

The efficacy of (+)-4-propyl-9-hydroxynaphthoxazine as adjunctive therapy in Parkinson's disease

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SUMMARY (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) is a novel selective D2 agonist. The efficacy and safety of PHNO was studied in 10 Parkinsonian patients (Hoehn and Yahr Stage II or III) who continued to receive levodopa/carbidopa. At the lowest dose administered (0.25 mg tid), nine of the 10 patients improved with respect to rigidity, bradykinesia and tremor. At this dose there was one dropout because of severe orthostasis. Although there was a trend towards improvement in motor scores with the higher doses (0.5-1.0 mg tid), this was not statistically significant. At higher doses there were a total of four dropouts because of adverse effects such as nausea, vomiting and orthostatic hypotension. It appears that PHNO may prove to be efficacious in the treatment of Parkinson's disease.

(+)-4-propyl-9-hydroxynaphthoxazine (PHNO) is a new dopamine agonist that is not structurally related to the morphine or ergot derivatives which have been used to treat Parkinson's disease. PHNO acts as a selective D-2 agonist in a variety of in vitro and in vivo systems.¹ Preliminary clinical studies of PHNO in Parkinson's disease patients have suggested that this drug may be efficacious in the treatment of Parkinson's disease.²⁻⁴ This study was an open label, multiple rising dose, add-on investigation of PHNO in patients with stage II or III Parkinson's disease who were also receiving levodopa/carbidopa. The objective of the study was to evaluate efficacy and safety of PHNO in the treatment of Parkinson's disease.

Methods

Ten Parkinsonian patients classified as Stage II or III on the Hoehn and Yahr scale were enrolled in the study. All patients had histories of improvement in symptoms with initiation of levodopa/carbidopa therapy. The mean age of the patients was 60 years. The mean duration of disease was 7 years. The mean duration of levodopa therapy was 5.4 years with a mean number of 4.2 doses per day. Three of ten patients exhibited motor fluctuations consisting of the "wearing-off" phenomenon (3/10), peak dose dyskinesia (3/10) and one

sudden "on-off" phenomenon (1/10). All patients signed informed consent before participation in the study.

PHNO was administered during four 3-day treatment periods, each separated by a washout period of at least 4 days. Levodopa/carbidopa was administered at the lowest dosage which provided acceptable clinical response (mean SEM = 527, 62.0 mg). No anticholinergic medications, direct-acting dopamine agonists or amantadine were permitted to be taken from at least one week prior to the start of the initial baseline period. Following a baseline week, during which physical and laboratory examinations were conducted, patients remained in the outpatient clinic for the first day of the initial 3-day PHNO treatment period. The lowest dosage of PHNO (0.25 mg tid) was administered during this first period. Patients were allowed to return home for the second and third day and returned to the clinic on the afternoon of the third day for repeat safety and efficacy evaluations (two hours after the mid-day dose of PHNO).

Following a minimum 4-day washout period, the patients were readmitted to the outpatient clinic for the first day of treatment with the second dosage of PHNO (0.5 mg tid). The second and third days were again outpatient treatments, with a clinic visit on day 3. This procedure was continued in a rising-dose fashion until maximum dosage was administered or dose-limiting side effects were observed. The four doses of PHNO administered on a tid schedule were 0.25 mg, 0.5 mg, 0.75 mg and 1.0 mg.

Clinical assessment of neurological signs and symptoms were graded every 2 hours during baseline and on the third day (2 hrs after the mid-day dose) of treatment with PHNO at each dosage. The Parkinson's disease rating scale included four items from the motor examination of the Unified Rating Scale for Parkinson's disease: rigidity (0-4 for neck and each extremity), tremor (0-4), bradykinesia (0-4), and postural stability (0-4). Laboratory tests (serum chemistry,

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haematology, urinalysis, and ECG) were performed at baseline and on day 3 at each dose of PHNO. Adverse experiences were noted, and if severe enough, the patient was discontinued from the study. Vital signs were recorded at hourly intervals during day 1 at each dose of PHNO. Vital signs were also recorded at 1400 h during re-evaluation on day 3 at each dose of PHNO.

Statistical analysis employed a *t* test comparing two samples of paired observations (scores at baseline 1400 h and after 3 days of PHNO at 1400 h).

Results

At the lowest dose of PHNO administered (0.25 mg tid) the mean scores for rigidity, tremor and bradykinesia (but not for postural stability) improved significantly ($p < 0.05$). (See fig 1). At this dose, one patient dropped out because of nausea, orthostatic hypotension and syncope.

PHNO administered at a dose of 0.5 mg tid resulted in improvement of motor scores in five of seven patients, but the mean improvement was not statistically significant (fig 2). One patient dropped out because of an unrelated illness, and a second patient dropped out because of nausea, vomiting and orthostasis. Doses of 0.75 mg tid resulted in improvement in total motor score in five of six patients though this was not statistically significant (fig 2). One patient dropped out at this dosage level because of nausea, vomiting and excessive drowsiness. At the highest dosage tested (1.0 mg tid), four of the five remaining patients showed improvement in motor scores, but comparison with the baseline scores failed to demonstrate a statistically significant effect (fig 2). One patient who suffered "end-of-dose" dystonia of the foot reported improvement in this symptom with all doses of PHNO tested. As the dose escalated, adverse effects were more evident. The most common complaints were drowsi-

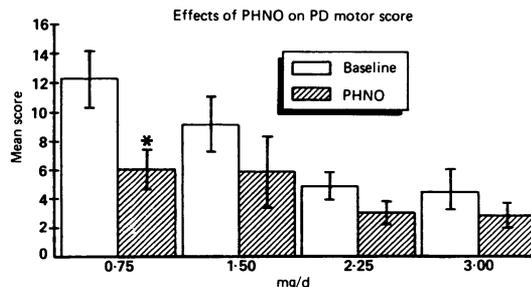


Fig 2 The Parkinson's disease motor score is the sum of the scores for rigidity, tremor, bradykinesia and postural stability. The mean Parkinson's disease motor score was determined from the Parkinson's disease motor scores of the individual subjects. Asterisk denotes a statistically significant difference ($p < 0.05$). (9 patients were tested with 0.75 mg/day, 7 with 1.5 mg/day, 6 with 2.25 mg/day, 5 with 3.0 mg/day).

ness (four patients), nausea/vomiting (three patients), a mild increase in dyskinesias (three patients), syncope (two patients) and an episode of urinary retention (one patient). The episode of urinary retention occurred after the third day of 0.75 mg tid dosage of PHNO, and was reversed after stopping the medication without further intervention.

Discussion

Previous clinical investigations of PHNO in Parkinson's disease have included a double-blind, dose-ranging study on eight patients in which it was shown to be efficacious.² A second study evaluated five patients with the "on-off" phenomenon in an open rising-dose study, using a levodopa control.³ All patients in that study had significant improvement in Parkinsonian symptoms and signs for a duration ranging from 1 to 6 hours. The effects of single oral doses of PHNO was compared with the anti-parkinsonian activity of carbidopa/levodopa. All five patients showed improvement in Parkinsonian symptoms and signs with a single dose of 2 mg of PHNO. Some benefit was noted in one patient with a 0.5 mg dose and in four patients with a 1 mg dose. It was determined that one tablet of carbidopa/levodopa (25/250) was equivalent to a single dose of 4 mg of PHNO.³ The adverse effects were comparable to those produced by other dopamine agonists and included drowsiness, slight nausea without vomiting, postural hypotension and transient confusional states.³ The nausea and vomiting were attenuated with domperidone (20 mg PO) administered one hour before PHNO.³

In a series of studies in 10 patients, PHNO monotherapy resulted in improvement in nine of 10 patients receiving the drug over 30 days.⁴ Objective

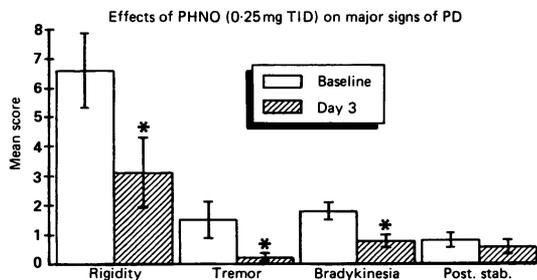


Fig 1 The mean score for the major signs of Parkinson's disease was determined by computing the mean of the individual scores for rigidity (0-4 in neck and in each limb), tremor (0-4), bradykinesia (0-4) and postural instability (0-4) at baseline and on day 3 (1400 h) of PHNO treatment. Asterisk denotes a statistically significant difference ($p < 0.05$) between baseline score and test drug score.

improvement in signs of Parkinson's disease lasted 3 to 4 hours after each dose of PHNO monotherapy, but subjective improvement in symptoms occasionally lasted up to 3 days after the last dose.⁴ With a time-release formulation of PHNO, the objective therapeutic response was prolonged for up to 12 h in some patients.⁴ No attempt was made to systematically compare the efficacy of PHNO to carbidopa/levodopa, but the investigators were impressed that the magnitude of response to PHNO was similar to that expected from carbidopa/levodopa.⁴ The adverse effects experienced in that study were comparable to those in other studies of PHNO.

The present report demonstrates that low dose PHNO, when added on to levodopa/carbidopa, ameliorates rigidity, tremor and bradykinesia. The effective doses in this study are lower than in the previous studies because PHNO is added on to the carbidopa/levodopa regimen rather than compared as a single agent to carbidopa/levodopa. Only one patient experienced nausea, vomiting and orthostatic hypotension at this low dose. However, higher doses of PHNO were less well tolerated and tended to produce drowsiness, nausea/vomiting, and orthostasis. Domperidone was not used to prevent nausea and vomiting. When higher doses of PHNO (1.5 mg/day or greater) were administered, there was a trend towards improvement in the total Parkinson's disease motor score, but the improvement was not statistically significant compared to baseline. There are several possible explanations for the failure to improve motor scores at the higher doses. One possibility is related to diminished effectiveness of the drug at the level of receptor interactions, perhaps attributable to a loss of D-2 receptor selectivity at higher concentrations. This is unlikely since the maximum daily dose of PHNO in this study (3 mg) was less than the single dose of 4 mg reported to be effective in ameliorating motor signs of Parkinsonism.³ Another possibility is that the patients who remained in the study for the higher doses were those with better baseline motor scores (carbidopa/levodopa alone—see fig 2) and those patients were less likely to show significant improvement in already excellent motor scores. In other words the failure to detect improvement with PHNO at higher doses might have been a consequence of the elimination from the study, due to adverse effects, of the more severely affected patients. The gradual improvement seen in the baseline scores over the four weeks of the studies could also be interpreted to be a consequence of accumulation of PHNO in the striatum. This is unlikely because a four day washout period preceded the escalation to the next (higher) dose of PHNO. Moreover, tolerance did not develop to the adverse effects of PHNO with this schedule arguing against the possibility that PHNO is retained within the striatum for prolonged

periods. Finally, the lack of statistical significance in the comparison of motor scores following higher doses of PHNO might reflect an inadequate number of patients, since only five of the 10 original patients were able to complete the study. Further clinical studies are needed to determine whether slow increments in dosage will reduce adverse effects, produce greater improvements in Parkinson's disease motor scores and whether or not efficacy can be maintained over long periods of time.

Three of the ten patients who experienced mild dyskinesias with levodopa/carbidopa reported a slight increase in dyskinesias while taking the combination of PHNO and levodopa/carbidopa. One of these patients noted a decrease in end-of-dose foot dystonia. By contrast, single doses of PHNO were reported to reduce the intensity, but not the quality, of the dyskinesias compared with those produced by levodopa/carbidopa alone in two of five patients with "on-off" phenomenon and dyskinesias.³ It is not possible to compare the results of these two studies since the latter consisted of patients with more severe motor fluctuations and possibly biphasic dyskinesias, while the present study included only three of 10 patients with mild motor fluctuations who received a combination of levodopa/carbidopa and PHNO.

Although a recent animal study has suggested that intracerebro-ventricular infusion of PHNO might play a role in the treatment of motor fluctuations in Parkinson's disease,⁵ the current interest in parenteral administration of PHNO in Parkinson's disease patients is in transdermal and intravenous routes.^{2,6} It is probable that because of PHNO's potency, solubility, and duration of effect, parenteral routes of administration of this agent may prove helpful in Parkinson's disease patients experiencing motor fluctuations. Since the exact profile of Parkinson's disease signs which are ameliorated by PHNO is still not clear, further investigation will be necessary to clarify this point and to determine if there is a subgroup of patients who will respond to this non-ergot derivative who have failed on ergot derivative treatment.

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West's syndrome

In a lengthy letter to the *Lancet*, dated 26 January, 1841, Dr W J West of Tunbridge described "a very rare and singular species of convulsion . . . the only case I have witnessed is in my own child." The child, nearly a year old, was healthy till 4 months of age, then developed bobbings of the head forwards, which

"became so frequent and powerful, as to cause a complete heaving of the head forwards towards his knees, and then immediately relaxing into the upright position, something similar to the attacks of emprosthotonus: these bowings and relaxings would be repeated alternately at intervals of a few seconds and repeated from ten to twenty or more times, for two or three minutes; he sometimes has two, three or more attacks in the day . . . just before they come on he is all alive and in motion, making a strange noise, and then all of a sudden down goes his head and upwards his knees; he then appears frightened and screams out. . . . A fine grown child, but he possesses neither the intellectual vivacity or the power of moving his limbs, of a child of his age . . . looks placid and pitiful, yet his hearing and vision are good; he has no power of holding himself upright or using his limbs and his head falls without support."

West describes a wide variety of (noxious) treatments he applied, in vain. He consulted Sir Charles Clarke and Dr Locock; the former had seen four cases and referred to it as salaam convulsion, the latter two cases. The cases he had ascertained had become paralytic and idiotic, dying between the ages of 17 and 19 years; one perfectly recovered. It appeared to West

"to be either due to irritation of the nervous system from teething," though Sir Astley Cooper had opined in another case 'disease of the brain and the child will not recover, or it proceeds merely from teething, and, when the child cuts all its teeth, may probably get well' "

Thus West takes full credit for the tragic but lucid exposition of hypsarrhythmic infantile spasms, and Sir Charles Clarke for coining the apt description of "salaam convulsion", which has stood the test of time.

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