Short report

Aggravation of Parkinson's disease by cinnarizine

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SUMMARY The effect of cinnarizine on motor function in Parkinson's disease was evaluated in a randomised double-blind parallel study of 20 patients. Both groups were comparable in age, duration of the disease, dose of levodopa and degree of disability. A significant worsening of mobility was observed in patients treated with cinnarizine (75 mg bd), whilst no change was recorded in patients receiving placebo. Cinnarizine should be added to the list of drugs capable of aggravating Parkinson's disease.

Cinnarizine is a piperazine derivative with anti-histaminic and calcium antagonist activity. It is widely prescribed in Spain for the treatment of dizziness, unsteadiness and cognitive disorders, particularly in the elderly population, on the basis of possible labyrinthine sedative and psychotropic actions.¹ In 1982 one of the authors (JFMM) had the chance to study in detail a 78 year old woman in whom a Parkinsonian syndrome developed during chronic ingestion of cinnarizine (75 mg bd). A causal relationship was proved by observing resolution and recurrence of the symptoms on two different occasions, when discontinuing and reassuming cinnarizine ingestion respectively. Following this initial case we were able to examine in a short period of time 10 other patients with Parkinsonism while under treatment with cinnarizine, during a period of 5 months to 7 years.² None of these patients was concomitantly taking any anti-dopaminergic drug. The Parkinsonian syndrome resolved in all but one case within one to 7 months after cinnarizine withdrawal.

In order to obtain further knowledge about the action of cinnarizine on motor function, a double-blind study against placebo was undertaken in patients with Parkinson's disease. The conclusion of this study as well as the experience obtained by the authors working in two different health areas, over the last 3 years are now reported.

Patients and method

Patients

Twenty patients with a diagnosis of Parkinson's disease (11 females and 9 males) were included in the study. The group had a mean age of 59 ± 83 years. They were all in stage I or II of Hoehn and Yahr classification. All but one patient, who was receiving treatment with benzhexol and amantadine, were under levodopa therapy (Sinemet^R of Madopar^R).

Protocol

The study consists of a randomised double-blind parallel design during a 3 month period. After an initial basal clinical evaluation, patients were randomly divided in two halves and assigned to one of the two treatment groups: Group I, cinnarizine 75 mg bd and Group II, placebo tablets of identical presentation twice a day. Throughout the trial no change in the underlying antiparkinsonian treatment was allowed.

Assessment

Clinical evaluation was undertaken using the Webster and Northwestern University disability scales, as well as by measuring the time taken to walk 10 metres in a straight line, time to turn around in bed and time to write a given sentence. Patients were rated before entering the study and at the end of the first and third month of the trial. The U-Mann-Whitney test and Student's *t* test were used to analyse the homogeneity of the groups. The Wilcoxon signed rank test for non-parametric data was used to assess the evolution within groups, whilst the Chi-square test was applied for between groups comparison.

Results

Both groups were comparable in age (62.5 ± 15.8 vs 56.2 ± 6.2 yr), duration of the disease (4.3 ± 1.1 vs

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Table Effect of cinnarizine vs placebo on motor function

Scale	Group I (Cinnarizine 75 mg bd)	Group II (Placebo)
Webster		
Control	14.4 ± 7.5	10.5 ± 8.75
Treatment	22.9 ± 10.0*	9.8 ± 10.46
Northwestern		
Control	44.4 ± 3.9	46.3 ± 1.83
Treatment	41 ± 7.2	45.6 ± 2.63
Time taken to:		
a) Walk 10 m		
Control	10.8 ± 4.9	9.2 ± 1.4
Treatment	12.0 ± 5.6	10.0 ± 2.4
b) To turn in bed		
Control	25.4 ± 17.9	19.4 ± 16.1
Treatment	38.1 ± 22.4*	18.2 ± 15.3
c) To write a sentence		
Control	28.3 ± 15.0	20.2 ± 7.5
Treatment	35.8 ± 18.8	21.2 ± 8.3

*p < 0.05.

5.1 ± 1.6 yr) and daily levodopa dose (550 ± 317 vs 440 ± 120 mg). There was no significant difference between the two groups regarding the mean values recorded in the scales and tasks used for clinical assessment before initiation of the study (table). Four out of the 10 patients in the cinnarizine's group abandoned the trial after 4, 6, 11 and 58 days of treatment due to clear cut deterioration of motor function. All patients included in Group II completed the study. Statistical evaluation of the results was made excluding the drop-outs. The table summarises the main results. A significant worsening of mobility as reflected by an increment in the Webster scale and time for turning in bed occurred in Group I. The Northwestern University scale, time required to walk 10 metres and time taken to write a sentence were not modified by treatment with cinnarizine. No significant variation in any scale was observed in Group II.

The only subject in the study not taking levodopa was in Group I. He was a 75 year old patient with a 3 year history of Parkinson's disease of mild severity. After adding cinnarizine to his normal treatment (amantadine 100 mg bd), a clear-cut deterioration in mobility was noticed. This was expressed by a 30 and 50% increment in Webster's scale scoring and time to turn around in bed respectively.

Discussion

This study plus the accumulated (uncontrolled) experience of the authors over the last 3 years lead to the following conclusions: (1) cinnarizine used at the average dose of 150 mg daily can aggravate motor

function in patients with Parkinson's disease. (2) This effect is reversible, but may last several days or weeks. (3) Cinnarizine may induce a Parkinsonian syndrome in relatively old patients (above 60 years old), who had no prior symptoms suggestive of Parkinson's disease. In all but one of the 22 patients personally examined by us, the Parkinsonian features disappeared upon cinnarizine withdrawal. Whether or not all these patients are in a pre-clinical state of Parkinson's disease can not be determined at present.

The mechanism(s) by which cinnarizine induces or aggravates Parkinsonian signs is not yet established. Flunarizine, the difluorinated derivative of cinnarizine, may also produce Parkinsonism, tardive dyskinesia, akathisia and depression, mimicking the side-effects caused by neuroleptics.³ The pharmacological activity of calcium entry blockers is not only related to their action on blood vessels but also due to inhibition of neuronal membrane calcium channels. Recently, it has been shown that nimodipine reduces the release and synthesis of striatal dopamine in the mouse,⁴ perhaps by an effect on calcium dependent activation of tyrosine hydroxylase.

However, we are not aware of any other pharmacological or biochemical evidence indicating an antidopaminergic action of calcium antagonists. Thus, no clinical report of Parkinsonian syndrome associated with chronic use of several other calcium blocking agents (nifedipine, nicardipine, nimodipine) is available.⁵

In conclusion, we believe that cinnarizine has a risk of disturbing motor function and should be used with caution. Patients who already have a diagnosis of Parkinson's disease should never be treated with cinnarizine. Understanding the mechanism by which this drug induces motor disturbances may provide further insight into the pathophysiology of basal ganglia disorders.

References

- 1 Hauth H. Chemistry of gerontopsychopharmacological agents. In: Hoffmeister F, Stille G, eds. *Psychotropic Agents*. Berlin: Springer-Verlag, 1981:409-31.
- 2 Marti Masso JF, Carrera N, De La Puente E. Posible parkinsonismo por cinaricina. *Med Clin (Barc)* 1985;85:614-6.
- 3 Chouza C, Scaramelli A, Caamaño JL, et al. Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986;i:1303-4.
- 4 Pileblad E, Carlsson A. In vivo effects of the Ca⁺⁺ antagonist nimodipine on dopamine metabolism in mice brain. *J Neural Transm* 1986;66:171-87.
- 5 Traber J, Hoffmeister F, Kuhlmann J. Dihydropyridines and parkinsonism. *Lancet* 1986;ii:292.