caused exclusion from the study.

The clinical examination was performed by using eight subitems of the Unified Parkinson's Disease Rating Scale (UPDRS) [i.e., subitems 19 (facial espression), 20 (tremor at rest), 21 (action or postural tremor of hands), 22 (rigidity), 23 (finger taps), 26 (leg agility), 30 (postural stability), and 31 (body bradykinesia and hypokinesia)] at three subsequent times (i.e., basal, intermediate, and final), which occurred at variable intervals between patients during the follow-up. The natural clinical course of parkinsonism was evaluated by calculating the total number of patients with different motor signs and the change of UPDRS scores in individual patients at subsequent times in the follow-up. Based on these findings at the end of the study, each patient was assigned to a different pattern of clinical outcome of the parkinsonian syndrome, as defined according to the following criteria: (a) completely reversible (disappearance of all cardinal signs); (b) partially reversible (one residual cardinal sign); (c) remittent (disappearance of one sign if more than two or decrease in score severity by at least two points for one or more cardinal signs); (d) persistent and not progressive [persistence and stabilization of previous cardinal signs (i.e., scores unvaried or changed by only one point for one or more cardinal signs)]; and (e) persistent and progressive (increase in score severity by at least two points for one or more cardinal signs coupled or not with the occurrence of additional signs). The correlation between the different patterns and some variables, such as total duration of exposure to CNZ and FNZ, their respective cumulative dosages (up to drug discontinuation), and age at onset of parkinsonism was made by using Spearman's rank correlation test. The frequency of family history of essential tremor (ET) or parkinsonism (one or more affected relatives among siblings, parents, grandfathers and grandmothers, uncles and aunts) or both, as ascertained by careful interview of the patients and their spouses, was investigated in the patients with the different patterns by means of the χ^2 test. The occurrence of other extrapyramidal signs, such as dyskinesias and dystonias, was evaluated in terms of number of patients affected, body areas involved, and degree of severity as measured according to the Abnormal Involuntary Movement Scale (AIMS, subitems 1 to 7) (5) at the same times in the follow-up. The number of the patients with head tremor was also determined throughout the study.

TABLE 1. *Clinical features of the patients*

Number of patients	13
Sex (male/female)	0/13
Age (yr)	69.5 (63–78)
Age at onset of symptoms (yr)	68.5 (62.5–76)
Duration (mo) of exposure to	
CNZ (n = 4)	48 (28–68)
FNZ (n = 8)	27 (5–54)
CNZ and FNZ (n = 1)	5/24
Total duration (mo) of exposure to CNZ and FNZ (n = 13)	30 (5–68)
Daily dosage (mg) of	
CNZ (n = 4)	150 (75–200)
FNZ (n = 8)	10 (5–10)
CNZ and FNZ (n = 1)	75/10
Cumulative dosages (g) of	
CNZ (n = 5)	168 (11.25–216)
FNZ (n = 9)	7.2 (1.5–10.8)
Interval (mo) between beginning of exposure to CNZ or FNZ (or both) and onset of symptoms	7 (3–63)
Interval (mo) between onset of symptoms and discontinuation of CNZ or FNZ or both	12 (2–48)

Values are median (range).
CNZ, cinnarizine; FNZ, flunarizine.

RESULTS

Table 2 shows the number of patients with different clinical signs at subsequent times during the follow-up. At the baseline evaluation, the parkinsonian syndrome was expressed by the full motor triad in eight patients (median UPDRS score, 17; range, 9–28; maximum total UPDRS score for items considered, 76), whereas in the remaining five patients only two motor signs were present (median UPDRS score, 8; range, 6–18). The parkinsonism occurred unilaterally in three patients; it was bilateral with side-to-side asymmetry in severity in nine patients. An upper/lower body gradient was found in 10 patients, with an exclusive involvement of the upper limbs in five of them.

During the follow-up period, the parkinsonism was severe enough to warrant drug treatment only in one patient who required anticholinergics at baseline through a 3-year period for the symptomatic control of resting tremor. At the intermediate evaluation, the diagnosis of parkinsonism could still be made in all but two patients, who had only residual bradykinesia. According to these

TABLE 2. *Absolute number and percentage of patients with clinical signs at different times of follow-up*

	Baseline n (%)	Intermediate 2.5 yr (1–5)[a] n (%)	Final 5 yr (2–7)[a] n (%)
Bradykinesia/ hypokinesia	11 (84.6)	11 (84.6)	11 (84.6)
Rigidity	11 (84.6)	10 (76.9)	10 (76.9)
Tremor			
Limbs resting	3 (23.1)	1 (7.7)	1 (7.7)
postural/ kinetic	—	1 (7.7)	3 (23.1)
mixed	9 (69.2)	9 (69.2)	9 (69.2)
Other body sites			
Head	5 (38.5)	1 (7.7)	1 (7.7)
Chin	3 (23.1)	—	2 (15.4)
Tongue	2 (15.4)	—	—
Postural instability	6 (46.1)	8 (61.5)	11 (84.6)
Dyskinesias			
Buccolingual	2 (15.4)	7 (53.8)	6 (46.1)
Segmental	—	2 (15.4)	3 (23.1)

[a] Values reported as median (range).

criteria, at the end of the follow-up, the parkinsonism was "completely reversible" in none of the patients. Two main patterns of clinical course of CNZ- or FNZ-induced parkinsonism or both were recognized (i.e., "remittent" in six (46.1%) patients and "persistent and not progressive" in four (30.8%) patients). Two (15.4%) patients showed the "partially reversible" pattern (they were the same as those with residual bradykinesia at the intermediate assessment). Only one patient was found to develop the persistent and progressive pattern of parkinsonism. Among the six patients with remittent parkinsonism, one showed a reduction both in the number of clinical signs and in UPDRS scores, and the remaining five patients had only a decrease of UPDRS scores.

No significant correlation was found between the two main patterns of clinical outcome and the variables tested [i.e., total duration of exposure to CNZ and FNZ (13 patients), cumulative dosage of FNZ (nine patients), and age at onset of parkinsonism]. Overall, a family history of ET or parkinsonism or both was detected in five (38.5%) patients, but there was not significant difference in its frequency between the patients with the two main patterns of clinical course (i.e., "remittent" and "persistent and not progressive" parkinsonism, respectively).

Eight patients of 13 had dyskinesias during the course of the study. The abnormal movements first appeared during CNZ or FNZ treatment or both (two patients) and after its withdrawal (six patients), the number of affected patients reaching the peak prevalence at the intermediate evaluation (seven patients), and persisting unvaried thereafter (Table 2). When all times of assessment for individual patients were considered, it was found that the dyskinesias affected mainly the orofacial muscles either alone (five patients) or in association with the involvement of upper or lower extremities (three patients). At baseline evaluation (two patients), the median degree of severity of dyskinesia scored 2, and at the subsequent assessment (seven patients), it ranged from 2 to 11 (median, 2). At the final assessment (six patients), the dyskinesias (range of severity from 1 to 11, median 2) were found the first time in one patient, worsened in one patient, persisted unchanged in two patients, showed a partial improvement in two patients, and were not more detectable in two patients. In none of the patients were dystonic signs observed.The occurrence of head tremor during the follow-up is shown in Table 2.

DISCUSSION

The results of this follow-up study indicate that the long-term outcome of CNZ- and FNZ-induced parkinsonism is less benign than previously reported, because none of the patients showed complete disappearance of extrapyramidal signs over a period lasting ≤7 years after discontinuation of calcium entry blockers. Indeed, at the end of the follow-up, a diagnosis of parkinsonian syndrome (not progressive) could still be made in 10 (76.9%) patients, indicating that a relatively "stable" parkinsonism may persist long after the offending drug has been withdrawn. This supports the view that in the elderly, the spontaneous compensatory mechanisms are unable to achieve a long-term complete recovery of the syndrome in most of the exposed subjects. The finding that the persistent and progressive course pattern was observed in one patient suggests that the exposure to CNZ or FNZ or both may unmask a preexisting subclinical "primary" degenerative process like that underlying idiopathic parkinsonism, as was hypothesized for neuroleptics (6). Furthermore, the prolonged and variable assessment intervals in these patients could have hindered in some of them the detection of a symptom-free period with subsequent recurrence and ongoing progression of parkinsonism, as has already been reported in neuroleptic-induced parkinsonism (7). Should this further pattern of clinical course occur (a longer follow-up period in these patients might be required for it to became apparent), the initial reversible iatrogenic parkinsonism could reflect an increased susceptibility in the same patients of ultimately developing Parkinson's disease.

The family history of ET or parkinsonism or both previously reported in patients with calcium channel–entry blocker-induced parkinsonism (8,9) does not appear related to the long-term prognosis of DIP, even though in this study, it was not possible to compare the occurrence of genetic predisposing factors among pa-

tients with stable versus progressive syndrome because of the small number of patients with the latter. The finding that all the patients in this series were women suggests that female gender could be regarded as a potential additional risk factor for developing DIP, at least in the elderly, in agreement with previous reports (3,10).

CNZ- or FNZ-induced parkinsonism at onset was similar to parkinsonism resulting from neuroleptics in terms of asymmetric distribution of motor signs (7), but it differed in the presence of an upper/lower body gradient, with greater involvement of upper limbs. Another distinctive feature of calcium entry blockers versus neuroleptic-induced parkinsonism was the comparatively longer latency of onset of the former (as from the beginning of exposure to offending drugs) (10).

In this series, both the clinical features of parkinsonism at onset and the overall results of the long-term study were similar to those reported by Garcia-Ruiz et al. (3), except for a lower proportion of their patients (33%) who were still fulfilling the diagnostic criteria for parkinsonism at the end of a 18-month follow-up period. In addition, the lack of difference in the recovery time of various motor signs observed in this study could be ascribed to the prolonged time-lag between sequential clinical assessments, which unabled an early surveying of the spontaneous course of parkinsonism.

To our knowledge, this report also represents the first long-term follow-up on dyskinesias induced by CNZ or FNZ or both. In these patients, the dyskinesias did not show a unique pattern in terms of distribution, time of appearance, and course, similar to dyskinesias occurring after chronic exposure to neuroleptics (11).

During the follow-up period, a higher percentage (61.5%) of our patients had coexisting parkinsonism and dyskinesias in comparison with previous reports (3). The course of the abnormal movements paralleled that of parkinsonism and showed a long-term prognosis less favorable than that found in a shorter follow-up study (1).

REFERENCES

1. Micheli FE, Fernandez Pardal MM, Giannaula R, et al. Movement disorders and depression due to flunarizine and cinnarizine *Mov Disord* 1989;4:139–146.
2. Mangone CA, Herskovits E. Extrapyramidal and depressive side reactions with flunarizine and cinarizine [Letter] *J Neurol Neurosurg Psychiatry* 1989;52:288–289.
3. Garcia Ruiz PJ, Garcia de Yebenes J, Jimenez-Jimenez FJ, Vazquez A, Garcia Urra D, Morales B. Parkinsonism associated with calcium-channel blockers: a prospective follow-up study. *Clin Neuropharmacol* 1992;15:19–26.
4. Calne DB, Zigmond MJ. Compensatory mechanisms in degenerative neurologic diseases: insights from parkinsonism. *Arch Neurol* 1981;48:361–363.
5. Baldesserini RJ, Cole JO, Davis JM, et al. *Tardive Dyskinesia Task Force Report 18.* Washington, DC: American Psychiatric Association, 1981.
6. Melamed E, Achiron A, Shapira A, Davidovicz S. Persistent and progressive parkinsonism after discontinuation of chronic neuroleptic therapy: an additional tardive syndrome? *Clin Neuropharmacol* 1991;14:273–278.
7. Hardie RJ, Lees AJ. Neuroleptic-induced Parkinson's syndrome: clinical features and results of treatment with levodopa. *J Neurol Neurosurg Psychiatry* 1988;51:850–854.
8. Negrotti A, Calzetti S, Sasso E. Calcium-entry blockers-induced parkinsonism: possible role of inherited susceptibility. *Neurotoxicology* 1992;13:261–264.
9. Giménez-Roldàn S, Mateo D. Cinnarizine-induced parkinsonism: susceptibility related to aging and essential tremor. *Clin Neuropharmacol* 1991;14:156–164.
10. Friedman JH. Drug-induced parkinsonism. In: Lang AE, Weiner WJ, ed. *Drug-induced movement disorders.* Mount Kisco, NY: Futura Publishing, 1992:41–83.
11. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia [Letter]. *Arch Gen Psychiatry* 1982;39:486–487.