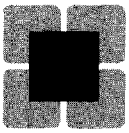

Deprenyl and Parkinson's disease: new use for an old drug

THE WAVE of enthusiasm for the drug deprenyl (Eldepryl) makes it timely to review the old uses of this agent and comment on the unique new applications that may be of value in the treatment of Parkinson's disease.

Dr. Joseph Knoll, of Budapest, Hungary, conceived of L-deprenyl, also known as selegiline HCl, in 1960.[1] Soon thereafter, the drug was synthesized as a "psychic energizer." The rationale for its use as a psychic stimulant and antidepressant can be better understood by considering its metabolism. When taken orally, selegiline has an initial half-life of only 10 minutes! It is then converted to des-methyl-deprenyl, which has a half-life of 2 to 3 hours. There is further metabolism to methamphetamine and amphetamine, with about half of the oral dose excreted in these forms in the urine. The ultimate amphetamine product explains why the medication was initially marketed as a psychic energizer. The first patients treated in the early 1960s were depressed Soviet soldiers.

By the mid-1960s the major adverse effects of the monoamine oxidase (MAO) inhibitors were appreciated and deprenyl, which belongs to this class of drugs, temporarily fell out of favor. With the 1968 discovery of MAO inhibitor subtypes, it was determined that deprenyl was a selective MAO-B inhibitor and that tyramine-induced hypertensive crisis could be avoided. With this selectivity in mind, Birkmayer, in 1974,[2] initiated the first treatment of Parkinson's patients using this compound and in 1977 reported on a series of 223 patients.[3] The beneficial effect of deprenyl on Parkinson's disease, through the mechanism of dopamine sparing, seemed to be established. Dopamine, the deficient neurotransmitter in Parkinson's disease, is degraded by the MAO-B enzyme system. Inhibiting this breakdown would allow central nervous system accumulation of dopamine and, theoretically, improve the patient's clinical status.

WIDESPREAD USE IN EUROPE

Based on this understanding of the drug's mechanisms of action, deprenyl has been used often in Europe since 1975 for the treatment of Parkinson's disease.[4] The reported benefits have always been modest and the drug has never been considered a major "breakthrough." However, it has been associated with consistent clinical improvement and its use has permitted lower dosages of carbidopa-levodopa (Sinemet).

In the United States, deprenyl is marketed by Somerset Pharmaceuticals as Eldepryl; the manufacturer is Chinoin Pharmaceuticals Ltd., Budapest, Hungary. Depending on the country, the drug is marketed under different names, such as Jumex in Austria and Italy, Movergan in Germany, and Eldepryl in Great Britain and Ireland.

For treatment of Parkinson's disease, the drug is administered twice daily in doses of 5 mg at breakfast and 5 mg at lunch. If taken later in the day, insomnia from the amphetamine metabolite is a potential adverse effect. The total daily dosage should never exceed 10 mg because, above this range, selective MAO-B inhibition is lost and hypertensive crisis may occur if the patient eats amine-containing food. Deprenyl is very expensive (a 1-month supply of 60 5-mg pills costs between $120 and $140).

NEW THEORIES ABOUT MECHANISM

In the mid-1980s the mechanism of the "designer drug" MPTP in the induction of Parkinson's disease was elucidated. Deprenyl was shown to have the ability to retard the biochemical cascade induced by MPTP; investigators observed that the medication could prevent the development of MPTP-induced extrapyramidal disease when given to animals before exposure to MPTP. It

was theorized then that deprenyl may have the unique effect of retarding a suggested mechanism of Parkinson's disease—ie, substantia, nigra cell death consequent to free radical production.

These findings led to a large clinical study, referred to as DATATOP, involving 28 institutions throughout North America. This ongoing investigation is evaluating the ability of deprenyl and of vitamin E (also believed to be an effective free radical scavenger) to retard the progression of Parkinson's disease.

Two preliminary reports indicate that deprenyl does indeed have the ability to slow the progression of Parkinson's disease. Tetrud and Langston[5] found that with deprenyl, disease progression slowed by 40% to 83% per year.

In November 1989 the investigators involved in DATATOP documented the beneficial effects of deprenyl.[6] They reported that the risk of reaching "endpoint," or disease progression to the point where functional disability required L-dopa treatment, was 57% lower for patients who received deprenyl. Deprenyl patients also enjoyed a significantly reduced risk of loss of employment because of Parkinsonian disability.

CONFLICTING STUDIES

Not all studies, however, have found deprenyl to be valuable. Elizan and Yahr[7,8] failed to find beneficial effects in either early Parkinson's disease or as adjunctive therapy in later stages of the disease.

Despite the lack of unanimity about the value of the deprenyl, physicians, researchers, and Parkinson's disease patients all will follow, with interest, the fortunes of this drug in the coming years with the hope that it does indeed achieve the goal of Parkinson's disease retardation.

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