J Neural Transm [P-D Sect] (1989) 1: 297–302

Journal of Neural Transmission

The coenzyme nicotinamide adenine dinucleotide (NADH) improves the disability of Parkinsonian patients

Short Communication

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Accepted July 29, 1989

Summary. The coenzyme nicotinamide adenine dinucleotide (NADH) has been used in an open label trial as novel medication in 34 patients with Parkinson's disease, using an intravenous administration technique. In all patients a beneficial clinical effect was observed. 21 patients (61.7%) showed a very good (better than 30%) improvement of disability, 13 patients (38.3%) a moderate (up to 30%) improvement. Concomitant with the improvement of the disability the urine level of homovanillic acid (HVA) increased significantly in all patients (in some patients by more than a 100%). The daily "on phases" of the patients could be increased from 2 up to 9 hours in the individual patients by NADH administration.

Keywords: Nicotinamide adenine dinucleotide, tyrosine hydroxylase, DOPA, Parkinson.

Introduction

Parkinson's disease (PD) is characterized by a motoric impairment of the patients the most distinctive clinical symptoms of which consist of tremor, bradykinesia, rigidity and loss of postural reflexes. The biochemical cause of this motoric disability is a shortage of the catecholamine dopamine in the basal ganglia of the brain due to a loss of dopaminergic neurons in the substantia nigra. The immediate precursor of dopamine, L-DOPA, was the first rational therapy of Parkinson's disease, which has been introduced by Birkmayer and Hornykiewicz (1961). Meanwhile it has been found that the L-DOPA producing enzyme tyrosine hydroxylase (TH) plays a central role in Parkinson's disease.

because its enzymatic activity is considerably reduced in the brain of these patients. The very first indirect evidence for this enzyme-defect was gained after therapeutic application of α-methyl-p-tyrosine, an inhibitor of TH which evoked a deterioration of the patients disability (Birkmayer, 1969).

A few years later biochemical analysis of brain tissue revealed that the activity of TH is diminished in substantia nigra of parkinsonian patients (Lloyd et al., 1975). These findings were confirmed and extended by Riederer and coworkers in showing that TH is reduced not only in the brain but also in the adrenal medulla of parkinsonian patients (Riederer et al., 1978).

Nevertheless L-DOPA remained the first choice of therapy either alone or in combination with inhibitors of DOPA-decarboxylase and monoamine oxidase. Despite of these additives clinicians are faced with the problems that L-DOPA does not work in a number of Parkinsonian patients in particular after longterm treatment. Other therapeutic strategies have to be considered. One possibility might be the stimulation of the endogenous L-DOPA biosynthesis by activating the defect TH. As shown by Nagatsu (Nagatsu et al., 1981) this enzyme is an iron containing enzyme with tetrahydrobiopterin (BH4) as coenzyme. BH4 has been used in clinical trials. The results were not very promising, only partial relief of some symptoms in a few patients could be observed. All the patients treated from one of the authors (WB) did not respond at all (Birkmayer W. unpublished observations).

On the other hand it has been shown that the iron compound Oxyferriscorbone (R) is able to improve the symptoms of Parkinsonian patients (Birkmayer and Birkmayer, 1986; 1987). Since exogenous applied L-DOPA also improves the disability of Parkinsonian patients, we believe that Oxyferriscorbone stimulates the endogenous L-DOPA biosynthesis. The most likely target of Oxyferriscorbone seems to be TH, the key enzyme for L-DOPA synthesis, which is an iron containing enzyme.

Oxygenases such as TH are often coupled with other redox systems. For TH it is the redox system NAD^+ $NADH + H^+$ which restores the consumed oxidized coenzyme BH2 into the active BH4 form (Nichol et al., 1985). As shown by Nagatsu et al. (1985) this coenzyme is considerably reduced in the brain of Parkinsonian patients. At least two reasons may be responsible for this deficit. Either BH4 is not synthesized in sufficient amounts or is not activated enough into its reduced state. If the latter is the case, activation of the consumed oxidized BH2 should yield a higher TH activity and due to this an increased endogenous L-DOPA synthesis. Under this aspect we tried NADH as medication for Parkinsonian patients.

Materials and methods

Diagnosis and disability scores of the Parkinsonian patients were established according the scale of Birkmayer and Neumayer (1972).

β-Nicotinamide adenine dinucleotide, reduced from disodium salt abbreviated NADH (synonyms: β-NADH, reduced DPN, β-DPNH) was purchased from Sigma Diagnostics (St. Louis, MO, U.S.A.).

25 mg of sterile, lyophilized NADH were dissolved in 100 ml of 0.9 percent sterile sodium chloride, pH 7.4, filtered through filter (size 0.2 µm, Schleicher & Schüll, FRG) and intravenously infused in 30 minutes. NADH solutions were prepared always fresh immediately prior to use. Disability scores were determined before, four hours, 1 day and 4 days after the NADH application. Patients received NADH infusion either every day or every second day depending on their disability score and their improvement. Treatment was continued for 10 to 14 days. Then the NADH treatment was interrupted, to see whether the improvement was based on NADH. If this is the case, the patients should deteriorate after withdrawal of NADH. As soon as the patient's disability became significantly greater than that observed during NADH treatment, the intravenous NADH medication was restarted. Only patients who obtained Madopar(R) or Sinemet(R) as only medication before NADH application were included in this study. In addition we collected the first morning urine (22:00–8:00 collection time) for HVA measurements. The urine was brought to pH 2.0 by adding HCl immediately after production and kept frozen at − 20 °C until HVA analysis by HPLC. At day 4 after the first application of therapy the 22:00–8:00 urine was again collected and processed in the same way as the urine before therapy.

Results

All patients treated with NADH exhibited a drop of their disability score after 4 days of therapy. Details of the individual patients, their age, duration of disease, therapy and disability are summarized on Table 1. The age of the patients was in the range from 56 to 85, the duration of the disease in the range from 2 to 20 years. The overall improvement of the disability of all 34 patients was 37.0 + − 18.0. 21 patients (61.7%) exhibited a very good improvement of disability (better than 30%), 13 patients (38.3%) a moderate response (up to 30%). In particular, the walking and pushing ability improved considerably and so did posture, speech and mimic.

The action of NADH lasted between 1 and 2 days depending on the severity of the symptoms. After withdrawal of NADH from the usual medication a worsening of the patients' disability was observed. This indicates the improvement of the symptoms to be based on the NADH applied. In addition to the improvement another effect of NADH was observed. Four patients (no. 28, 29, 30, 34) exhibited an improvement of their symptoms with NADH alone. In these cases the standard Parkinson therapy Madopar(R) need not be added. In all the other patients the dosage of L-DOPA could be reduced up to 30% of the original dose. Fifteen patients could be examined with regard to the duration of the daily "on-" and "off-phases" because they were hospitalized patients (the other 19 patients were observed on an out-patient basis). The results are given in Fig. 1. The daily on-phases could be increased in these 15 patients in the range from 2 to 9 hours. In twenty patients the urine level of the dopamine metabolite homovanillic acid (HVA) was determined before and 4 days after beginning of NADH treatment. In all the patients examined a remarkable increase of the concentration of HVA in the urine was found (Fig. 2). The patients with the initials K. O. (no. 30 in Table 1) and G. R. (no. 34 in Table 1) are two of those who have been treated with NADH alone. These patients do also exhibit an increase in the urine level of HVA in the range from 1.66

Table 1. Expose of 34 patients with Parkinson's Disease treated with NADH

Patient	Age	Duration of disease (years)	Previous therapy	New therapy	Percent disability before new therapy	Percent disability after 4 days of NADH
(1)	65	12	Madopar 750 mg/d	Madopar 500 mg/d + NADH 25 mg/d	60	10
(2)	70	19	Madopar 250 mg/d	Madopar 125 mg/d + NADH 25 mg/d	70	40
(3)	56	4	Sinemet 750 mg/d	Sinemet 375 mg/d + NADH 25 mg/d	50	20
(4)	62	8	Madopar 750 mg/d	Madopar 750 mg/d + NADH 25 mg/d	60	45
(5)	72	10	Madopar 1 500 mg/d	Madopar 375 mg/d + NADH 25 mg/d	70	20
(6)	66	12	Sinemet 375 mg/d	Sinemet 187 mg/d + NADH 25 mg/d	70	20
(7)	74	14	Sinemet 375 mg/d	Sinemet 300 mg/d + NADH 25 mg/d	50	30
(8)	66	11	Madopar 1 250 mg/d	Madopar 750 mg/d + NADH 25 mg/d	80	40
(9)	56	6	Sinemet 375 mg/d	Sinemet 375 mg/d + NADH 25 mg/d	70	20
(10)	66	14	Sinemet 2 250 mg/d	Sinemet 750 mg/d + NADH 25 mg/d	75	25
(11)	58	3	Madopar 750 mg/d	Madopar 750 mg/d + NADH 25 mg/d	40	25
(12)	70	8	Sinemet 375 mg/d	Sinemet 125 mg/d + NADH 25 mg/d	30	15
(13)	40	2	Sinemet 375 mg/d	Sinemet 125 mg/d + NADH 25 mg/d	30	20
(14)	70	6	Madopar 750 mg/d	Madopar 750 mg/d + NADH 25 mg/d	50	40
(15)	71	8	Madopar 750 mg/d	Madopar 129 mg/d + NADH 25 mg/d	60	30
(16)	61	15	Madopar 750 mg/d	Madopar 187 mg/d + NADH 25 mg/d	70	30
(17)	70	8	Madopar 750 mg/d	Madopar 375 mg/d + NADH 25 mg/d	75	20
(18)	56	8	Madopar 1 500 mg/d	Madopar 375 mg/d + NADH 25 mg/d	70	20
(19)	62	8	Madopar 2 000 mg/d	Madopar 750 mg/d + NADH 25 mg/d	75	25
(20)	62	8	Madopar 750 mg/d	Madopar 375 mg/d + NADH 25 mg/d	50	20
(21)	62	6	Madopar 2 000 mg/d	Madopar 750 mg/d + NADH 25 mg/d	70	20
(22)	85	15	Madopar 750 mg/d	Madopar 375 mg/d + NADH 25 mg/d	75	40
(23)	72	20	Madopar 750 mg/d	Madopar 375 mg/d + NADH 25 mg/d	70	40
(24)	62	12	Madopar 375 mg/d	Madopar 375 mg/d + NADH 25 mg/d	40	20
(25)	48	4	Madopar 750 mg/d	Madopar 375 mg/d + NADH 25 mg/d	70	20
(26)	72	15	Sinemet 612 mg/d	Sinemet 612 mg/d + NADH 25 mg/d	75	20
(27)	71	10	Madopar 2 500 mg/d	Madopar 750 mg/d + NADH 25 mg/d	70	40
(28)	70	10	No medication	only NADH 25 mg/d	70	20
(29)	63	10	No medication	only NADH 25 mg/d	60	20
(30)	70	19	No medication	only NADH 25 mg/d	70	20
(31)	84	12	Madopar 750 mg/d	Madopar 250 mg/d + NADH 25 mg/d	80	50
(32)	65	10	Madopar 1 750 mg/d	Madopar 750 mg/d + NADH 25 mg/d	60	30
(33)	75	15	Madopar 500 mg/d	Madopar 250 mg/d + NADH 25 mg/d	50	15
(34)	66	16	No medication	only NADH 25 mg/d	60	20
				mean	62.5	26.2*
				SD	13.7	9.9

* $p < 0.0001$ (paired sample test; Wilcoxon matched-pairs signed rank test)

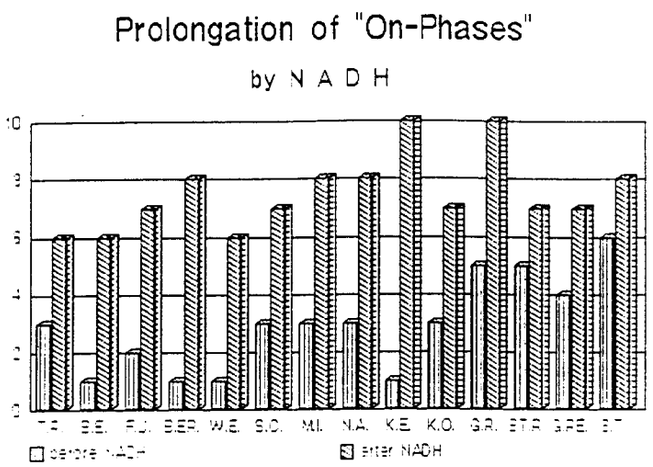

Fig. 1

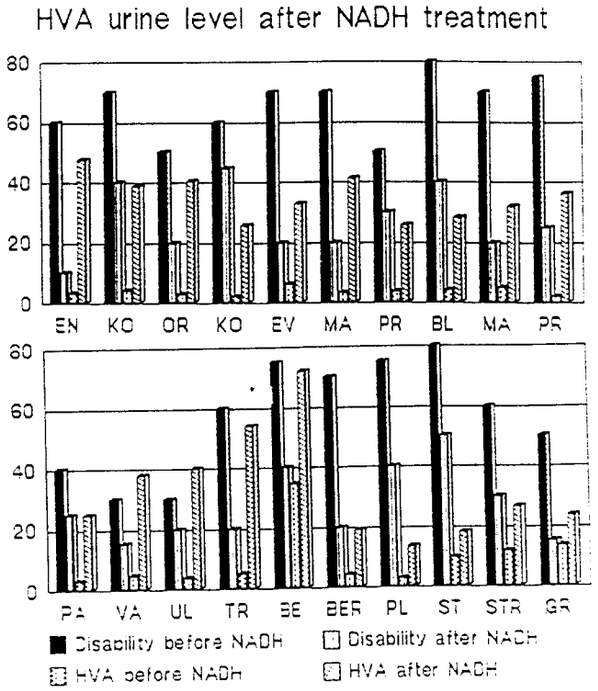

Fig. 2

and 10 fold resp. Treatment with NADH appears to have the same effect as L-DOPA namely an increase of the urinary HVA concentrations. This would mean that NADH may substitute for L-DOPA. However, NADH is not a precursor of L-DOPA. It may be involved, therefore only indirectly, in the endogenous L-DOPA biosynthesis. Support for this assumption is gained by studies of Herken (personal communication) in showing that cells of dopa-

minergic neurons, cultured in vitro, produce more L-DOPA after adding NADH to the culture medium.

The clinical effect of NADH which closely resembles that of L-DOPA is also in line with this view. Indirect indications for the stimulation of endogenous L-DOPA biosynthesis may be derived from the increase in the urine level of HVA after NADH treatment which parallels the short-lasting clinical improvement. We are, however, aware of the fact that NADH is a coenzyme which can act on a great number of enzymes. Therefore its beneficial effects in Parkinson's disease might include other enzymic reactions as well and its action may be a peripheral rather than a central one. This assumption is not far fetched, as NADH has an extremely short half-life time and it is assumed that it does not cross the blood-brain barrier. Therefore, biochemical studies are in progress to elucidate the mechanism of the action of NADH in order to gain a more rational basis for its anti-parkinson efficacy. Furthermore, a double blind clinical trial is essential to confirm our findings.

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Received September 22, 1988

Printed in Austria