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Nomifensine in Parkinsonism

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SYNOPSIS Nomifensine, a tetrahydroisoquinoline antidepressant which facilitates dopaminergic and noradrenergic transmission, was studied in 28 Parkinsonism patients most of whom were also receiving conventional medications. Double-blind evaluations revealed a moderate therapeutic action at a mean dose level of 150 mg daily. Adverse reactions were encountered, similar to those induced by levodopa.

Nomifensine (8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline) is a drug currently being evaluated as an antidepressant. It inhibits the reuptake of noradrenaline in the same way as tricyclic antidepressants, but unlike tricyclics it also decreases the reuptake of dopamine and has a direct agonist effect on dopaminergic receptors (Hoffmann, 1973; Gerhards *et al.*, 1974; Schacht and Heptner, 1974; Costall *et al.*, 1975; Costall and Naylor, 1975). Nomifensine should therefore potentiate both noradrenergic and dopaminergic synaptic transmission. There is evidence, deriving from animal studies, which suggests that optimal anti-Parkinsonism therapy should augment both noradrenergic and dopaminergic transmission (Hornykiewicz, 1973); for this reason, we have studied the action of nomifensine in Parkinsonism.

METHODS

PATIENTS

Twenty-eight patients (14 male, 14 female) with idiopathic Parkinsonism and one patient with post-encephalitic Parkinsonism were studied. Informed consent was obtained from all subjects, who were warned that they might experience a temporary deterioration at some stage during the trial. Twenty patients (13 men, seven women) of mean age 68 years (range 55 to 83) completed the study. Of these, 16 were on maximum tolerated doses of levodopa (eight taking carbidopa and five receiving anticholinergic agents); two patients were on anticholinergics alone, and two were not taking any drugs.

DESIGN

The study was performed in three consecutive stages. (1) Nomifensine was gradually introduced, building up to maximum tolerated dosage over a period of two weeks; (2) when optimum dose levels were obtained, treatment was continued for between six and 15 weeks; (3) a placebo was substituted for nomifensine over the final six weeks.

The initial dose of nomifensine varied between 25 and 50 mg daily. No patient received more than an arbitrarily set upper limit, 200 mg. In five subjects, because of transient unwanted effects, the dose of nomifensine was reduced by 25% of their maximum level.

The major adverse effect was dyskinesia. In four patients this was controlled by a reduction in levodopa from a mean of 3.63 g (range 4.5 to 3) to a mean of 2.5 g (range 3.5 to 1.5) and in two subjects by a reduction of Sinemet (250 mg levodopa combined with 25 mg carbidopa) from an average of 3.75 tablets (range 5 to 2.5) to an average of two (range 3 to 1). Other concomitant therapy was maintained without alteration throughout the study.

EVALUATIONS

The method for evaluation of physical signs and functional disability was that used previously (Calne *et al.*, 1974), scores ranging from 0 (representing normality) to 4 (maximum deficit). Timed tests were employed for walking, writing, repetitively opposing

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thumb to fingers in each hand, and alternate full finger extension and flexion in each hand. These assessments were made on outpatients, every two weeks, by the same evaluator. The patient's weight was measured at each visit, an electrocardiogram was recorded before and during the phase of treatment with active drug, and routine haematological and biochemical tests were performed every two weeks, without detection of any significant abnormality.

RESULTS

Nineteen of the 20 patients completed three placebo evaluations. One patient sustained a Colles fracture after only one placebo assessment; administration of placebo was not continued in this patient. The mean maximum tolerated dose of nomifensine was 150 mg daily (range 75–200).

The results of the last three evaluations on nomifensine were compared with the three evaluations on placebo. When placebo was substituted for active drug, deterioration of physical signs and functional disability were significant (Fig. 1) at the 0.1% level (paired *t* test). Of the physical signs, tremor and facial expression improved most during treatment with nomifensine, but there was also some amelioration of rigidity, speech disorder, balance, finger dexterity, gait, posture, and drooling of saliva. Of the functional disabilities, dressing, washing, eating, and writing all improved. All timed tests showed a beneficial trend during treatment with nomifensine, for finger flexion (Fig. 2) the improvement was significant at the 1% level (paired *t* test).

No statistical difference was found in either clinical scoring or timed tests between the patients receiving nomifensine for six, eight, 10, 12, 14 or 15 weeks.

Although all clinical features which were evaluated displayed some improvement during the phase of nomifensine therapy, gains were moderate and dramatic individual improvements were not seen.

The frequency of unwanted effects, in the 19 patients who completed the study, is shown in the Table. All adverse reactions were dose dependent and the drug was well tolerated once optimum maintenance levels of intake were established.

Of the nine patients omitted from the analysis, one failed to attend regularly and another had a continuing depressive illness, resistant to nomifensine. The other seven patients were withdrawn because of the development of involuntary movements; three of these were not receiving levodopa. Additional adverse effects in the excluded group included insomnia (two), confusion (two) and akathisia, headache, vertigo, faintness, emesis or constipation (one patient each). Some patients experienced more than one unwanted effect, but all the adverse reactions were abolished by stopping nomifensine.

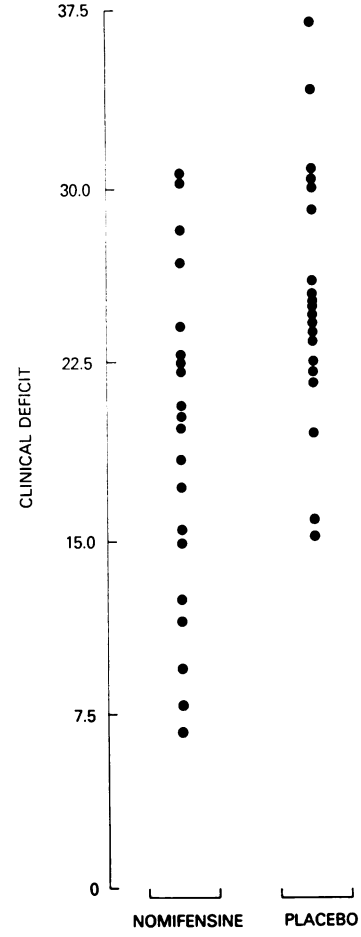

FIG. 1 *Total clinical deficit in each patient during nomifensine and placebo therapy (arbitrary clinical score for tremor, rigidity, dysarthria, facial expression, rising from chair, balance, finger dexterity, drooling, sweating, gait, posture, dressing, washing, eating, writing—0=normal; 4=maximal disability). Average of three separate evaluations at fortnightly intervals.*

DISCUSSION

Tricyclic antidepressants, theoretically feasible agents to treat Parkinsonism, have not achieved a prominent place in therapy. They act predominantly on noradrenergic and serotonergic terminals by inhibiting the reuptake of noradrenaline and serotonin respectively. Nomifensine, a tetrahydroisoquinoline with antidepressant properties, is of interest in Parkinsonism because it also inhibits the reuptake of dopamine and activates dopaminergic receptors.

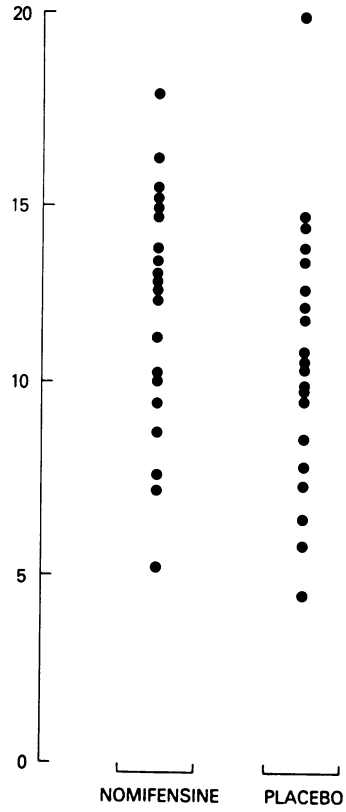

FIG. 2 *Mean of the number of complete flexion–extension movements of fingers performed with both hands in 10 seconds. Average of three separate evaluations at fortnightly intervals.*

Our results suggest that nomifensine is effective in the treatment of Parkinsonism.

The frequency of adverse effects is similar to those produced by levodopa and bromocriptine. The prevalence of involuntary movements suggests that the pharmacological effect of nomifensine is similar to these agents, though many of the patients were concomitantly receiving levodopa. It is therefore difficult to evaluate the contribution of nomifensine to these reactions.

The M_1-metabolite of nomifensine has similar activity to its parent compound in animal studies (Costall and Naylor, 1975). Important topics for future investigation include the contribution of this metabolite, and the relative roles of noradrenergic and dopaminergic activity in generating therapeutic and adverse responses to anti-Parkinsonism drugs. More extensive studies are desirable before drawing any firm conclusions concerning the potency and toxicity of nomifensine as a therapeutic agent for Parkinsonism.

TABLE

DOSE DEPENDENT ADVERSE REACTIONS ENCOUNTERED IN THE 19 PATIENTS WHO COMPLETED THE STUDY

Adverse reactions	*Number of patients affected*
Dyskinesia	10
Emesis	4
Insomnia	4
Sedation	3
Constipation	3
Dry mouth	1
Light-headedness	1
Hallucinations	1
Nightmares	1
Paraesthesiae	1
'On–off' phenomena	1

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