F.J.G.	François J.G.	Vingerhoets
R.J.	Ryan J.	Uitti
D.B.	Donald B.	Caine

Deprenyl and the Issue of Neuroprotection

F. Vingerhoets, MD, Neurodegenerative Disorders Centre, University Hospital, UBC Site, Purdy Pavilion, 2211 Wesbrook Mall, Vancouver, BC V6T 2B5 (Canada)

The Parkinson Disease Study Group (PDSG) recently published its findings concerning antioxidant drug therapy for early Parkinson’s disease [1] (idiopathic parkinsonism (IP)) as follow-up to an earlier report published in 1989 [2]. After almost 4 years of controversy [3, 4], the sole firm conclusion that could be drawn concerning the use of deprenyl, a monoamine oxidase (MAO) type B inhibitor was that it allowed the introduction of levodopa treatment to be postponed by somewhat less than 1 year. For this reason, the authors argue, deprenyl should be considered among the available therapeutic options for the initial treatment of early Parkinson’s disease. A discussion of when and how symptomatic treatment of early Parkinson’s disease should be carried out is beyond the scope of this editorial and has recently been addressed elsewhere [5]. Our discussion here will be restricted to the issue of neuroprotection as illustrated by the DATATOP experience.

Few would argue against neuroprotection being a goal worth pursuing. However, for the concept to be meaningfully assessed a specific definition is required. On the cellular level, the definition of neuroprotection is relatively straightforward. Most would accept an agent as neuroprotective if it reduced the death rate in a population of cells. In this context, visual examination of cells surviving in culture, following a toxic stressor, would allow conclusions regarding the neuroprotective effect of an agent. In experiments where neuropathological studies can be performed serially, for example in an experimental group of animals, comments concerning cellular neuroprotection can likewise be made. In this context, experimental models can be constructed, based on knowledge of a given deleterious phenomenon, including its mechanisms and natural evolution, and potential neuroprotective influences proposed (e.g. MPTP-induced parkinsonism – oxidative stress/excitotoxicity – MAO inhibitors). Similarly, when the cause of a human disease is known, as in the case of Wilson’s disease or subacute combined degeneration of the cord, chelation and vitamin therapy may be regarded as providing a kind of neuroprotection. By contrast, in the distinctly human condition of IP, the mechanism and natural evolution of the disorder are not known or quantifi-ably defined. Furthermore, practical access to visualizing neuronal populations from the brains of living patients is impossible. Consequently, it is difficult to define neuroprotection in this context.

This difficulty has been recognized by the PDSG. The DATATOP design [1, 2, 6] is representative of the framework for several human neuroprotective studies and therefore worthy of further consideration. Information from three sources seems essential for establishing a convincing neuroprotective story:

(1) An ongoing pathogenic mechanism must be identified. In IP, some evidence suggests a disturbance in oxidative pathways in the substantia nigra. This has been taken, in the DATATOP study, as indicating a primary role for free radical/oxidative stress in the development of parkinsonism [6]. However, others speak with equal conviction and evidence against the oxidative stress hypothesis [7]. Alternatively, or perhaps additionally, it has been postulated that continuous exposure to an environmental pro-toxin may contribute to the demise of nigral neuronal function [6]. However, to date no relevant protoxin has been identified in the environment. Furthermore, it has been shown that, at least in some other forms of parkinsonism, a transient exposure to a toxic agent such as manganese [8] or MPTP [9] may lead to a chronically pro-gresssive condition. One can only speculate as to whether the cause(s) of IP is (are) an event or process [10].

© 1994 S. Karger AG, Basel
0014-3022/94/0341-0001
\$5.00/0

The neuroprotective agent must have a predominant effect on the identified pathogenic mechanism. De-prenyl was thought to afford cellular neuroprotection by decreasing the propensity of MAO B to produce free radical compounds resulting from deamination of catecholamines [6]. However, as has been subsequently pointed out by others, including the PDSG [1], the termination of dopamine synaptic action is primarily mediated by reuptake and MAO type A is actually the isoform which predominates in striatal neurons (rather than type B). Consequently, inhibitors of MAO A have been postulated as potentially superior neuroprotective agents. Another confounding factor in the literature is the recent report that deprenyl may also rescue neurons through a neuro-trophic-like effect [11].

Neuroprotection must be operationally defined in a way that allows experimental study and, more specifically, measurement. The DATATOP study relied on clinical assessment for quantifying neuroprotection. Unfortunately, there is a major gap in our knowledge concerning the pathological evolution of IP and its clinical progression. Clinical features seem to appear only when some half of the normal complement of nigro-striatal dopaminergic neurons remain; from that point onward the relationship becomes uncharted. However, even if this relationship were known, it would be an impossible task to distinguish symptomatic from neuroprotective effects if clinical indices were the sole measuring instrument. The theoretical possibility of differentiating the two mechanisms by wash-in and wash-out examinations [4] is saddled with the problem of separating a delayed (post wash-in) or prolonged (post wash-out) symptomatic effect from neuroprotection. A good example of this complication was provided by the DATATOP study which demonstrated, by an extended wash-out [1], that part of the symptomatic effect had initially been missed [2]. Using clinical assessment as the sole yardstick, the DATATOP study showed that the symptomatic effect of deprenyl may have been sufficient to explain the difference in outcome for the patients treated with

deprenyl versus placebo [12]. It also showed that this effect was sustained after a wash-out period, and remained even if the subjects whose clinical measures obviously improved initially (after 1 month of treatment) were excluded from the analysis. Neuroprotection could be neither proved nor disproved [1]. Even a divergent evolution (i.e., a slower progression after wash-in of the treated subjects versus controls [12], which would require serial clinical evaluations to be noticed) may be misleading. The clinical evolution of a partially symptomatically treated patient may also differ from the natural clinical evolution in an untreated patient.

To avoid such a problem in the future, it has been suggested that only drugs without short-term symptomatic effect be tested. This approach faces a difficulty and a paradox. The difficulty is to assess the absence of any symptomatic effect. In this respect, the very carefully designed DATATOP study is again exemplary, as it disclosed the significant symptomatic effect of deprenyl that some previous studies had failed to identify. The paradox is that such an approach discards any drugs which potentially are neuroprotective and symptomatically beneficial. Certain both symptomatic treatments of IP may have neuroprotective effects e.g.: (1) dopaminergic agonists – which may reduce free-radical production by decreasing dopamine turnover because of their direct action on dopaminergic pre-synaptic auto-receptors [13]; (2) amantadine – which reduces dopamine reuptake [14] (and likewise may reduce uptake of toxins like MPTP). Amantadine is also an NMDA antagonist (possibly protecting against excitotoxicity) [14]. One can speculate that amantadine could have been substituted for deprenyl in the DATATOP study and would have led to the same conclusions. Symptomatic treatments may also improve prognosis by means other than neuroprotection. For example, reduced cardiovascular catastrophies have been reported in patients taking bromocriptine with levodopa compared with levodopa alone [15]. It seems unfortunate to exclude evaluation of these treatments as protective agents in an attempt to simplify the interpretative process.

We consider that the importance of generating an operational definition has been overlooked in human studies designed to evaluate neuroprotection. If this issue is not resolved, the DATATOP destination will be revisited. Consequently we suggest that the term neuroprotection be avoided when referring to purely clinical studies in the absence of a practical operational definition.

What possibilities are there for assessing neuroprotection? The relationship between nigral cell counts and the striatal fluorodopa uptake, as measured by PET, has recently been shown to be linear [16]. With accumulating evidence that the rate of neuronal death in IP exceeds that of normal aging [17, 18], we suggest measuring the neuroprotective effect in terms of reducing the velocity of abnormal nigral decay in IP. Neuroprotection of 100% would decrease the speed of neuronal death to that of normal aging. The current reproducibility of fluorodopa PET [19], coupled with the relatively slow natural evolution of IP, suggests that a large number of subjects would have to be studied for a long period of time. We estimate

2
Vingerhoets/Uitti/Calne

Deprenyl and the Issue of Neuroprotection

that at least 30 patients (and as many controls) would have to be scanned twice over an interval of 7 years, to identify (with a power of 80%) a completely neuroprotective treatment (i.e. one that slowed the rate of nigral neuronal loss to that of normal aging).

We realize that substantial investments of time and resources are required to complete clinical studies of this kind. However, as in the case of striatal transplantation [20], such an investment may be warranted and allow expansion of potential neuroprotective agents to include more than merely the ‘losers on the symptomatic battlefield’.

References

The Parkinson Study Group: Effect of tocopherol and deprenyl on the progression of disability in early Parkinson’s disease. N Engl J Med 1993;328:176-183.
The Parkinson Study Group: Effect of deprenyl on the progression of disability in early Parkinson’s disease. N Engl J Med 1989;321:1364-1371.
Landau WM: Clinical neuro-mythology IX, Pyramid sale in the bucket shop: DATATOP bottoms out. Neurology 1990;40:1337-1339.
The Parkinson Study Group: DATATOP and Clinical Neuromythology IX. Neurology 1991;41:771-773.
Calne DB: Treatment of Parkinson’s disease. N Engl J Med 1993;329:1021-1027.
The Parkinson Study Group: DATATOP: A multicenter controlled clinical trial in early Parkinson’s disease. Arch Neurol 1989;46: 1052-1060.
Calne DB: The free radical hypothesis in idiopathic parkinsonism: Evidence against it. Ann Neurol 1992;32:799-803.
Huang CC, Lu CS, Chu NS, Hochberg F, Li-lienfield D, Olanow W, Calne DB: Progression after chronic manganese exposure. Neurology 1993;43:1479-1482.
9 Vingerhoets FJG, Snow BJ, Langston JW, Te- 16 trud JW, Schulzer M, Calne DB: Evolution of subclinical dopaminergic lesions in MPTP-ex-posed humans (abstract). Neurology 1993; 43(suppl 2):A389.
Calne DB: Is idiopathic parkinsonism the consequence of an event or a process? Neurology, 17 in press.
Salo PT, Tatton WG: Deprenyl reduces the death of motoneurons caused by axotomy. J 18 Neurosci Res 1992;31:394-400.
Schulzer M, Mak E, Calne DB: The antiparkin-son efficacy of deprenyl derives from transient 19 improvement which is likely to be symptomatic. Ann Neurol 1993;32:795-798.
Lieberman A: Dopamine agonists used as monotherapy in de novo PD patients: Comparisons with selegiline. Neurology 1992;42(suppl 4):37-40. 20
Lustig HS, Ahern KV, Greenberg DA: Antiparkinsonian drugs and in vitro excitotoxicity. Brain Res 1992;597:148-150.
Prunzke H, Weizel D, Blumner B, et al: Bromocriptine lessens the incidence of mortality in L-dopa-treated parkinsonian patients: Prado study discontinued. J Clin Pharmacol 1992;43: 357-363.
Snow BJ, Tooyama I, Takahashi H, McGeer EG, Calne DB: Premortem 18F]fluorodopa uptake correlates with post-mortem dopaminergic cell counts and striatal dopamine in humans (abstract). J Cereb Blood Flow Meta-bo 1993;13:S251.
Fearnley JM, Lee JL: Ageing and Parkinson’s disease: substantia nigra regional selectivity. Brain 1991; 114:2283-2301. McGeer PL, McGeer EG, Suzuki JS: Aging and extrapyramidal function. Arch Neurol 1977; 34:33-35.
Vingerhoets FJG, Snow BJ, Schulzer M, Morrison S, Ruth TJ, Holden JE, Cooper S, Calne DB: Reproducibility of [18]-6-fluorodopa positron emission tomography in normal human subjects (abstract). J Cereb Blood Flow Metab 1993;13(suppl 1):S289.
CAPIT Committee: Core assessment program for intracerebral transplantations (CAPIT); in Lindvall O, Bjorklund A, Widner H (eds): Intracerebral Transplantation in Movement Disorders. Amsterdam, Elsevier, 1991, pp 227-241.