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Treatment of Parkinson's disease with NADH

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It has earlier been claimed that clinical improvement of patients with Parkinson's disease is obtained by treatment with NADH. This has to be verified by double-blind, clinical studies and measurement of biochemical effects of the treatment. In a double blind study five patients with clinically moderate Parkinson's disease were treated with NADH, 25 mg, given intravenously once a day for four days. Then they were given 25 mg NADH intramuscularly after 2 and 4 weeks. Disability scores were determined before each treatment and two weeks after the final injection. A control group (n = 4) with the same degree of Parkinson's disease obtained sodium chloride with the same schedule. According to the Unified Parkinson's Disease Rating Scale a tendency to clinical improvement was seen after the iv infusions in both treatment and placebo groups. However, the changes were not statistically significant, and no changes occurred during the following weeks. No changes were found neither in the study nor the control group regarding cerebrospinal fluid concentrations of dynorfin, metenkefalin, somatostatin, hydroxy-methoxy-phenylglycol, homovanillic acid and 5-hydroxyindole acetic acid. The results indicate that no great changes are obtained after short-term treatment of parkinsonian patients with NADH, neither clinically nor biochemically.

Key words: Parkinson's; NADH freatment.

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The drug of choice for treatment of patients with Parkinson's disease (PD) is L-dopa in combination with dopa decarboxylase inhibitors. However, with time the therapeutic window becomes narrower, and the patients lack the beneficial effects of this drug, and disabling side effects appear. Thus there is an imperative need for L-dopa complementary drugs.

In parkinsonian patients there is a deficit of dopamine (DA) in the neurostriatum due to a decreased synthesis and to the loss of dopaminergic neurons in this area (1). The shortage of DA is probably also due to the diminished activity of tyrosine hydroxylase (TH) (2), the rate limiting enzyme in the biosynthesis of DA from tyrosine and L-dopa (3). It has also been shown, in autopsy material, that H_4biopterin, the coenzyme of TH, is reduced up to 50% in Parkinson's disease (4). Treatment of parkinsonian patients with H_4biopterin has been tried to stimulate the endogenous DA synthesis without any clinical improvement (5). This was shown to be due to the impermeability of the blood brain barrier for H_4biopterin (4). Therefore, treatment with NADH was considered to increase the endogenous DA synthesis as NADH is the coenzyme of quinoid H_2pteridin reductase, which is the key enzyme in H_4biopterin biosynthesis (6).

Birkmeyer et al. (7, 8) studied the possibility to increase the endogenous DA production by stimulating TH with an increased availability of NADH. Thus, they gave NADH both intravenously, intramuscularly and orally to patients with PD. However the clinical studies with NADH treatment have hitherto been open, and double-blind studies are lacking. Furthermore only few data are available regarding urine excretion of the DA metabolite homovanillic acid. We have therefore performed a pilot double-blind study to obtain personal experience with this treatment and to get some indications on the effects of this treatment.

Material and methods

In a double-blind pilot trial 10 patients were randomised into a study group and a control group.

Diagnosis and disability scores were established according to the Hoehn and Yahr staging (9) and the Unified Parkinson's Disease Rating Scale (10). Both groups had moderate PD scorings of 2.2 (study group) and of 2.5 (control group). One patient was excluded because of sciatic pain.

The patients were admitted to the Department of Neurology for one week. After initial clinical examination they were allotted to either of two coded treatments. The injection solutions were prepared at the Department of pharmacy and coded. After disclosure of the codes at the end of the study it was revealed that 5 patients obtained active drug and 4 obtained placebo.

For venous infusion 25 mg of NADH (Sigma) were dissolved in 100 ml of 0.9% sterile sodium chloride. The solution was prepared immediately prior to use and given as a continuous infusion for 30 min. The infusion was given daily for four days. Also 25 mg of NADH were dissolved in 5 ml of 0.9% sterile sodium chloride for intramuscular injection. Two injections were given at two and four weeks after the last intravenous infusion. The placebo group obtained 0.9% sterile sodium chloride with the same time schedule. The disability scores were determined in "on"-phase with the same time schedule before each treatment and two weeks after the last intramuscular NADH injection. The previous antiparkinsonian treatment was maintained.

Laboratory routine analyses were made and cerebrospinal fluid (CSF) was taken for analysis of the monoamines homovanillic acid (HVA), 5-hydroxyindole acetic acid (5-HIAA), and hydroxy-methoxyphenylglycol (HMPG) and also the neuropeptides dynorphin, metenkephalin, and somatostatin. These analyses were made blindly before and after the study.

Results and discussion

Fig. 1 shows the individual clinical results during NADH and placebo administration. It can be seen that 4/5 patients given NADH improved their clinical score during the first phase, but thereafter the results returned to the initial levels. However, it should also be noted that similar changes occured in the placebo group. In spite of these individual changes, statistically significant changes could not be demonstrated, neither between nor within the groups.

The concentrations of the monoamines and the neuropeptides in the CSF remained unchanged during treatment with intravenous and intramuscular NADH (Table 1).

The amount of NADH infused was relatively small but the volume was chosen as the Birkmayer group reported good results and no adverse effects

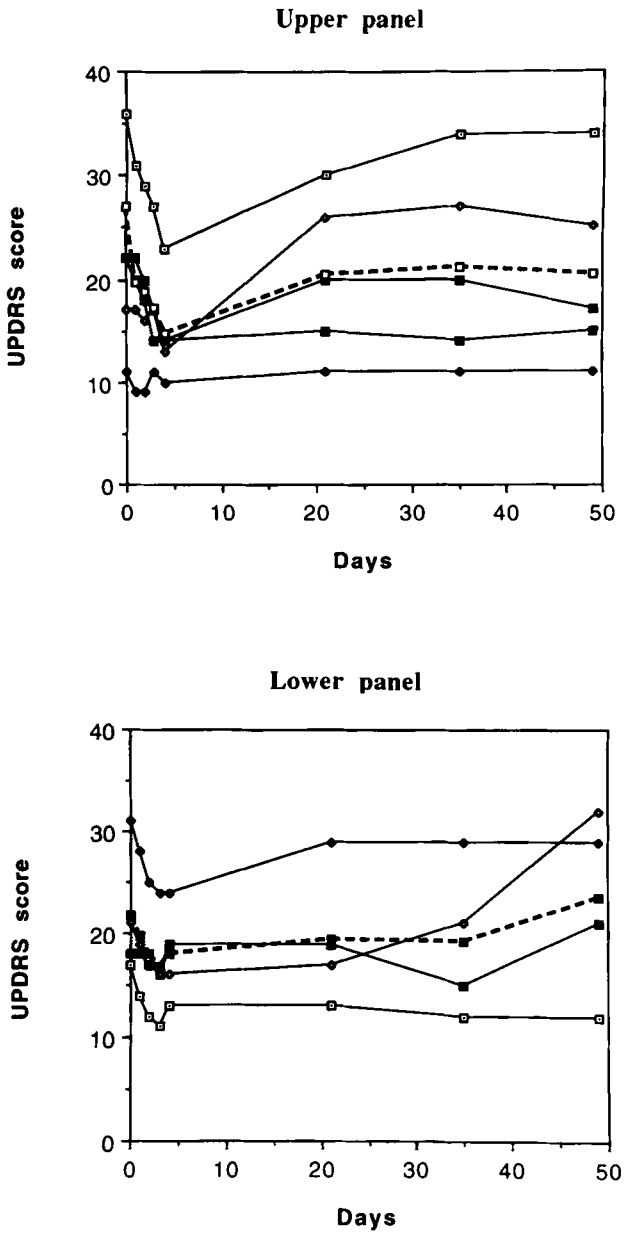

Fig. 1. UPDRS scores in parkinsonian patients given NADH (upper panel) and placebo (lower panel). Intravenous infusion (25 mg NADH or placebo) was given after the first recording and intramuscular injections were given Day 20 and Day 35. Each line represents an individual patient and broken line represents the mean of the group.

(1). It remains uncertain whether this compound reached the CNS. Thus, there are still several factors who remain to be studied.

In conclusion our pilot study indicates that large-scale double-blind studies are needed to evaluate the possible beneficial effects of NADH in parkinsonian patients. Our results also shows a clear placebo effect of the intravenous therapy showing the importance of blind studies when evaluating new therapies in Parkinson's disease. It is also uncertain whether

Table 1. Monoamine and neuropeptide concentrations in CFS before and after treatment with NADH (n=5) and placebo (n=4) in Parkinsonian patients. No statistical differences between the two groups were found.

	Treatment with NADH		Control group	
	Before	After	Before	After
Dynorphin pmol/L	22.4±4.0	26.0±5.3	25.8±3.7	24.2±1.71
Metenkephalin pmol/L	123±23	129±23	136±28	142±29
Somatostatin pmol/L	20.4±8.1	24.6±6.8	22.8±5.4	21.0±2.9
Homovanillic acid nmol/L	187±65	201±94	401±188	334±111
5-Hydroxyindole acetate nmol/L	84.6±17.9	89.4±12.9	107±19	114±21
Hydroxy-methoxy-phenylglycol nmol/L	33.2±6.22	34.6±6.8	33.8±9.1	36.0±5.1

NADH reaches the CNS. It has been suggested that NADH might increase the peripheral L-dopa synthesis and, thus, indirectly also increase the DA concentrations in CNS, but since the HVA concentrations in the CSF remain unchanged we have not been able to confirm this theory (8). Thus we have not been able to find any clinical or laboratory indications of an increased DA synthesis after NADH treatment in Parkinson's disease.

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