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Monoamine Oxidase Inhibitors in Parkinson's Disease

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HISTORY

Monoamine oxidase (MAO) is an enzyme involved in the breakdown of catecholamines including dopamine, norepinephrine, and serotonin. MAO inhibitors were discovered in the late 1950s and were first utilized in the treatment of depression. In 1962 Bernheimer showed that MAO inhibitors could potentiate the antiparkinsonian effect of levodopa but caused severe hypertensive crisis (1). In 1968, Johnston identified two types of monoamine oxidase: A and B (2). Each has a separate affinity for various catecholamines and works in different parts of the body. MAO-B is found predominantly in the human brain (3) and platelets and has an affinity for dopamine and benzylamine. MAO-A is found predominantly in the intestinal tract and has an affinity for serotonin and norepinephrine. Both types can oxidize tyramine, though MAO-B does so only at higher concentrations.

In 1972, Knoll and Maygar described selegiline (Deprenyl®) as a selective irreversible MAO-B inhibitor (4). They also showed that at low doses selegiline did not potentiate the pressor effect of tyramine also known as the "cheese effect." That same year Squires (3) reported that 80% of

MAO activity in the brain is MAO-B. In autopsied brains, 10 mg of selegiline was found to be sufficient to selectively inhibit 90% of MAO-B in such areas as the caudate, substantia nigra, globus pallidus, and thalamus (5). Hence, it was shown that selective MAO-B inhibitors such as selegiline could inhibit the MAO that has strong affinity for the basal ganglia. This may augment the concentration of dopamine in areas in which it is deficient.

For over two decades MAO-B inhibitors have been used in Parkinson's disease (PD). They were originally developed as antidepressants but were later found to have benefit in patients with PD. Knoll's study showed that selegiline, a selective nonreversible MAO-B inhibitor, lengthened the life span of rodents by 50% (6). The neuroprotective properties of MAO inhibitors were evaluated over the next two decades. There was much interest in their ability to protect neurons against neurodegenerative processes such as PD. The bulk of the scientific interest revolves around selegiline, while more recent studies have looked at rasagiline (a selective irreversible MAO-B inhibitor) and lazabemide (a selective reversible, competitive inhibitor of MAO-B). In clinical practice, selegiline is used as monotherapy or as adjunctive therapy to levodopa.

MECHANISMS OF ACTION

In PD there is a loss of dopaminergic neurons in the substantia nigra pars compacta. The mechanisms involved in the destruction of these cells are complex. Abnormalities found in PD include abnormal iron metabolism (7), increased free radical production (8), and decreased scavenging systems such as reduced glutathione (GSH). The latter two comprise the "oxidative stress" theory. Some mechanisms appear paradoxical. For instance, Mytilineou et al. (9) demonstrated both deleterious and beneficial effects from levodopa. Levodopa can produce free radicals, but it can also increase the rate of reduced GSH synthesis and protect against toxins such as L-buthionine sulfoximine (L-BSO) an inhibitor of GSH synthesis. There are three theories to justify the use of MAO inhibitors to slow progression of PD: oxidative stress, neurotoxicity, and potential regenerative properties of MAO-B inhibitors.

Oxidative Stress Theory

This theory proposes that the parkinsonian brain is under oxidative stress (10): there is an overabundance of free radicals or oxygen species in the brain causing damage to the dopaminergic cells. This skewed proportion of reactive oxygen species may be due to an increased production or a

decreased clearing of these products due to an impaired GSH system or abnormal iron cycling (7,11). One pathway in the degradation of dopamine is through MAO-B or autooxidation. This degradative process can produce free radicals such as hydrogen peroxide and hydroxyl radicals that in turn may cause cellular damage. A solution is to reduce formation of these free oxygen species by inhibiting the degradation of dopamine. Selegiline slows the rate of dopamine degradation and, hence, the rate of free radical production. Selegiline also allows for an increase in GSH that helps clear free radicals from the system (8).

MPTP and Neurotoxicity

Studies have shown that various chemicals including dopamine, levodopa, and 6-hydroxydopamine act as neurotoxins (12,13). Selegiline has been shown to protect against these neurotoxins through mechanisms other than MAO-B inhibition.

In 1982, Tetrud and Langston (14) reported that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produced a parkinsonism indistinguishable from PD in young drug addicts. This was later found to be due to its oxidative byproduct 1-methyl-4-phenylpyridinium ion (MPP^+). Others have demonstrated MPTP's toxic properties on dopaminergic neurons (15). MAO-B inhibitors successfully prevent the conversion of MPTP to MPP^+ (16) and protect dopaminergic neurons from this toxicity (15,17). MAO-B inhibitors were originally thought to prevent this conversion via MAO inhibition. Since then, MPTP has been shown to inhibit mitochondrial respiration via complex I, through free radical synthesis (18). In a study by Vizuete et al. (19), selegiline protected cells from MPP^+ toxicity, but not through inhibition of the conversion of MPTP to MPP^+. Matsubara and others (20) showed selegiline prevented mitochondrial toxicity elicited by MPTP and 2,9-Me_2NH^+, which is an *N*-methylated β-carbolinium cation and an analog of MPTP with protoxic activity. They hypothesized that selegiline impacts mitochondrial electron transport, resulting in membrane potential stabilization.

Tatton and Greenwood (21) exposed rats to MPTP for 72 hours. Selegiline or saline was then given. These rats were sacrificed and the substantia nigra compacta stained with tyrosine hydroxylase (TH +) immunostain to measure the amount of dopaminergic cells. Selegiline was shown to prevent 50% of the loss due to MPTP. The importance of this observation was the absence of MAO-B activity in those regions implying a different mechanism for selegiline's action.

Maygar et al. (22) showed that selegiline and other MAO-B inhibitors were effective in blocking *N*-(2-chloroethyl-)-*N*-ethyl-2-bromobenzylamine

(DSP-4) toxicity. DSP-4 is a neurotoxin that inhibits ^{3}H-noradrenaline uptake into central and peripheral noradrenergic neurons in rodents. Knoll (23) found that selegiline could protect striatal dopaminergic cells from 6-hydroxydopamine (6-OHDA) neurotoxicity. These studies suggest that MAO-B inhibitors may have other neuroprotective properties besides that of MAO inhibition.

Potential Regenerative Properties

Li et al. (24) reported that selegiline and other irreversible MAO-B inhibitors decreased the messenger RNA for glial fibrillary acidic protein (GFAP), a biological marker of cell injury, in C6 rat glomeruli cells. Increased GFAP expression contributes to tissue scarring and creates a physical barrier near damaged neurons. Presumably, MAO-B inhibitors either inhibit the physical barrier, prohibiting vital repairs to damaged neurons, or they protect neurons from damage directly, thus producing less GFAP expression. In the PC12 cell apoptosis model, Tatton et al. (25) documented increased cell survival with selegiline. In this study, selegiline induced new protein synthesis. These experiments give credence to neuronal protection. De Girolamo et al. (26) reported that selegiline not only protected N2a cells from MPTP but also reversed the toxic effects on axonal growth, suggesting that selegiline may help regenerate damaged neurons. The possible mechanisms include direct neuronal survival, regeneration, or indirect induction of cellular changes.

BIOCHEMICAL PROPERTIES

Selegiline is a selective irreversible MAO-B inhibitor. Taken orally, it is readily absorbed from the intestine and reaches plasma levels in 30–120 minutes. It has a mean half-life of 2 hours. Its major metabolites, L-methamphetamine and L-amphetamine, have half-lives of 20.5 and 17.7 hours, respectively. At doses of 5 and 10 mg it has mild antiparkinsonian effects without causing pressor effects. At higher doses such as 30 and 60 mg it has greater antidepressant effects but is associated with an increased pressor effect via tyramine, requiring patients to adhere to a low-tyramine diet. It has an extremely long half-life as confirmed with positron emission tomography (PET) imaging (27,28). Withdrawal from selegiline is not associated with an amphetamine-like withdrawal. Selegiline also significantly increases phenylethylamine (PEA) output. PEA is a strong dopamine uptake inhibitor and induces dopamine release (29). The reader is referred to Heinonen et al.'s article on the pharmacokinetics and metabolism of selegiline for further details (30).

CLINICAL APPLICATIONS

Selegiline is primarily used in patients with early PD as monotherapy or as adjunctive therapy to levodopa. It is usually used as 5 mg every morning or 5 mg twice a day, in the morning and afternoon. It is not given at night to avoid insomnia from methamphetamine metabolites. Hubble et al. (31) did not find a significant difference using 10 mg versus 5 mg daily in patients with moderately advanced PD.

The Quality Standards Subcommittee of the American Academy of Neurology (32) confirmed that selegiline has only mild symptomatic antiparkinsonian effects when used as monotherapy. Compared to placebo, selegiline improves motor scores in PD patients (33–35). Withdrawal of selegiline results in a worsening of the Unified Parkinson's Disease Rating Scale (UPDRS) tremor and bradykinesia scores (36). These scores recover with resumption of this drug.

Selegiline decreases the amount of disability in early PD. Palhagen et al. (34) noted patients on selegiline had better UPDRS scores over time and had a delay to reach disability or need for levodopa. Myllyla et al. (37) described a slowing of disability in PD patients on selegiline and a delay in the need for levodopa therapy.

DATATOP STUDY

The DATATOP study was a large prospective double-blind, four-arm study that included over 800 patients. It compared the effects of placebo, selegiline, tocopherol (vitamin E), and selegiline plus tocopherol in early PD. Endpoints were the need to start levodopa therapy and the onset of disability. Patients were evaluated by clinical exams and cerebrospinal fluid analysis (38). Selegiline delayed the onset of levodopa therapy and slowed parkinsonian disability. Patients on placebo demonstrated a 50% faster decline than those on drug. However, this phenomenon occurred largely in the first year and was not sustained (39). A 53% reduction in the development of freezing of gait (FOG) was also observed with selegiline (40). Benefit with selegiline on FOG waned after selegiline was discontinued. The mechanism behind selegiline's protection against FOG is unknown. A potential benefit in FOG would be important because there are no proven treatments to help FOG. However, the clinical significance of the reduction in FOG with selegiline is questionable.

ADJUNCTIVE THERAPY

As adjunctive therapy MAO-B inhibitors decrease motor fluctuations, improve UPDRS scores, and allow for a reduction in levodopa dosing. In the late 1970s, Lee et al. (41) and Rinne et al. (42) reported that selegiline added to levodopa therapy reduced the "on-off" episodes in PD patients. However, Golbe (43) found that selegiline added to levodopa therapy only reduced "off" time without an increase in "on" time. This benefit was lost after about one year. Lieberman (44) showed that selegiline added to levodopa improved UPDRS scores in early PD patients without motor fluctuations more than in patients with fluctuations. In various studies selegiline allows a reduction in the total dosage of levodopa. Both Myllyla et al. (45) and Larsen et al. (46) showed in double-blind trials that selegiline use in early PD delays the need for levodopa, decreases the amount of levodopa needed, and decreases the rate of escalation of levodopa compared with placebo. The Parkinson's Disease Research Group of the United Kingdom found no clinical delay in disability with adjunctive therapy (47).

ADVERSE EFFECTS

Most of the common side effects of selegiline are due to its dopaminergic properties, such as nausea, constipation, diaphoresis, hallucinations, and dyskinesias (43). Often these effects are found in patients using selegiline in conjunction with levodopa. Reducing the levodopa dosage may diminish these side effects. The average reduction in levodopa needed to alleviate side effects seen in combination therapy has been estimated at 20% (48,49). Nausea may be ameliorated in many cases by taking the medication postprandially.

Selegiline and levodopa can produce orthostatic hypotension (45,48). Churchyard et al. (33) found that 30% of patients on long-term selegiline therapy (in combination with levodopa or other antiparkinsonian agents) had postural hypotension. Other concerns with MAO-B inhibitors are drug interactions and hepatic toxicity. Golbe (43) reported that, although there was a trend for liver function tests to rise, none of the patients had levels outside the normal range.

Serotonin syndrome may develop with the combined use of selective serotonin reuptake inhibitors (SSRIs) and MAO-B inhibitors. The serotonin syndrome consists of diaphoresis, hypertension, and confusion. Richard et al. (50) reviewed over 4000 cases in which both drugs were used together, including case reports and adverse events reported to the U.S. Food and Drug Administration and the manufacturer of selegiline. Of 4000 patients, only 11 fulfilled criteria for this syndrome. They concluded that if the

interaction does exist, it is extremely rare. In this report the one death was in a patient without PD (FDA report). This is consistent with a previous report by Waters (51).

MORTALITY

The Parkinson's Disease Research Group of the United Kingdom found a significantly higher rate of mortality in patients treated with selegiline and levodopa than levodopa alone. The study was criticized for technical reasons: half of the participants did not complete the study, the study was not double-blind, and patients were rerandomized into a different trial arm. Another retrospective study by Thorogood et al. (52) found an increase in mortality in patients on selegiline, especially in younger patients on selegiline alone and in elderly patients with combined therapy.

The DATATOP study was reviewed to examine mortality (53). There was a 2.1% death rate per year found in all patients for the 10 years of observation. This was unaffected by selegiline or tocopherol or both combined. The initial selegiline patients and tocopherol patients had slightly higher mortality, but the numbers were not found to be statistically significant. Statistical analysis found no differences between early and late users of selegiline. Hence, the investigators did not find a significant increase or decrease in mortality with selegiline.

A meta-analysis done by Olanow et al. in 1998 (54) concluded that there was no evidence for increased mortality with selegiline use. Recently the Quality Standards Subcommittee of the American Academy of Neurology also concluded that there was no convincing evidence for an increased mortality with selegiline (32).

LAZABEMIDE

The Parkinson Study Group investigated the clinical use of lazabemide at various strengths in a double-blind study (55). It showed that at a single oral dose of 200 mg, lazabemide inhibited MAO-B for 24 hours. However, it gave only a modest benefit in activities of daily living (ADL) scores and none in motor scores. At 400 mg it caused asymptomatic elevations of liver enzymes and creatinine. A later study in 1996 (56) showed that 43.9% of patients on placebo reached the endpoint of requiring symptomatic therapy versus 31.4% of patients on varying doses of lazabemide. UPDRS scores were not significantly different between those on lazabemide and placebo. The study was not able to distinguish a true neuroprotective property of lazabemide. Lazabemide will not be marketed because of its mild

symptomatic efficacy and concerns regarding possible liver and renal toxicity.

RASAGILINE

Rasagiline is an irreversible selective MAO-B inhibitor that is five times more potent than selegiline. Its major metabolite is 1-(R)-aminoidan. Rasagiline is devoid of amphetamine properties, and thus, it does not have a pressor effect. It is currently in Phase III studies. It is said to have symptomatic dopaminergic effects. It is purported to have neuroprotective effects seen in mouse models, in which it rescues dopaminergic neurons from neurotoxins (57).

Finberg et al. (58) investigated rasagiline, an isomer of *N*-propargyl-1-aminoindane, in rat fetal mesencephalic cells containing 95% neurons, 20% of which were tyrosine hydroxylase positive. Rasagiline was shown in the mitochondria to have selective MAO-B inhibitory properties similar to selegiline but with greater potency in a single oral preparation. Both increased the striatal dopamine level after chronic ingestion. In another experiment selegiline and rasagiline increased the percentage of positive tyrosine hydroxylase neurons. Rasagiline increased the number of surviving cells in serum medium and the number of surviving cells in the absence of serum.

Rabey et al. (59) studied rasagiline given at various strengths (0.5, 1, and 2 mg) versus placebo as adjunctive therapy to levodopa for 12 weeks with evaluation at 12 and 18 weeks. Rasagiline had greater improvement in UPDRS scores than placebo, particularly for motor and ADL scores at all strengths and time points. However, due to a strong placebo effect, the difference was deemed insignificant.

Kieburtz et al. (57) studied 400 patients with early PD on rasagiline at either 1 or 2 mg versus placebo for 26 weeks. A subset of 55 patients received a challenge of 75 mg oral dose of tyramine. The study showed improved UPDRS scores in the rasagiline group versus controls. There was no significant increase in mean systolic blood pressure in either group. None of the patients who received the tyramine challenge had an adverse reaction. They concluded that rasagiline was safe and useful as monotherapy in early PD.

CONCLUSION

The role of MAO-B inhibitors for treatment of PD continues to be explored. It is possible that with its modest symptomatic effect, selegiline will be replaced by other MAO-B inhibitors. Rasagiline has a stronger potency and

a possible role as a neuroprotective agent. Selegiline continues to be used as monotherapy and as an adjunctive agent to levodopa for motor fluctuations. When adding selegiline to levodopa, it must be remembered that the dopaminergic side effects of levodopa can be enhanced. MAO-B inhibitors will continue to be studied in the laboratory as potential neuroprotective agents.

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