NOMIFENSINE IN PARKINSON'S DISEASE

P. BEDARD, J.D. PARKES & C.D. MARSDEN

University Department of Neurology, Institute of Psychiatry, and King's College Hospital Medical School, Denmark Hill, London SE5, UK

- 1 Eight patients who failed or ceased to respond to levodopa, or who had developed the 'on-off' phenomenon were treated additionally with nomifensine.
- 2 The dosage of nomifensine started at 50 mg, was increased to 150 mg daily, and other medication was continued unchanged. The duration of treatment was from 2-5 months. Assessments were carried out at 2-week intervals using a validated rating scale.
- 4 Loss of dopaminergic nigrostriatal neurones characterizes Parkinson's disease, and it is probably for this reason that indirect dopamine (DA) agonists, whose actions depend on intact presynaptic mechanisms, are less active.
- 3 Nomifensine was not shown to be of antiparkinsonian value in these patients but may be of value as an antidepressant in patients with Parkinson's disease.

Introduction

Nomifensine (8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline hydrogen maleate) (Hoffman, 1973) possesses some therapeutic action in Parkinson's disease (Teychenne *et al.*, 1976; Park, 1977). Although primarily developed as an antidepressant, nomifensine differs from typical tricyclic antidepressants in exhibiting dopaminergic agonist properties in animals (Costall *et al.*, 1975), which was why it was chosen for study in Parkinson's disease.

The treatment of Parkinson's disease today is more complex than was appreciated some years ago when levodopa was first introduced. It has become apparent that not only do some 15% of patients never respond to levodopa, but also that some two-thirds of patients lose the benefits of treatment after a few years of therapy. Accordingly, the pressing need now is for drugs that can replace levodopa when its benefits begin to wane. Therefore, we have examined the role of nomifensine in those patients in whom the therapeutic action of levodopa has declined. This occurs in one of two ways: either there is a progressive recurrence of disease; or oscillations in performance develop, with increasingly severe swings from mobility with dyskinesias to mobility without dyskinesias (the 'on-off' phenomenon, or 'swinging'). We have studied the effects of nomifensine, added to levodopa therapy, in patients with these two types of long-term levodopa failure. Unfortunately, nomifensine has not proved of value to these patients. This is not too surprising, however, in view of the mode of action of the drug, which is discussed.

Nevertheless, nomifensine may prove to be an antidepressant of choice in Parkinson's disease.

Methods

Eight patients with idiopathic Parkinson's disease (aged 41-73 yr; 5 male, 3 female) were specially selected for study. Four had failed to respond or had lost all response to levodopa therapy. Four had developed clear-cut fluctuations in response to levodopa ('on-off' swings) after treatment for 3-6 yr. All but two were on optimum levodopa therapy, taking levodopa in doses of 500-1,500 mg daily combined with carbidopa 50-150 mg daily (as Sinemet tablets). The other two patients, and two of the six on Sinemet, were taking anticholinergic drugs, usually benzhexol.

Nomifensine was started at a dose of 25 mg twice daily, increasing to 25 mg three times daily, after 3 d, and then to 50 mg three times daily 2 weeks later. Other drugs were continued unchanged.

Parkinsonian disability was rated according to the King's College Scoring System (Marsden *et al.*, 1973) before and at 2-week intervals after starting nomifensine, which was continued for between 2-5 months. The trial was single blind, in that the patient, but not the observer, was unaware of whether he was taking an active drug or a placebo. Subjective response and side-effects of treatment were recorded, and the full blood count, erythrocyte sedimentation rate, plasma electrolytes, urea, alkaline phosphatase,

bilirubin, SGOT and SGPT, plasma proteins, uric acid and glucose were monitored before and at monthly intervals during nomifensine therapy.

Results

Three of the eight patients reported slight subjective improvement in disability, but this was not confirmed objectively. None of the patients showed any dramatic response to nomifensine treatment. Total disability scores improved in five and deteriorated in three, but the changes were no more than plus or minus some 10%, and no significant change from pretreatment mean total disability scores occurred (Table 1). Withdrawal of nomifensine also had no subjective or objective effect.

None of the four progressive levodopa failures showed any benefit from nomifensine. Two of the four patients with 'on-off' swings reported initial lengthening of 'on' periods, but this effect did not last, and was not observed in the other two similar patients.

Two of the eight patients were pathologically depressed when started on nomifensine, but in neither was the depression cured.

Four patients reported low lumbar backache during nomifensine treatment, which disappeared when the nomifensine was discontinued. No other side-effects were noted. In particular, blood pressure was not altered and levodopa-induced dyskinesias, which were present in five of the eight patients, were not noticeably enhanced. There were no changes in the haematological or biochemical indices during nomifensine therapy.

Discussion

The primary pathology of Parkinson's disease is a progressive death of substantia nigra neurones with

loss of nigrostriatal dopaminergic pathways. The progression of the pathology responsible for the illness is not influenced by levodopa therapy, so that long-term loss of the response to levodopa may be due, at least in part, to increasingly severe degeneration of the nigrostriatal system. Dopaminergic agonists which act directly on the presynaptic neurone to release DA into the synaptic cleft would be expected to have only a modest and temporary effect on the illness. Such has proved to be the case with amphetamine (Parkes *et al.*, 1975), which produces only a slight improvement (of the order of 10–20%) in disability.

Nomifensine, which contains a β -phenylethylamine structure, resembles amphetamine in stimulating locomotor activity (Gerhards *et al.*, 1974) and causes stereotypies in rodents (Costall *et al.*, 1975), both pharmacological actions being considered indices of cerebral DA receptor activation. Nomifensine, like amphetamine, also inhibits DA uptake into rat striatal synaptosomes *in vitro* (Hunt *et al.*, 1974); inhibits noradrenaline (NA) uptake into rat hypothalamic synaptosomes (Schacht & Heptner, 1974); and increases rat striatal DA turnover and stimulates cyclic AMP formation in the rat striatum *in vivo* (Gerhards *et al.*, 1974). Nomifensine differs, however, from amphetamine in not releasing NA (or DA) from rat brain synaptosomes *in vitro* (Schacht & Heptner, 1974; Hunt *et al.*, 1974). From this biochemical data it has been concluded that nomifensine causes DA-mediated increase in locomotor activity and stereotypies by its capacity to inhibit DA re-uptake mechanisms in the presynaptic neurone. The locomotor hyperactivity and stereotypies, however, provoked by nomifensine are not prevented by previous administration of α -methyl-*p*-tyrosine (Gerhards *et al.*, 1974; Costall *et al.*, 1975; Braestrup & Scheel-Krüger, 1976) which, by inhibition of synthesis of DA (and NA), does abolish the similar actions of amphetamine. These, and other, observations led Costall *et al.*, (1975) to suggest that nomifensine possessed direct postsynaptic DA agonist activity. This seems unlikely, however, for nomifensine causes circling towards a unilateral 6-hydroxydopamine-induced lesion of the nigrostriatal dopaminergic pathway, in this respect resembling amphetamine; directly acting DA agonists such as apomorphine and bromocryptine provoke circling in the opposite direction (Pycock *et al.*, 1976). Furthermore, the locomotor hyperactivity and stereotypy induced by nomifensine is inhibited by pretreatment with α -methyl-*p*-tyrosine combined with reserpine (Gerhards *et al.*, 1974; Costall *et al.*, 1975), indicating that these actions are dependent on some presynaptic effect. Indeed, in this respect nomifensine resembles a group of indirectly acting CNS stimulants, of which methylphenidate is representative, whose ability to increase locomotor

Table 1 Mean total disability scores in eight patients with Parkinson's disease treated with nomifensine 150 mg daily in addition to the usual therapy

Time	Change in score (± 1 s.e.m.) as % pretreatment score
3 yr before nomifensine	72 $\pm$ 7
1 yr before nomifensine	92 $\pm$ 10
On commencing nomifensine	0
2 weeks of nomifensine	86 $\pm$ 10
4 weeks of nomifensine	89 $\pm$ 8
8 weeks of nomifensine	92 $\pm$ 9

The deterioration in score over the 3 yr before nomifensine reflects the selection of levodopa failures for this study.

activity, and cause stereotypy, is not affected by α -methyl-*p*-tyrosine, but is abolished by α -methyl-*p*-tyrosine combined with reserpine (Scheel-Krüger, 1971; Sayers & Handley, 1973). The actions of such drugs seem to depend on intact granular stores of amine in presynaptic neurones, whereas those of amphetamine, which are abolished by α -methyl-*p*-tyrosine, but not by reserpine, may be due to release of non-granular pools of amine. The overall conclusion is that nomifensine acts, like methylphenidate, by way of presynaptic mechanisms, perhaps by blocking re-uptake of DA released by nerve impulse traffic.

The conclusion that nomifensine appears to act presynaptically may explain why it exerts only modest therapeutic action in unselected patients with Parkinson's disease (Park, 1977), and why it was of no benefit to those levodopa failures with advanced disease selected for study in this investigation. Nomifensine may have a useful role, however, in the treatment of Parkinson's disease, not as a potent antiparkinsonian drug, but as an effective

antidepressant. Depression is very common in this illness. In a psychiatric evaluation of 50 patients, no less than 24 exhibited an affective disorder before therapy, and 22 developed a depressive disorder during a subsequent 6-month period of treatment (Mindham *et al.*, 1976). Tricyclic antidepressants, which do not affect dopaminergic mechanisms, are used currently to treat depression in Parkinson's disease; MAO inhibitors are contra-indicated in those on levodopa, and electroconvulsive therapy is used only as a last resort. Nomifensine, with its additional capacity to exert some dopaminergic activity, albeit by way of presynaptic mechanisms, may prove to be an antidepressant of choice in Parkinson's disease. It also remains to be established whether nomifensine exerts antiparkinsonian effects on mildly affected patients, and whether higher doses may exert a more obvious therapeutic action.

We thank Hoechst (UK) Limited for supplies of nomifensine.

References

- BRAESTRUP, C. & SCHEEL-KRÜGER, J. (1976). Methylphenidate-like effects of the new antidepressant drug, nomifensine (HOE 984). *Eur. J. Pharmac.*, **38**, 305-312.
- COSTALL, B., KELLY, D.M. & NAYLOR, R.J. (1975). Nomifensine: A potent dopaminergic agonist of antiparkinsonian potential. *Psychopharmacologia Berl.*, **41**, (2), 153-164.
- GERHARDS, H.J., CARENZI, A. & COSTA, E. (1974). Effect of nomifensine on motor activity, dopamine turnover rate and cyclic 3',5'-adenosine monophosphate concentrations of rat striatum. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmac.*, **286**, (1), 49-63.
- HOFFMANN, I. (1973). 8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, a new antidepressant. *Arzneimittel.-Forsch.*, **23**, 45-50.
- HUNT, P., KANNENGISSER, M.H. & RAYNAUD, J.-P. (1974). Nomifensine: a new potent inhibitor of dopamine uptake into synaptosomes from rat brain corpus striatum. *J. Pharm. Pharmac.*, **26**, 370-371.
- MINDHAM, R.H.S., MARSDEN, C.D. & PARKES, J.D. (1976). Psychiatric symptoms during L-dopa therapy for Parkinson's disease and their relationship to physical disability. *Psychol. med.*, **6**, 23-33.
- PARK, D.M., FINDLEY L.J. & TEYCHENNE, P.F. (1977). Nomifensine in parkinsonism. *Br. J. clin. Pharmac.*, **4**, 185S-186S.
- PARKES, J.D., TARSY, D., MARSDEN, C.D., BOVILL, K.T., PHIPPS, J.A., ROSE, P. & ASSELMAN, P. (1975). Amphetamines in the treatment of Parkinson's disease. *J. Neur. Neurosurg. Psychiat.*, **38**, 232-237.
- PYCOCK, C., MILSON, J.A., TARSY, D. & MARSDEN, C. D. (1976). The effects of blocking catecholamine uptake on amphetamine-induced circling behaviour in mice with unilateral destruction of striatal dopaminergic nerve terminals. *J. Pharm. Pharmac.*, **28**, 530-532.
- SAYERS, A.C. & HANDLEY, S.L. (1973). A study of the role of catecholamines in the response to various central stimulants. *Eur. J. Pharmac.*, **23**, 47-55.
- SCHACHT, U. & HEPTNER, W. (1974). Effect of nomifensine (HOE 984), a new antidepressant, on uptake of noradrenaline and serotonin and on release of noradrenaline in rat brain synaptosomes. *Biochem. Pharmac.*, **23**, 3413-3422.
- SCHEEL-KRÜGER, J. (1971). Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. *Eur. J. Pharmac.*, **14**, 47-59.
- TEYCHENNE, P.F., PARK, D.M., FINDLEY, L.J., ROSE, F.C. & CALNE, D.B. (1976). Nomifensine in parkinsonism. *J. Neur., Neurosurg., Psychiat.*, **39**, 1219-1221.