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# Movement Disorders and Depression Due to Flunarizine and Cinnarizine

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**Summary:** Over the last few years, cases of movement disorders induced by flunarizine and cinnarizine have been increasingly reported. We describe a series of 101 patients, whose ages ranged from 37 to 84 years (mean 69.1), developing abnormal movements frequently associated with depression, secondary to treatment with either or both drugs. Symptoms closely resembled those induced by neuroleptic drugs and remitted on drug discontinuance in all but five cases after 5–22 months' follow-up. Whether or not such undesirable side effects are attributable to calcium antagonism and/or dopamine receptor blockade, long-term treatment with flunarizine or cinnarizine should be discouraged, particularly in the elderly. **Key Words:** Flunarizine—Cinnarizine—Depression.

Parkinsonism, acute and tardive akathisia, acute and tardive dystonia, tardive dyskinesia, myoclonus, tics, and neuroleptic malignant syndrome are now well-known complications of antipsychotic drug treatment. In addition to neuroleptic drugs, an increasing number of drugs have proven capable of impairing basal ganglia function, thus inducing extrapyramidal reactions.

Recent studies, mainly from Latin America and Europe, have described the occurrence or aggravation of movement disorders and depression secondary to the administration of the calcium antagonists flunarizine (Fz) and/or cinnarizine (Cz) (1–5).

Widely employed in Argentina, specially among the elderly population, for the treatment of dizziness, vertigo, tinnitus, and cognitive disorders, both Fz and Cz are piperazine derivatives with antihistaminic, antiserotoninergic, and antidopaminergic activity (6). Fz has also been reported useful in the treatment of convulsive disorders, migraine, and alternating hemiplegia (7–11).

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Although sharing a common pharmacological profile with Cz, Fz is more potent and has a longer plasma half-life (12). Given their mild $D_2$ receptor blocking effect (13), it has been speculated whether this property and/or the calcium entry blocking activity could account for their extrapyramidal side effects.

We describe a series of 101 patients who developed extrapyramidal syndromes frequently associated with depression secondary to Fz and/or Cz intake. Of the above, an initial group of 15 cases has been reported elsewhere (2).

## PATIENTS AND METHODS

During the past 2 years we studied 101 patients, 68 women and 33 men aged 37–84 years (mean 69.1) who developed movement disorders while receiving treatment with Cz and/or Fz. None received any other antidopaminergic or calcium entry blocker drug. Cases whose prior extrapyramidal syndromes had been aggravated by Cz or Fz were excluded.

Tardive dyskinesia is defined here as continuous, stereotyped, choreic movements involving orofacial muscles, neck, trunk, or limbs, occurring either during Fz or Cz intake or within 3 months after withdrawal. Tardive dystonia was diagnosed according to the criteria advanced by Burke et al. (14). Parkinsonism is defined by the presence of at least three of the following major signs: rigidity, resting tremor, bradykinesia, and impaired postural reflexes. Akathisia was recognized by inner restlessness only relieved by movement, regardless of the motor pattern: it was considered acute when self-limited symptoms appeared early during treatment or with drug increase, and tardive when such symptoms presented at least 3 months after starting therapy and/or proved persistent or permanent. Acute dystonia is defined as sustained muscular spasms occurring after initiating treatment or with dose increase.

Depression was diagnosed according to DSM III criteria (15).

On the basis of the above guidelines, 93 patients had parkinsonism, 15 had tardive dyskinetic syndromes, 1 had acute dystonia, 5 had orofacial tremor, and 1 had acute akathisia. A certain degree of symptom overlapping was observed (Table 1). In addition, 57 cases had depression.

Fifty-five patients were taking Fz, 35 received Cz, and 11 took both drugs. Doses ranged from 10 to 50 mg (mean 13.2 mg) for Fz and from 50 to 225 mg (mean 152.1 mg) for Cz. The medication period before onset varied from 1 to 120 months (mean 20.8), except for one patient who developed acute akathisia within 4 h of his first Cz dose and a further one who presented an acute dystonic reaction after 3 days of taking Fz.

Cz and Fz were discontinued and serial neurological examinations were carried out without prescribing any alternative therapy. Formal psychological testing was not routinely available in this patient population.

## RESULTS

All 93 parkinsonian patients fully recovered within 7–270 days (mean 92.4) after drug withdrawal.

TABLE 1. *Extrapyramidal symptoms and depression in 101 patients*

| No. of patients | Parkinsonism | Depression | Tardive akathisia | Orofacial diskinesia | Orofacial tremor | Blepharospasm/ oromandibular dystonia | Bruxism | Acute dystonia | Acute akathisia |
|---|---|---|---|---|---|---|---|---|---|
| 48 | X | X | | | | | | | |
| 31 | X | | | | | | | | |
| 3 | X | X | X | | | | | | |
| 3 | X | | | X | | | | | |
| 2 | X | X | | X | | | | | |
| 2 | X | X | | | X | | | | |
| 2 | | | X | X | | | | | |
| 2 | | | | | X | | | | |
| 1 | X | X | X | X | | | | | |
| 1 | X | | X | | | | | | |
| 1 | X | | X | | | | X | | |
| 1 | X | | | | X | | | | |
| 1 | | X | X | X | | | | | X |
| 1 | | | | | | X | | X | |
| 1 | | | | | | | | | |
| Totals 101 | 93 | 57 | 9 | 9 | 5 | 1 | 1 | 1 | 1 |

Of these, 19 had been previously diagnosed as having Parkinson's disease and were unsuccessfully treated with L-Dopa, anticholinergic drugs, or bromocriptine. Their clinical features are listed in Table 2.

There was complete recovery from tardive dyskinetic syndromes in 10/15 patients within 15 days to 8 months (mean 87 days), partial improvement in one and none in 4 after 6–22 months (mean 12 months). All patients who failed to recover had been on Fz; in 3 cases the dose was 10 mg, though in one it was associated to Cz, as well as in the 4th with a 20 mg Fz dose (Table 3).

Although orofacial dyskinesia and tardive akathisia were the most common tardive syndromes, the latter presented the worst recovery index, because 33% of the cases became permanent.

Depressive symptoms subsided more rapidly than movement disorders, disappearing within the first 3 weeks after Fz and/or Cz discontinuance.

The single acute dystonia and acute akathisia cases resolved spontaneously.

## DISCUSSION

The overwhelming majority of drug-induced extrapyramidal reactions reported to date have been ascribed to neuroleptic drugs, a poorly defined group of drugs sharing postsynaptic dopaminergic blocking effects.

Recently attention has been focused on similar side-effects secondary to calcium entry blockers. Although these reactions have been caused mostly by Fz and Cz, occasional observations of myoclonic dystonia after nifedipine (16) or verapamil (17), and diltiazem-induced akathisia (18) have also been described.

Our findings confirm previous reports on the risks of long-term treatment with Fz or Cz even in therapeutic recommended doses. However, their mechanism of action is still a matter of conjecture. Both Cz and Fz are piperazine derivatives with chemical structures outwardly resembling trifluoperazine. In addition they have proven capable of inducing extrapyramidal reactions such as tardive dyskinesia/dystonia and acute dystonia, which are known to be caused almost exclusively by a postsynaptic dopamine receptor blocking mechanism. However, recalling that piribedil is likewise a piperazine derivative (19) but acts as a dopamine agonist, Cz and Fz should also be expected to differ from trifluoperazine on the basis of their radically dissimilar tridimensional structure, besides their milder $D_2$ blocking properties (13).

It is well known that the bioavailability of intracellular calcium, depending in turn on calcium entry, regulates the release of neurotransmitters at the presynaptic terminal. Passive $Ca^{2+}$ entry to the cell occurs through glycoproteins, which admit $Ca^{2+}$ to the cell through two distinct mechanisms, either voltage dependent or receptor operated (20). Several $Ca^{2+}$ channel subtypes have been discerned in diverse organ tissue (21), and there are several binding sites at the channel with varying affinities for different drugs (22). Calcium antagonists impair channel opening and therefore could well account for induced movement disorders and depression.

Fernandez Pardal et al. (23,24) studied the effects of Cz, Fz, and nifedipine on the release of $^3H$ dopamine from rat caudate nucleus by labeling endogenous

TABLE 2. *Characteristics of 93 parkinsonian cases*

| | n | % | Age ($\bar{X}$ ± SE) | Range (ages) |
|---|---|---|---|---|
| Female | 62 | 66.6 | 69.7 ± 0.9 | 48–82 |
| Male | 31 | 33.3 | 69.6 ± 1.4 | 54–84 |
| Total | 93 | 100.0 | 69.7 ± 0.7 | 48–84 |

| | n | dose (X ± SE) | Range | Medication period before onset (mo) $\bar{X}$ ± SE | Range | Recovery time (days)[a] X ± SE | Range | Unilateral | Presenting symptoms Bilateral | R | T | B | I | U |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cinnarizine | 34 | 154.4 ± 9.8 | 50–225 | 32.11 ± 5.83 | 2–120 | 80.5 ± 10.3 | 7–270 | 1 | 33 | 7 | 16 | 8 | 1 | 2 |
| Flunarizine | 51 | 13.4 ± 1.0 | 10–50 | 14.11 ± 1.65 | 1–36 | 105.6 ± 9.0 | | 5 | 46 | 18 | 17 | 5 | 2 | 9 |
| Cinnarizine plus flunarizine | 8 | 121.8 ± 10.6<br>13.1 ± 1.5 | 75–150<br>10–20 | 17.12 ± 5.37<br>11.25 ± 4.12 | 1–36<br>2–36 | 55.0 ± 17.0 | 30–180 | 2 | 6 | 3 | 3 | 2 | | |
| Total | 93 | | | 21.33 ± 2.56 | 1–120 | 92.4 ± 6.6 | 7–270 | 8 | 85 | 28 | 36 | 15 | 3 | 11 |

[a] After drug withdrawal. mg per day.
R, rigidity; T, tremor; B, bradykinesia; I, impaired postural reflexes; U, undetermined.

TABLE 3. *Tardive dyskinesia/dystonia*

| Sex/age (yr) | Dyskinesia-dystonia | Drug/dose | Medication period before onset (mo) | Recovery (mo)[a] | Associated symptoms |
|---|---|---|---|---|---|
| F/74 | Orofacial dyskinesia, tardive akathisia | Fz 10 mg | 36 | None (at 7 mo) | — |
| F/67 | Blepharospasm, oromandibular dystonia | Fz 20 mg Cz 150 mg | 18 | None (at 13 mo) | Parkinsonism |
| F/70 | Tardive akathisia, bruxism | Fz 30 mg | 48 | 2 | Parkinsonism |
| M/59 | Orofacial dyskinesia | Cz 225 mg | 36 | 1/2 | Parkinsonism, depression |
| F/76 | Orofacial dyskinesia | Cz 150 mg | 24 | 1 | Parkinsonism |
| M/62 | Tardive akathisia | Cz 225 mg | 24 | 2 1/2 | Parkinsonism |
| F/64 | Orofacial dyskinesia | Fz 10 mg | 4 | 1 | Parkinsonism |
| F/49 | Tardive akathisia | Fz 20 mg | 8 | 2 | Parkinsonism, depression |
| F/66 | Tardive akathisia | Fz 10 mg | 18 | 2 | Parkinsonism, depression |
| F/61 | Tardive akathisia, orofacial dyskinesia | Fz 11.5 mg | 3 | 5 | Parkinsonism, depression |
| F/70 | Tardive akathisia, orofacial dyskinesia | Fz 10 mg Cz 25 mg | 24 | None (at 6 mo) | — |
| M/74 | Tardive akathisia | Fz 20 mg | 18 | 8 | Parkinsonism, depression |
| F/68 | Orofacial dyskinesia | Fz 10 mg | 48 | 5 | Parkinsonism, depression |
| F/64 | Tardive akathisia, orofacial dyskinesia | Fz 10 mg | 24 | None (at 22 mo) | Depression |
| M/84 | Orofacial dyskinesia | Cz 150 mg | 4 | 5, partial recovery | Parkinsonism |

[a] Time after drug discontinuance.

dopamine stores in vitro, and found that, given in doses capable of blocking calcium channels, all three drugs lowered the potassium-elicited tritium overflow. In rats pretreated with Fz there was a significant drop in $^{3}H$ dopamine release by stimulation with potassium but not with tyramine, suggesting a calcium-dependent mechanism.

The considerable frequency of movement disorders secondary to Fz or Cz intake in comparison to other nonpiperazine calcium antagonists could be partly explained by varying affinity for calcium receptors and/or diverse degrees of passage through the blood–brain barrier. In support of the latter, potassium-induced $^{3}H$ dopamine release from rat caudate slices is inhibited by pretreatment with Fz but not with nifedipine (24).

From the body of evidence available on the side effects of Fz and Cz, several conclusions can be drawn.

1. Fz- and Cz-induced extrapyramidal reactions and depression have become increasingly common in Argentina, although no data on prevalence or incidence are yet available.
2. These side effects can even be induced by recommended therapeutic doses.

3. Movement disorders closely resemble those induced by neuroleptic drugs.
4. Most symptoms are reversible, but some can persist for varying periods. Thus, acute akathisia resolves rapidly, but parkinsonism may last several months.
5. Among the more disabling syndromes, tardive dyskinesia is prone to manifest as a permanent movement disorder, which is particularly distressing in nonpsychotic patients.
6. Depression usually subsides more rapidly than extrapyramidal syndromes.
7. No evidence is available so far that patients exhibiting Fz- or Cz-induced parkinsonism are prone to develop Parkinson's disease in spite of drug discontinuance. However, it is entirely feasible that latent Parkinson's disease may become manifest by treatment with either Cz or Fz.
8. It seems that elderly patients are more liable to develop these complications, but (so far) young patients seldom receive these drugs in Argentina.

Our findings suggest that overeagerness in prescribing calcium antagonists should be tempered by a fuller review of their harmful collateral effects.

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## REFERENCES

1. Chouza C, Scaramelli A, Caamaño JL, De Medina O, Aljanati R, Romero S. Parkinsonism, tardive dyskinesia, akathisia and depression induced by flunarizine. *Lancet* 1986;1:1303–4.
2. Micheli F, Fernandez Pardal M, Gatto M, et al. Flunarizine- and cinnarizine-induced extrapyramidal reactions. *Neurology* 1987;37:881–4.
3. Marti Masso JF, Carrera N, De la Puente E. Posible parkinsonismo por cinaricina. *Med Clin (Barc)* 1985;85:614–6.
4. Marti Masso JF, Obeso JA, Carrera N, Martinez Lage JM. Aggravation of Parkinson's disease by cinnarizine. *J Neurol Neurosurg Psychiatry* 1987;50:804–5.
5. Di Rosa AE, Morgante L, Meduri M, Leggiadro N, Coraci M, Crisafulli A, Di Perri R. Parkinson-like side effects during prolonged treatment with flunarizine. *Funct Neurol* 1987;1:47–50.
6. Godfrain T, Towse G, Van Nueten JM. Cinnarizine: a selective calcium entry blocker. *Drugs of Today* 1982;18:27–42.
7. Wauquier A, Ashton D, Clincke G, Fransen J, Gillardin JM, Janseer PAJ. Anticonvulsant profile of flunarizine. *Drugs Dev Res* 1986;7:49–60.
8. Amery WK, Caers LI, Aerts TJL. Flunarizine, a calcium entry blocker in migraine prophylaxis. *Headache* 1985;25:249–54.
9. Diamand S, Schenbaum H. Flunarizine, a calcium channel blocker in the prophylaxis of migraine. *Headache* 1983;23:39–42.
10. Caers LI, De Beukelaar F, Amery WK. Flunarizine a calcium-entry blocker, in childhood migraine, epilepsy and alternating hemiplegia. *Clin Neuropharmacol* 1987;10:162–8.
11. Casaer P, Azov M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984;2:579.
12. Holmes B, Brogden RN, Heel RC, Speight TM, Avery GS. Flunarizine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984;27:6–44.
13. Leysen JE, Gommeren W. Receptor binding profile of flunarizine: preclinical research report. Janssen Pharmaceutical Research Laboratories, R 14950/24, March 1983.
14. Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: Late-onset and persistent dystonia caused by antipsychotic drugs. *Neurology* 1982;32:1335–46.
15. American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and statistical manual of mental disorders, ed. III.* Washington, DC: American Psychiatric Association, 1980.
16. De Medina A, Biasini O, Rivera A, Sampera A. Nifedipine and myoclonyc dystonia. *Ann Intern Med* 1986;104:125.
17. Hicks CB, Abraham K. Verapamil and myoclonic dystonia. Ann Intern Med 1985;103:154.
18. Jacobs MB. Diltiazem and akathisia. *Ann Intern Med* 1983;99:794–5.

19. Arnott G, Blondel M, Persuy P, Delandsheer E. Piribedil in the treatment of Parkinson's disease. A follow up from two to ten years, of forty patients. Presented at the 9th International symposium on Parkinson's disease. Jerusalem, Israel, June 5–9, 1988.
20. Greenberg DA. Calcium channels and calcium channel antagonists. *Ann Neurol* 1987;21:317–30.
21. Nonycky MC, Fox AP, Tsien RW. Three types of neuronal calcium channel with different calcium agonist sensitivity. *Nature* 1985;316:440–3.
22. Murphy KMM, Gould RJ, Largent BL, Snydersh SH. A unitary mechanism of calcium antagonist drug action. *Proc Natl Acad Sci USA* 1983;80:860–4.
23. Fernandez Pardal MM, Fernandez Pardal J, Micheli F. Effect of flunarizine and nifedipine on the $^{3}H$ dopamine release by potassium in the rat caudate nucleus. *Acta Physiol Pharmacol Latinoam* 1987;37:156–8.
24. Fernandez Pardal MM, Fernandez Pardal J, Micheli F. Aggravation of Parkinson's disease by cinnarizine. *J Neurol Neurosurg Psychiatry* 1988;51:158–9.