Viewpoints on Deprenyl

Deprenyl: Protective vs. Symptomatic Effect

Oscar S. Kofman

The symptomatic treatment of moderate or advanced Parkinson's disease with the use of deprenyl as adjunct therapy in combination with levodopa has been clearly established over the past fifteen years. The first report was that of Birkmayer[1] in 1975 followed by Lees[2] and reports from a number of other authors.

Clinical observations have concluded that deprenyl combined with levodopa does have a moderate beneficial effect in relieving wearing off or end of dose fluctuations and morning akinesia in fifty percent of subjects. This beneficial effect may continue for a year or longer in one-half of the subjects and may allow for a reduction of levodopa of twenty to thirty percent. This is essentially supported by our own observations on eighty-six patients treated with deprenyl.

A controlled cooperative study by Golbe et al[3] with ninety-six subjects indicated that deprenyl was of moderate benefit in improving the symptom fluctuations in fifty-eight percent of subjects. Golbe subsequently observed that the improvement disappeared in most of his subjects within eight months, although in others improvement continued. A recent report by Elizan et al[4] with two hundred chronic Parkinson patients treated with levodopa and with added deprenyl indicated improvement of end of dose response in one-third to one-half of the subjects. The improvement was not maintained in the majority. In addition these authors concluded that there is no evidence that deprenyl with levodopa decreased the excess mortality of Parkinson's disease contrary to Birkmayer et al retrospective study that suggested increased life expectancy.[5] The ratio of observed to expected deaths was 1.6 as compared to 1.46 on levodopa alone. The use of deprenyl did not appear to prevent progression of Parkinson's disease.

The pharmacological mechanisms of deprenyl in Parkinson's disease are somewhat complex. Primarily deprenyl could exert an effect on symptoms by increasing the availability of nigrostriatal dopamine by preventing oxidation of dopamine through the inhibition of monoamine oxidase-B (MAO-B). In addition there may be inhibition of the re-uptake of dopamine and increased synthesis of dopamine. Deprenyl is also known to have an amphetamine like effect as well as an antidepressant effect and anticholinergic effect.

With this acknowledged response one would therefore anticipate some degree of symptomatic improvement in early Parkinson's disease with either deprenyl monotherapy or deprenyl in combination with levodopa.

Discussion

Studies relative to deprenyl monotherapy in Parkinson patients who have not received levodopa in the past are limited. Generally they have been associated with no response or minimal to modest response with inconsistent symptomatic effects, some of which however have been of significance. A study by Csanda and Tarczy[6] of thirty subjects with early Parkinson's disease concluded that there was slight but significant improvement relative to disability in ten subjects. A recent study by Elizan et al[7] with deprenyl monotherapy indicated mild improvement which was subjective and transitory in most subjects. They concluded that the use of deprenyl in early Parkinson's disease "neither prevents emergence of new signs nor halts progression. Whether it reduces the rate of progression remains open".

An important recent double blinded study by Myllyla et al[8] on fifty-two subjects, twenty-seven of whom were on 10 mg of deprenyl daily and twenty-five on placebo, was carried on for a period of at least twelve months. Measurements included Webster Rating Scale, Northwestern University Disability Scale and Columbia University Rating Scale. The study concluded that deprenyl monotherapy has therapeutic value in early Parkinson's disease. Conclusions could not be drawn relative to deprenyl's effect on altering the progression of the disease process. Lieberman et al[9] described observations on twenty-one early Parkinson patients which indicated that five had an anti-Parkinson effect with deprenyl monotherapy. Three of these were studied with PET scans which showed striatal MAO-B inhibition.

A pilot study by Tetrud and Langston[10] on early Parkinson's disease with deprenyl was subsequently followed by the report of the Parkinson Study Group,[11] DATATOP Study, in November of 1989. These results are now well known and have been the subject of considerable interest, optimism and some controversy. There is little disagreement relative to the evidence of the delayed onset of disability and need for levodopa with deprenyl monotherapy in early untreated Parkinson's diseases. However the fundamental consideration is how these clinical observations should be interpreted relative to either symptomatic or protective mechanisms. The authors have indicated that "the effects of treatment are not fully explained by the apparently variable and clinically trivial short term effect of deprenyl on symptoms". This is accompanied by a further comment that "even if the effect of deprenyl is entirely symptomatic patients with Parkinson's disease so treated in early stages of disease should be able to function longer before requiring levodopa". These statements do not appear to be entirely compatible and should, as a minimum requirement, be accompanied by comparative studies of deprenyl with other non-levodopa anti-Parkinson treatment agents rather than placebo alone.

The study concludes that deprenyl "may delay the onset of severe disability by ameliorating an underlying process of

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Parkinson's disease, hence protective mechanism". Generally in the past science has acknowledged that amelioration of symptoms is a sign of effectiveness of treatment, not delay of disease progression.

Whether deprenyl has a symptomatic or protective effect, or both, remains unclear. This fundamental distinction requires considerable additional study and validation. A control group subjected to known anti-Parkinson therapy would be useful. A longer washout period of at least two months is required since deprenyl binds irreversibly with MAO-B and the activity of MAO-B may not return to the baseline within one month. It is of considerable significance to note that the Parkinson Study Group has added a more prolonged washout period of two months subsequent to their published preliminary reports. Following the longer washout period deprenyl is added in all subjects which unfortunately would tend to destroy a potentially significant control component of the study.

There are several other sources of concern and controversy. It should be noted that the statistics of the smaller pilot study of Tetrud and Langston[10] have recently been challenged. In addition it is of interest to note that at the end point of this study the examiner and patient guessed the experimental treatment sixty-two and sixty-one percent of the time, although this was not considered to be a factor in the results.

Subsequent to our initial discussions and provocative presentations,[12-15] Landau[16] has severely criticized the lack of conventional scientific analysis in the DATATOP Study. This includes what is regarded as inappropriate statistical analysis as well as the lack of a consistent and objective end point, which was regarded as the time when sufficient disability develops to require the use of levodopa, and is therefore essentially subjective. The validity of the end point decision is therefore dependent on many variable non standardized factors relative to each individual subject as well as the individual clinical judgement of each of the twenty-eight investigators. The study and some of its conclusions appear to represent "a remarkable reversal of conventional scientific analysis". Landau has concluded that "the proof of a protective effect of deprenyl cannot possibly be derived from this study".

There are many other factors that should be considered. Deprenyl is generally used experimentally prior to MPTP exposure to block the action of MPTP on nigral neurons and prevent the MAO dependent conversion to the active radical MPP+. There are however, no experimental studies on the action of deprenyl during the actual degenerative process relative to the progression of death or dysfunction of neurons which is induced by either toxic exposure or aging. Furthermore we do not actually know whether MPTP-like substances do actually play a role in the etiology of Parkinson's disease. If they do, there is evidence that MAO-B inhibition does not protect against neurotoxicity by analogs of MPTP.

It is established that eighty percent of nigral dopaminergic function is lost before the clinical presentation of Parkinson's disease, leaving a maximum of twenty percent of functioning neurons. Hence if Parkinson's disease is the result of damage by transient exposure to a neurotoxic agent such as an MPTP analog, decades before the first symptoms, superimposed on ongoing age related changes, deprenyl could be expected to do little as stated by Sonsalla and Golbe.[17] There should be no assumption that deprenyl protects an ongoing nigral neuronal degeneration based primarily on the evidence of pre-treatment of experimental animals. As Tetrud and Langston have stated "to actually prove the hypothesis that deprenyl slows the rate of progression of Parkinson's disease it would be necessary to show that the death of nigral neurons is prevented and as yet there is no way to determine this in living humans".[10]

Future Considerations

Before early Parkinson patients are committed to many years of daily "potential" therapy with deprenyl, which potentially could prove to be useless or harmful, there are many significant considerations that require further evaluation. These include the need for additional objective studies relative to deprenyl monotherapy. In addition the longterm effects relative to delay and the significance of delay in the need for levodopa in chronic Parkinson's disease are unknown. Of what eventual benefit is an eleven month delay in the need for levodopa therapy in a chronic disorder extending over twenty or thirty years? How long will the apparent beneficial effects of deprenyl endure, and will they persist with the addition of levodopa? The consequences both positive and negative of longterm deprenyl treatment are not really known. There are no data on the safety of deprenyl over several decades. Basic investigation relative to the mechanism of the waning of benefit of deprenyl is lacking. Studies to discount deprenyl in double blind fashion in longterm responders are needed. Studies relative to vitamin E are in progress and in theory the antioxidant mechanism of tocopherol should substantiate the results with deprenyl, otherwise additional theories and mechanisms may require consideration. Comparative studies with deprenyl, anticholinergics, bromocriptine, pergolide, etc. relative to the need and significance of delay of levodopa are lacking. Is the delayed administration of levodopa therapy in the early stages of Parkinson's disease beneficial or is there a possible negative effect in such a delay as suggested by Markham and Diamond?[18] Studies of alternative MAO inhibitors not metabolized to amphetamines and relatively devoid of antidepressants and anti-Parkinson effects have been suggested by the Parkinson Study Group. Valid, safe, practical, predictive tests of normals for preclinical Parkinson's disease by means of PET scan which indicates reduced striatal fluorodopa, possibly MRI, genetic linkage, biochemical, etc. will be useful relative to potential prophylactic therapy. Experimental studies with deprenyl relative to degeneration in process and hence not with the current MPTP model will be of special interest. If deprenyl provides a truly protective effect then the expected decline in CSF homovanillic acid, the major metabolite of dopamine, would be attenuated in actively treated subjects as suggested by the Parkinson Study Group. Why has the DATATOP Study to date not presented this potentially important component of their study? Measurements of oxygen free radicals during deprenyl administration would be useful and objective as well.

Does deprenyl have a role in other neurodegenerative diseases? There are positive statements in this respect with little scientific evidence. There are ongoing studies relative to Alzheimer's disease. However one would expect that with its known anticholinergic action and its known effect in enhancing confusion and hallucinations in Parkinson patients, the response will likely be unfavourable. Claims relative to ALS and multiple sclerosis are essentially unfounded and are reminiscent of the exaggerated and disproven claims for Vitamin E (tocopherol) in

the past. Whether there is any beneficial effect relative to the aging process and extension of the lifespan as observed in rats by Knoll[19] remains to be substantiated in additional rats as well as in humans.

Conclusions

The assumption that the delayed need for levodopa therapy in early Parkinson's disease is due to some protective action of deprenyl rather than symptomatic therapy should remain hypothetical until some of these as yet unknown considerations have been fully validated.

With the knowledge of this complex and controversial background a fundamental question arises. Should physicians and their patients be sprinkling deprenyl on cornflakes? Much of this overenthusiasm is media and patient driven. It would appear that at this stage the evidence and indicators that may suggest a possible protective role for deprenyl in early Parkinson's disease, as well as in other neurodegenerative disorders, unfortunately remains dubious and as yet unestablished.

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From the Department of Medicine (Neurology), University of Toronto, Toronto

Reprint requests to: Dr. O.S. Kofman, 99 Avenue Road, Suite 608, Toronto, Ontario, Canada M5R 2G5

Deprenyl: The Exciting Possibility of Protective Effect

J. David Grimes

Despite the great benefits of levodopa therapy Parkinson's disease remains slowly progressive. The most exciting development in the pharmacotherapy of Parkinson's disease in the last few years has been the possibility that the progression of the disease may be related to exogenous or endogenous neuronal toxicity and that this may be improved with antioxidative therapy.[1,2]

A recent study involving 800 patients showed that the use of deprenyl (10mg per day) delays the onset of disability associated with early, otherwise untreated Parkinson's disease. In this double-blind, placebo controlled study, the risk of having to start levodopa therapy (the end point of the study) was reduced by 57% for patients who received deprenyl.[3] The question has been raised as to whether this delay in requirement for levodopa treatment is secondary to slowing of disease progression or mild symptom improvement. This controversy has resulted in the publication of inaccurate, biased, misinterpretations of available data.[4]

Deprenyl has been used as monotherapy for de novo Parkinson's disease in a number of studies. The majority of these studies have involved small numbers (20 to 56) of patients with variable study design.[5-9] Csanda and Tarczy,[5] showed that 20 of 30 patients treated with deprenyl monotherapy required other antiparkinsonian therapy within six months. Another study of 22 patients attempted to assess whether deprenyl halted the progression of the disease; it did not; and the study ended with the conclusion that it may still reduce the rate of progression.[6] The study of Myllyla concluded that deprenyl monotherapy has some efficacy but the study is complicated by the fact that anticholinergic drugs were allowed as adjuvant therapy.[7] Terravainen has had experience that is probably closest to that of most clinical neurologists.[8] In a study of 20 levodopa naive patients he concluded that deprenyl improved clinical neurological disability by about 10% compared to placebo. He felt that the difference was

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