J. Neural Transmission 64, 113–127 (1985)

Journal of
Neural Transmission

Increased Life Expectancy Resulting from Addition of L-Deprenyl to Madopar® Treatment in Parkinson's Disease: A Longterm Study

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With 2 Figures

Received July 9, 1985

Summary

In an open, uncontrolled study the longterm (9 years) effect of treatment with Madopar® alone (n = 377) or in combination with l-deprenyl (selegiline, selective monoamine oxidase type B inhibitor) (n = 564) have been compared in Parkinsonian patients. In patients who lost their response to conventional Madopar therapy the addition of l-deprenyl resulted in a significant recouping of levodopa effect. The survival analysis revealed a significant increase of life expectancy in Madopar–l-deprenyl group regardless of the fact whether or not the significant demographic differences between the two groups were taken into account. Although the mechanism underlying this action of l-deprenyl is not known, the results are interpreted as indicating l-deprenyl's ability to prevent or retard the degeneration of striatal dopaminergic neurons. l-Deprenyl is the first anti-Parkinson drug having such a property. This hypothesis is not far fetched since l-deprenyl selectively prevents the degeneration of striatal dopaminergic neurons induced in animals by the illicit drug l-methyl-4-phenyl-1,2,3,6-tetrahydro-

pyridine (MPTP). Since latter compound is known to cause Parkinsonism in man and primates or Parkinson-like neurochemical and pathological changes in other animals the implications of the present study involving monoamine oxidase activity and l-deprenyl are apparent.

Introduction

The treatment of Parkinson's disease (PD) with levodopa (l-dopa) opened up a new era in the management of this disorder. The clinical and pharmacological action of l-dopa as is known today is a dopamine replacement therapy (*Birkmayer* and *Hornykiewicz,* 1962). The use of a monoamine oxidase (MAO) inhibitor to potentiate the action of dopamine (DA) formed from l-dopa had always been considered logical considering the essential role of MAO for DA deamination before or after release (*Green at al.,* 1977). The rationale implicit in this therapy was that the therapeutic effectiveness of MAO inhibitors in Parkinsonian patients would rely on a localized accumulation of DA at a specific site in the brain. The recognition of multiple forms of MAO (*Johnston,* 1968; *Youdim et al.,* 1969, 1971, 1972) and the discovery of l-deprenyl (*Knoll et al.,* 1965, 1968; *Knoll* and *Magyar,* 1972), a selective inhibitor of MAO-type B—devoid of the potentiation of the sympathomimetic action of tyramine, *i.e.* without the "cheese effect" (*Squires,* 1972; *Knoll,* 1972, 1980; *Elsworth et al.,* 1978)—have led to the application of this drug in combination with l-dopa for the management of PD since 1974. Subsequent to our original studies (*Birkmayer et al.,* 1975) almost all published reports (*Lees et al.,* 1977; *Yahr,* 1978; *Rinne,* 1983) have confirmed the l-dopa potentiating action of l-deprenyl, the clinical response being significant diminuation of patient's disability, a reduction in the incidence of "on-off" phenomenon and recouping the loss of response to l-dopa.

Calne and *Langston* (1983) have recently reviewed the aetiology of PD and implicate environmental toxic substances as being the main cause of PD, superimposed on a background of slow, sustained neuronal loss due to the process of aging. The discovery of an important toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which causes Parkinsonism in human (*Davis et al.,* 1979; *Langston et al.,* 1983; *Langston* and *Ballard,* 1983) and animals (*Burns et al.,* 1983; *Heikkila et al.,* 1984) with a selective loss of dopaminergic cells of the substantia nigra would support the toxin hypothesis. This finding with MPTP are made even more crucial since l-deprenyl and another selective MAO-B inhibitor, AGN 1135 (*Kalir et al.,* 1981) have been

shown to selectively inhibit the dopaminergic neurotoxicity of MPTP in monkeys, dogs and mice (*Heikkila et al.*, 1984; *Langston et al.*, 1984; *Markey et al.*, 1984; *Youdim et al.*, 1985).

The aim of this study was to compare the longterm (9 years) effect of conventional Madopar therapy with that of combined Madopar–l-deprenyl in a large group of Parkinsonian subjects. Since it is well known that the therapeutic effectiveness of l-dopa falls after the first 2–3 years it was important to know whether (a) the response to combined Madopar–l-deprenyl can be maintained over a long period and (b) the progressive degenerative aspect of Parkinson's disease, ultimately resulting in death, can be retarded by the addition of l-deprenyl to the therapy.

Patients and Methods

This open, uncontrolled study–the retrospective analysis of which is reported here–was finished by the end of August 1983, in the sense that data from the patients surviving were censored at that time. The total number of patients studied was 941, of which 377 were treated with Madopar, with no l-deprenyl added, while 564 were treated with Madopar plus l-deprenyl (Jumex®, Chinoin Pharmaceutical and Chemical Works Ltd, Budapest, Hungary; selegiline is available in U.K. as Eldepryl® from Britannia Pharmaceuticals Ltd). Madopar 62.5, 125, 250 mg capsules containing the four to one (w/w) combination of l-dopa and benserazide (a peripheral decarboxylase inhibitor) served for oral l-dopa substitution. The median year of l-dopa initiation was 1976 in the Madopar as well as in the combined Madopar–l-deprenyl treated group (with a mean of 1975.2 ± 0.21 and 1975.5 ± 0.15 respectively). In the group of patients on combined Madopar–l-deprenyl treatment the two drugs were started at the same time in 81 patients, while in remaining 483 cases l-deprenyl was added later at a varying interval after the start of the Madopar treatment. The daily dose of l-deprenyl was 5 to 10 mg and it was maintained until the patient died, dropped out, or the study was ended. All patients were seen at regular visits 1 to 4 times a year, when the Madopar dosage was adjusted according to the need of the patients as assessed by the level of disability score (*Birkmayer* and *Neumayer*, 1972). In the group where l-deprenyl was added later to the previous Madopar regimen it was started at the time, when the patients disability declined despite of an increase of the Madopar dose. l-Deprenyl treatment was started between the years of 1974 and 1983. The average length of l-deprenyl treatment was 3.92 ± 0.09 years (from 2 weeks to 9.3 years). The duration of l-deprenyl treatment was 2 years or less in 88, greater than 2 to 4 years in 202, greater then 4 to 6 years in 131, greater than 6 to 8 years in 105 and more than 8 in 38 patients. The mean age at the start of l-dopa substitution was 69.5 ± 0.42 years (range 39 to 89, median = 70 years) in the Madopar group, and 66.8 ± 0.36 years (range = 25 to 87; median = 67 years) in the Madopar–

l-deprenyl treated group ($p < 0.001$ between both groups). The time from the onset of Parkinsonism to the start of l-dopa substitution was significantly longer (3.9 ± 0.14 years, range = 0 to 28) in the group with combined Madopar–l-deprenyl treatment than that in the Madopar group (2.7 ± 0.14 years, range = 0 to 15). There were also differences between the two groups with respect to the male/female ratio ($p < 0.05$) and baseline disability score ($p < 0.05$) respectively. These were 181 male/196 female and 47.25 ± 0.97 (disability score) in the Madopar treated group while there were 309 males to 255 females with a disability score of 49.99 ± 0.69 in the group with combined Madopar–l-deprenyl treatment. The daily l-dopa dose averaged for the whole period of l-dopa substitution was lower 524.0 ± 15.0 mg in the Madopar group, than that in the group with combined treatment 627.6 ± 11.1 mg ($p < 0.001$ between both groups). Survival analysis was performed with a method (*Dixon* and *Brown*, 1981), which allows the use of data from cases for which the response (death) has not yet occured. Such data are usually called incomplete, or censored. The survival (time to death) distribution of the patients who have been observed over varying periods of time in the two treatment groups was estimated and tested for equality. Censoring was similar: 0.69 in the Madopar and 0.79 in the Madopar–l-deprenyl group. The Breslow and Mantel-Cox test statistics used are valid in large samples whether the censoring patterns are equal, or not.

Results

The Breslow and Mantel-Cox statistic (with a value of 92.7 and 49.5, respectively) revealed a significant difference ($p < 0.001$, both), between the two treatments, in favour of the Madopar–l-deprenyl combination. The estimated mean $\pm$ S.E. survival times calculated from the survival distribution curves were 129.2 ± 5.7 months in the Madopar and 144.5 ± 4.1 months for the Madopar–l-deprenyl treated patients. These estimates do not indicate survival from the time of diagnosis, but the interval between the initiation of l-dopa substitution and the response, *i.e.* death. In other words the l-deprenyl treated patients lived in average 15.3 months longer than those who were not. This difference in survival is even longer–28.6 months–in favour of the l-deprenyl treated patients if the dropouts were included into the data.

Looking at the frequency distribution of the patients dead, dropout and alive gave also a highly significant difference in the two treatment groups (Chi-square = 43.6, $p < 0.001$). The similar number of deads (114 vs. 118) and dropouts (92 vs. 71) in the Madopar compared to Madopar–l-deprenyl group are in sharp contrast to the 171 vs. 375 (46%) alive from the 377 vs. 564 (67%) total number of patients in the two respective treatment groups.

In view of the substantial demographic differences found between the two treatment groups the results reported sofar can be regarded as tentative evidence of the prolongation of the survival by the addition of l-deprenyl to the l-dopa substitution in patients with Parkinson's disease. Since it is obvious that the time-to-response is influenced by a number of explanatory, prognostic variables, or covariates, which represent inherent differences among the study subjects, a further analysis of the survival data was undertaken. This analysis is based upon the Cox proportional hazards regression model (*Dixon* and *Brown*, 1981) which presumes that the death rates may be modelled as loglinear functions of the covariates. The aim of this analysis was to quantify the relationship between the survival and a set of explanatory covariates by means of a set of estimated regression coefficients, which describe this relationship. This regression model was used further to test the treatment effect while simultaneously accounting for the differences in the patients baseline characteristics. Sex, age at the start of l-dopa substitution, daily l-dopa (dose averaged for the whole treatment period), the interval between diagnosis and start of l-dopa substitution, baseline disability score and the time (calendar year) when l-dopa substitution was initiated, were the components of the covariate vector with significant effects on survival as revealed by the stepwise regression analysis (global Chi-square $= 156.9$, $p < 0.001$). Older age at the start of l-dopa substitution, higher daily l-dopa dose and higher baseline disability score were shown to be in negative relationship with survival. However, female sex, later time (calendar year) of l-dopa initiation, a longer time between diagnosis and start of l-dopa substitution had a reverse effect, they decreased the value of the hazard function (Table 1). A graphical representation of the estimated survival function of the Madopar and Madopar–l-deprenyl treated patients after

Table 1. *Survival analysis with the prognostic variables (COX model)*

Covariates	Regression coefficient
Treatment	−0.8499
Sex	−0.3701
Calendar year of l-dopa start	−0.0804
Daily l-dopa dose	0.0006
Disability score at start	0.0153
Age at l-dopa start	0.0679

The regression coefficients indicate the relationship between the prognostic variable (covariate) and the hazard function. Positive coefficients increase the value of the hazard function and therefore indicate negative relationship with survival. A negative coefficient has a reverse effect.

appropriate accounting for significant differences between baseline characteristics is shown in Fig. 1. The effect of treatment is highly significant in favour of the l-deprenyl combination (Wald statistic Chi-square = 39.02, $p < 0.001$ [Fig. 1]). In other words if all significant differences in the patients baseline characteristics have been taken into consideration the addition of l-deprenyl to the conventional Madopar substitution brought about the significant prolongation of survival, an increase in the life expectancy of the patients with Parkinson's disease. The presence of demographic differences between the two groups has no influence on this conclusion. Similar to that shown in Fig. 1 the estimated survival functions of the same two groups of patients stratified into three age groups (A) below 65 years, (B) 65–75 years and (C) over 75 years at the start of l-dopa initiation are shown in Figs. 2 a, b, c. Survival is significantly longer

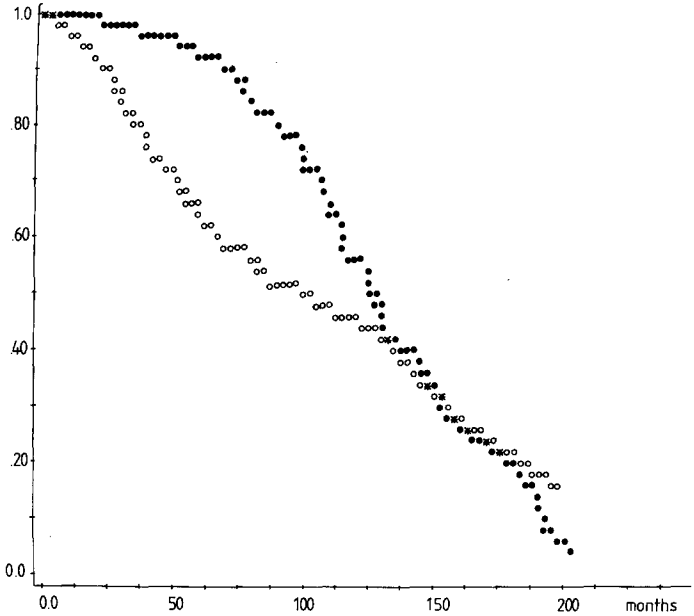


Fig. 1. Estimated survival function of the Madopar (O) (n = 377) and l-deprenyl plus Madopar (●) (n = 564) treated groups. The significant components of the covariate vector: age, disability and calendar year at levodopa initiation, mean daily levodopa dose, sex and the time between diagnosis and levodopa substitution are accounted for by the proportional hazard regression model. The effect of treatment is highly significant (Wald statistics Chi-square = 39.2, $p < 0.001$). It can be shown, that the probability of survival is significantly greater in the l-deprenyl plus Madopar group. Y-axis = (0 to 1.0) probability of survival, X-axis = survival time in months, curve = survival function, describing the probability of estimated survival in that age group

Table 2. *The effect of longterm Madopar and Madopar plus L-deprenyl treatment on the disability of parkinsonian patients*

Treatment	n	Baseline	Optimal response
Madopar	377	47.2 ± 0.97	26.8 ± 0.78
Madopar plus L-deprenyl*	81	51.0 ± 1.95	23.6 ± 1.64
		Madopar period	
Madopar plus L-deprenyl**	483	49.7 ± 0.73	24.5 ± 0.55
		Madopar + l-deprenyl period	
		39.4 ± 0.67	23.6 ± 0.60

* Madopar and l-deprenyl treatments were started at the same time.

** l-deprenyl was added at a varying interval after the initiation of Madopar treatment.

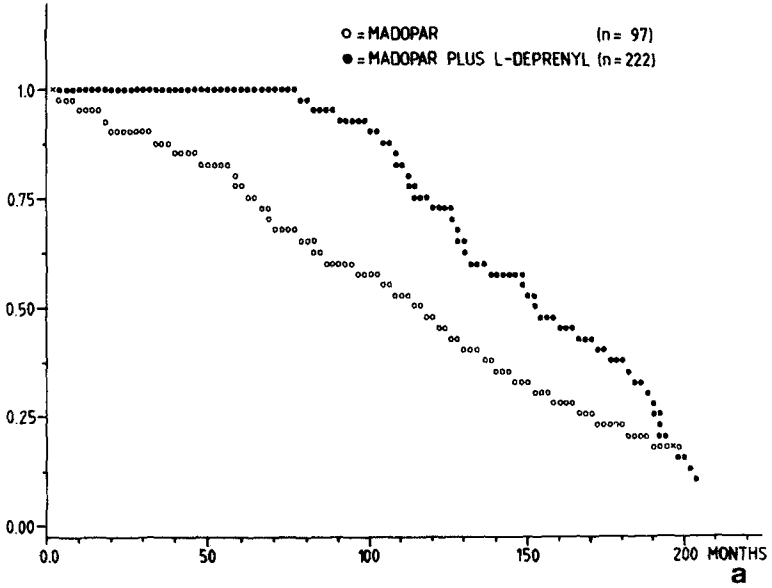
n = number of patients.

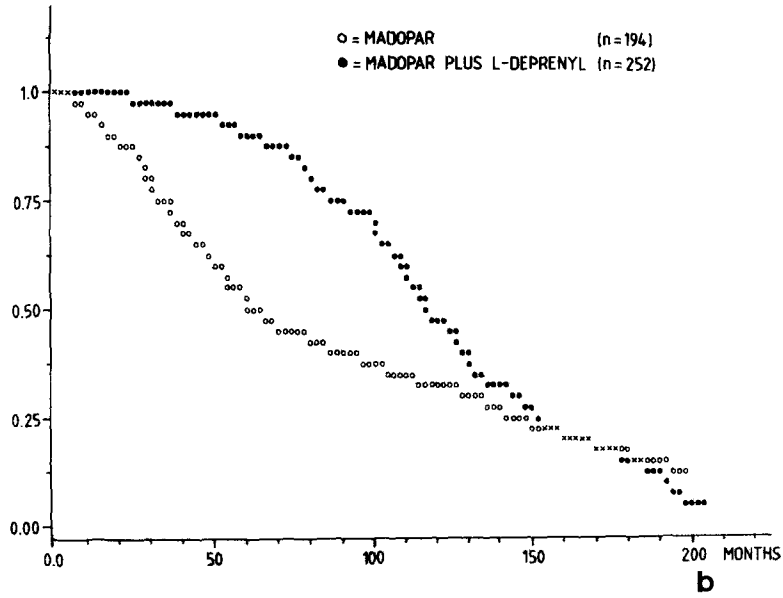
Disability was been rated according to *Birkmayer* and *Neumayer* (1972). For further details see section on results.

($p < 0.01$) in all age groups of patients treated with the Madopar–l-deprenyl combination.

Table 2 contains the outlines of the clinical course of the patients disability, where the ratings at baseline and at the time of the optimal response are shown. For technical reasons due to the differences in treatment schedule applied, two types of comparison had to be made. A parallel group type comparison was only possible between the Madopar treated (n = 377) and those of Madopar–l-deprenyl treated (n = 81) patients, when both treatments had been started at the same time and were given for the same period of time. The analysis of covariance, including all significant covariates, age at the start of l-dopa substitution, time from the diagnosis to the start of the l-dopa treatment, daily l-dopa dose and baseline disability gave a highly significant improvement of the patients disability in both groups ($p < 0.001$), sex had no significant influence on the disability. The disability score at the time of the optimal response predicted from the analysis of covariance was 27.1 for Madopar as compared to 22.1 in the Madopar–l-deprenyl treated groups of patients.

In the remaining 483 cases the treatment was applied according to a crossover design, requiring in the analysis the use of a model accommodating repeated measurements on the same subject at two levels of the treatment as a trial factor (Table 2). In this group of patients Madopar was always applied first and l-deprenyl was added later to the Madopar treatment. The first baseline rating corresponds


o = MADOPAR (n = 97)
● = MADOPAR PLUS L-DEPRENYL (n = 222)
1.0
0.75
0.50
0.25
0.00
0.0
50
100
150
200 MONTHS
a


o = MADOPAR (n = 194)
● = MADOPAR PLUS L-DEPRENYL (n = 252)
1.0
0.75
0.50
0.25
0.00
0.0
50
100
150
200 MONTHS
b

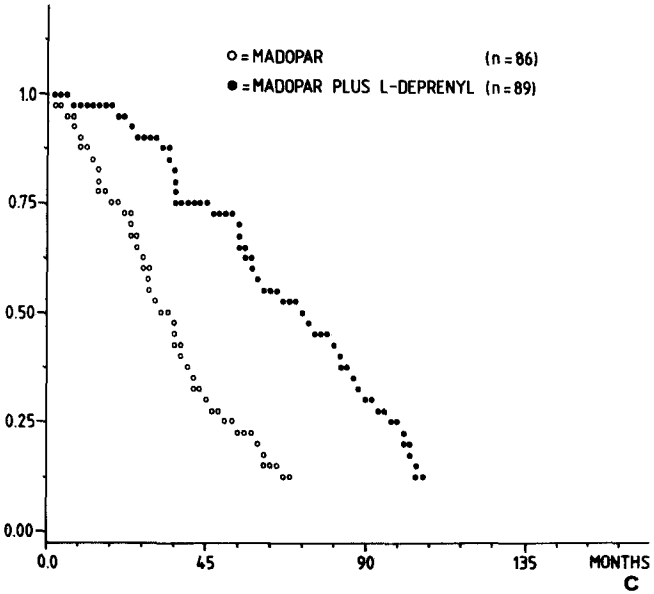


Fig. 2. Survival function of the Madopar (O) and l-deprenyl plus Madopar (●) treated groups of patients stratified according to age at levodopa initiation (life table analysis—the Cox proportional hazards regression model). (a) Age group less than 65 years, the mean survival on combined l-deprenyl plus Madopar (D + M) treatment was longer with 11 months ($p < 0.01$); (b) Age group between 65 and 75 years, mean survival in the treatment with (D + M) treatment was longer with 16 months ($p < 0.01$); (c) Age group over 75 years, mean survival in the group with combined (D + M) treatment was longer with 25 months ($p < 0.01$)

to the start of Madopar, the second to the start of combined Madopar—l-deprenyl treatment periods of the same patients. Optimal responses to the two sorts of treatment were determined as before. Patients improved first during the Madopar period, then relapsed in spite of the continued l-dopa substitution. l-Deprenyl was added at this stage and a further remission was observed. Thus patients who had lost the response to l-dopa can regain it with addition of l-deprenyl. The analysis of covariance accounting for the significant differences in baseline characteristics showed a significant improvement in both treatment periods alike ($p < 0.05$). The disability score predicted at the time of the optimal response in the Madopar treatment was 22.2, slightly better, than 25.8 for the combined Madopar—l-deprenyl period.

This difference in the efficiency of l-deprenyl in its effect on the patients disability between the above two types of comparison is well explained by the differences in experimental design between the two

groups. In the crossover type of treatment allocation, the combined treatment was always applied later, following a previous Madopar period of variable length, *i.e.* l-deprenyl was set in only in a later phase of a progressive, degenerative disease process. Admittedly the time course of the progression of the disease, or disability has not been reconstructed here. However, it seems obvious, that the prolongation of the life span of the patients who were treated with l-deprenyl during the course of their Parkinson's disease is at an expense of increased disability.

Age specific death rate of the parkinsonian patients before the l-dopa era has been reported to be about three times that of the general population (*Hoehn* and *Yahr,* 1967). The introduction of l-dopa treatment has substantially reduced the excess death rate to 1.3–1.9 time (*Yahr,* 1976), or down to the level of general population (*Diamond et al.,* 1976; *Birkmayer et al.,* 1983). A possible explanation for this lack of agreement between these results may be that in all of the above studies general mortality statistics were compared at each time with the life expectancy of one group of parkinsonian patients. In our study a direct comparison of two treatments has been made on comparable population of parkinsonian patients resulting perhaps in a more reliable approximation of the reality. Since there is no general consensus as to what extent l-dopa treatment has extended the life expectancy of the parkinsonian patients, the clinical significance of our findings is obvious.

Discussion

In the present study we have observed that longterm therapy with Madopar–l-deprenyl leads to recouping of l-dopa response as well as to a significant increase in the life expectancy of Parkinsonian patients. The higher daily l-dopa dose used in the group with l-deprenyl treatment is explained by the higher needs of the rather more severe cases in this group. Since higher daily l-dopa doses have been shown to have a significant negative influence on life expectancy in this analysis using the proportional hazard regression model, the interpretation that higher life expectancy is due to an adequate and, properly dosed l-dopa, while the shorter life span is due to an insufficient and underdosed l-dopa substitution can be excluded.

In a preliminary report, while being unaware of the studies with the dopaminergic neurotoxin MPTP (*Davis et al.,* 1979; *Langston et al.,* 1983) we (*Birkmayer et al.,* 1983) suggested that the increased life

expectancy due to addition of l-deprenyl can be explained by the ability of the monoamine oxidase inhibitor to retard the degeneration of dopaminergic neurons. So far no other anti-parkinson drug is known to have this property.

The limitations of DA replacement therapy in PD have become all too familiar (*Yahr,* 1976) since all drug treatments are palliative. Therefore search for aetiology of PD has continued. *Calne* and *Langston* (1983) have considered arguments for and against hereditary factors, aging of the nervous system and exposure to environmental toxins. They hypothetize that the latter factor is the major cause of PD and have presented various lines of evidence to support this view. Arguments favouring a neurotoxin induced mechanism of Parkinsonism are supported by the discovery of MPTP. This compound causes Parkinsonism in men and primates (*Davis et al.,* 1979; *Langston et al.,* 1983; *Langston* and *Ballard,* 1983) and Parkinson like neurochemical changes in other animals (*Burns et al.,* 1983; *Heikkila et al.,* 1984; *Langston et al.,* 1984, *Markey et al.,* 1984). Examination of brains from both have revealed loss of neurons in the zona compacta in the substantia nigra, resembling the changes seen in classical Parkinson's disease. Other changes include severe lowering of DA and its metabolites homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) (*Burns et al.,* 1983; *Heikkila et al.,* 1984).

MPTP is a non-polar highly lipophilic tertiary amine, which indicates that it could be a substrate for MAO. The recent exciting results showing that MAO inhibitors (*Langston et al.,* 1984; *Markey et al.,* 1984) and more percisely selective MAO-type B inhibitors, l-deprenyl (*Heikkila et al.,* 1984) and AGN 1135 (*Youdim et al.,* 1985), prevent the dopaminergic neurotoxicity of MPTP in animals support this hypothesis. Thus the analogy in our clinical results and the animal studies is apparent.

The exact mechanism by which l-deprenyl increases the life expectancy of Parkinsonian patients and inhibits the dopaminergic neurotoxicity of MPTP in animals is not known. Although these two phenomena might be unrelated evidence so far available suggests that inhibition of MAO-type B is most important. In Parkinsonian brains, obtained at autopsy from l-deprenyl (10 mg daily dose) treated subjects, MAO activity towards DA, a substrate for B enzyme (*Glover et al.,* 1977), has been shown to be completely inhibited (*Riederer et al.,* 1978), the resultant effect of this being an increase of DA in the striatum (*Riederer et al.,* 1984). In animal experiments MAO inhibitors increase brain levels of MPTP and prevent the accumulation of MPP^+ (1-methyl-4-phenylpyridinium), the main metabolite of MPTP (*Burns et al.,* 1983; *Langston et al.,* 1984). Furthermore the dehydrogenation

process associated with the formation of hydrogen peroxide during the reaction of monoamine deamination are selectively inhibited by MAO-B inhibitors (*Youdim,* 1985; *Youdim* and *Finberg,* 1985; *Youdim et al.,* 1985) and the conclusion reached is that MPTP like DA is a substrate for MAO-type B.

The formation of MPP^+ has been shown to be necessary for the expression of neurotoxicity induced by MPTP in animals (*Burns et al.,* 1983; *Langston et al.,* 1984). Whether an MPP^+ type compound or an unknown metabolite of DA, formed from the enzymatic reaction with MAO, is constantly accumulating in the human brain with the resultant neurotoxicity cannot be answered. An alternative would be the formation of toxic intermediates *e.g.* free radicals, N-oxides and hydrogen peroxide within the dopaminergic neurons via amine deamination (*Markey et al.,* 1984; *Cohen,* 1983). Free radicals are known to cause degeneration of membrane structures by the process of lipid peroxidation (*Halliwell* and *Cutteridge,* 1985).

In conclusion, whatever mechanisms are the underlying cause of the neurodegenerative process in PD or that caused by MPTP, it is apparent that MAO-type B inhibitors represent a new important approach for the treatment of PD. Furthermore these inhibitors will aid in elucidating the processes involved with the neurotoxic action of MPTP, which in turn could shed light on the degenerative process leading to Morbus Parkinson.

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