UPDATE OF THE NEUROPROTECTIVE EFFECT OF MAO-B INHIBITORS THERAPY ON PARKINSON’S DISEASE

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ABSTRACT

Parkinson’s disease was marked by stiffness, bradykinesia, resting tremor, and postural instability occurring due to various causes that were mainly idiopathic causes. Monoamine oxidase B inhibitor, also known as MAO-B inhibitor was crucial for therapy against Parkinson’s disease. The inhibitor metabolized dopamine selectively, blocking one of the enzymes that broke dopamine in brains and enhancing the effects. In Parkinson’s disease, Selegiline was the first generation of MAO-B inhibitors used for therapies; whereas Rasagiline was the second generation of the same inhibitor. The review emphasized the pharmacological aspect, side effect, and neuroprotective effect of Selegiline and Rasagiline on Parkinson’s disease.

KEYWORDS: Parkinson’s disease, neuroprotective effect, MAO-B inhibitors, Selegiline, Rasagiline.

I. INTRODUCTION

Parkinson is most common neurodegenerative disease after Alzheimer.[1] There are approximately seven to ten millions of people in the world that are diagnosed for suffering from Parkinson’s disease. The prevalence is about 41 of 100,000 people at the age of 40 year old until 1,900 of 100,000 at the age of 80 and over 80. Parkinson’s disease incident, or the level of recently-diagnosed cases generally increased by age, although stable in people aged more than 80 year old. There are 4% of people that were diagnosed Parkinson before 50 year old. Additionally, men are 1.5 times more potential than women.[2]
In pathological, Parkinson’s disease has special symptoms including degeneration of dopaminergic neurons in substantia nigra pars compacta (SNc), decreased striatal dopamine, and decreased intracytoplasmic proteinaceous inclusions, or Lewy bodies that contain protein alpha-synuclein.[1] Dopamine deficiency causes motor disorders marked by classical motor symptoms and non-motor symptoms that may appear years before the patient is positively diagnosed for suffering from the disease. However, usually, one of the early symptoms is declined sense of smell. It is manifested due to changed α-synuclein protein from dorsal motor nucleus from olfactory bulb and vagus. Furthermore, mood disorders (depression, anxiety, and altered personality) are also believed to be the early symptoms of Parkinson’s disease. Depression is a major contributor of bad life quality, future disability, and average life sustainability.[3] Nevertheless, there may be mildly-declined intellectual function. In addition to that, constipation and sleep disorder commonly happen to the patient with Parkinson’s disease as well.[4]

About 10% of patients suffer from Parkinson’s familial disease with identified genetic dysfunction. To the patients without any clear genetic hereditary, pathogenesis mechanism is more complex, so are several factors including environmental toxin, oxidative stress, and mitochondria dysfunction, as presented in Figure 1.[3]

![Figure 1: General Pathophysiology of Parkinson’s Disease](image)

In Parkinson’s disease, the most effective therapy for motor symptoms is to modulate dopamine system by either giving levodopa (exogenous dopamine), dopamine agonist
(increasing dopaminergic activities), or MAO-B inhibitors (disturbing dopamine catabolism).\textsuperscript{[5]} In striatum, either levodopa, dopamine agonist, or MAO-B inhibitors have dopaminergic effects.\textsuperscript{[6]}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{drug_site_of_action.png}
\caption{Illustration of Drug Site of Action by Dopaminergic Effects for Motor Symptoms\textsuperscript{[6]}}
\end{figure}

During early Parkinson’s disease, if compare to other dopamine agonists, MAO-B inhibitors is one of the options for early treatments regardless its weaker symptomatic effects than levodopa and dopamine agonist’s. The inhibitors may reduce the level of motor fluctuation better than levodopa initial therapy and produce less significant side effects than other dopamine agonists. However, our data are limited to provide any reliable conclusion.\textsuperscript{[7]} The article discuses pharmacological elements, side effects, and neuroprotective effects of Selegiline and Rasagiline on Parkinson’s disease.

\section*{II. DISCUSSION}

\textbf{MONOAMINE OXIDASE-B (MAO-B) INHIBITORS}

MAO (amine-oxygen oxidoreductase) was flavin adenine dinucleotide that having incovalent bound enzymes with cysteine residue and involving in catalyzing oxidative deamination from biogenic amine of neuromin, vasoactive amine, and exogenous, and xenobiotic amine including monoamine neurotransmitter and hormones in brain and
periphery tissue, hence generating modulation from their concentration. Physiological function of MAO related to their substrate properties. The wide series covered some well-known biogenic amines, i.e. indoleamines as serotonin and tryptamine; trace amines as β-phenylethylamine, tyramine, and octopamine; catecholamines as dopamine, norepinephrine, and epinephrine; and N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin (quickly converted into 1-methyl-4-phenylpyridinium [MPP⁺]).

MAO-A indicated larger affinity than hydroxylated amines as serotonin and noradrenaline. Several literatures had proven that in glial cells MPTP was oxidized to be 1-methyl-4-phenyl-2,3-dihydropyridinium (MPDP⁺) that had many MAO-B inhibitors near the terminal of striatal nerves and body of nigra nerves. MPDP⁺ was diffused out of glial cells and deoxidized to be MPP⁺.

Figure 3 shows MAO-B in brain catalyzing MPTP oxidation on allelic α-carbon to generate an instable product, then MPDP⁺ converted through auto-oxidation and mechanism catalyzed by enzymes to be a stable compound, MPP⁺. MAO-B was involved in the metabolism of dopamine and found in a large quantity in striatum. MAO-B inhibitors restricted the dopamine metabolism catalyzed by MAO-B in brain and extended the DA action in basal ganglia. In nigra substantia, the death of dopamine neuron cells continued and neuroprotective therapy became compulsory to stop neuron losing. In cellular and animal
models, neuronal cells are protected by Selegiline and Rasagiline from programmed cell death.\textsuperscript{[10]} Therefore, MAO-B inhibitors were frequently used for therapy of Parkinson.

A. Pharmacological Aspects

SELEGILINE

In 1960, Joseph Knoll developed what so-called as Selegiline or (-)-Deprenyl.\textsuperscript{[11]} It was the first drug that could selectively restrict isoform B from monoamine oxidase (MAO) enzyme and the first monoamine oxidase type B inhibitor approved for the treatment of Parkinson’s disease.\textsuperscript{[12]}

![Figure 4: Selegiline structure.\textsuperscript{[13]}](image)

Selegiline pharmacokinetic greatly varied. It had 10-hour half-life and was eliminated through urine.\textsuperscript{[14]} Selegiline was metabolized through the first pass, or experienced an extensive process in the heart, in that it was converted to be L-methamphetamine and Desmethyleselegiline through P450 cytochrome. The metabolite underwent the process and resulted in L-amphetamine, as indicated in Figure 5.\textsuperscript{[12]}
Figure 5: Biochemical Transformation of Selegiline.[15]

RASAGILINE
Irreversible MAO-B inhibitors Rasagiline was approved for the first time by Israel in January 2005 to cure idiopathic Parkinson’s disease as a monotherapy or additional therapy with Levodopa for patients with end-of-dose fluctuations. European Agency for the Evaluation of Medicinal Products approved Rasagiline for the same indication in February 2005, and US Federal Drug Administration approved Rasagiline in May 2006.

Figure 6: Structure of Rasagiline.[16]

Rasagiline pharmacokinetics could be well absorbed after oral provision and passed through the blood brain barrier (BBB).[17] Rasagiline was metabolized through CYP1A2. Rasagiline elimination was 7% of feces and 70% of urine (< 1% was unchanged). Rasagiline had 3-hour half-life.[14] Biochemical transformation of Rasagiline is shown in Figure 7.
B. Side Effects

MAO-B inhibitors have the most common side effects including mild nausea, dry mouth, mild fuzziness, constipation, perplexity (might occur to old patients), and hallucination (might occur to old patients). While MAO-B inhibitors were given simultaneously with cheese or wine with high tyramine, it potentially increased the blood pressure. Fortunately, the “cheese effect” had not been found in Selegiline and Rasagiline. FDA had reduced food limitation related to MAO-B inhibitors.\(^{[18]}\) If compared to other therapies for early Parkinson’s disease, MAO-B inhibitors produced less side effects than several dopamine agonists.\(^{[7]}\)

Selegiline could be well tolerated according to most reports. Side effects such as nausea and vomiting, dry mouth, sleep disorder, dyskinesia, and orthostatic hypotension were found in 2-5% of patients compared with placebo. Meanwhile, other side effects such as fuzziness, beating heart, dyspnea, perplexity, edema, mixy dysfunction, appetite loss, and anxiety had incidents of less than 2%.\(^{[9]}\)

Some studies clarified that subjects suffering from early Parkinson’s disease cured by Rasagiline monotherapy had less adverse effects and dropout rates than those cured by Pramipexole or Ropinirole. The highest adverse effects related to gastrointestinal and sleep/fatigue were suffered by subjects cured by Ropinirole; whereas those cured by Pramipexole indicated the highest cognitive AE incident.\(^{[19]}\) In their studies, TEMPO and PRESTO figured out that Rasagiline of 1 mg taken once a day might cure symptoms and motor fluctuation by patient with Parkinson in early, middle, or severe without any cognitive adverse effects and significant behaviors, mental alteration, or bad behaviors and mood.\(^{[20]}\)

C. Neuroprotective Effects of Mao-B Inhibitors

All MAO inhibitors came with neuroprotective characters, as they restricted H\(_2\)O\(_2\) and released toxic aldehyde which follows the amine oxidative metabolism. After all, the
individual inhibitor might conducted an intrinsic neuroprotective act as an addition.\cite{9} In Figure 8, suggested components as a neuroprotective effect of MAO inhibitors are explained.\cite{21}

![Figure 8: Target of Selegiline and Rasagiline in Toxicity of MPTP.\cite{22}](image)

In the body, neurotoxic MPTP compound was converted by MAO-B and became an active MPP\(^+\) compound. MPP\(^+\) compound is an efficient substrate for dopamine transporter and made dopaminergic neurotoxicity selective to human and other types of mammals.\cite{22} MPP\(^+\) was identified as mitochondria toxin in dopaminergic neurons. It restricted activities of Complex I from electron transport chains, caused compromised energy production, and increased oxidative stress. The similar alteration might be induced by a decrease in the expression of Complex I in brain suffering from post-mortem Parkinson’s disease with increased iron content that produced oxidative damage significantly. Auto-oxidation from the amount of dopamine released after the cell was damaged by toxin induction that acted as additional source might increase oxygen free radical generation.\cite{21}

**SELEGILINE**

Neuroprotective effects of Selegiline were indicated by Knoll and colleagues. They confirmed that Selegiline protected dopaminergic neurons against toxic effects from 6-hydroxydopamine (specific dopaminergic neurotoxin). Selegiline protected striatum against 6-hydroxydopamine through the blockage of MAO type B, restricted 6-hydroxydopamine uptake to the inside of neurons, facilitated scavenger function, and increased the neurotoxic emission of free radicals. The conclusion strengthened the finding that Selegiline significantly increased dismutase superoxide activities in striatum.\cite{11}
Another study figured out that increased activities of antioxidant enzymes after Selegilne treatment in the striatum of aged rats. In addition to antioxidant enzyme, level of glutathione increased as well. In in-vitro experiment of cell culture, Selegilne might had nerve growth factor (NGF) effects too that indicated its action on mRNA dismutase superoxide induction, i.e. NGF-independent. Selegilne restricted oxygen consumption from isolated mitochondria and induced adaptive increase in dismutase superoxide activities. However, the antioxidant properties due to antioxidant enzyme induction gradually developed by following chronic treatment. Consequently, it could not explain fast neuroprotective effects of Selegilne.\textsuperscript{[21]}

Further study declared that Selegilne protected neurons against various neurotoxic agents; such as DSP-4; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 5,6-dihydroxyserotonin; AF64A; increased production natural protecting agent of neurons; had immunostimulant effects, increased interleukin-2 and natural killer activities; in rats suffering from carcinogen-induced mammary tumors, impeded the growth of tumor, prolactin serum, and minimized monoamine brain metabolism, and was related to increased central and peripheral neurotransmission as well as immune activities.\textsuperscript{[11]}

Knoll and colleagues found Selegilne to extend the experimental rats’ life naturally. They found that Selegilne gave an anti-apoptosis effect on diverse tissues and cells that did not depend on MAO inhibition. It should be noticed that anti-apoptosis character of desmethylselegilne (Selegilne metabolite that was an active neuroprotective molecule) was more superior than Selegilne. Furthermore, R(-) methamphetamine, the main Selegine metabolite, was an antagonist by neuroprotective character of Selegilne and desmethylselegilne.\textsuperscript{[9]}
Table 1: Neuroprotection on Parkinson’s Disease by Selegiline (Prospective, Randomized, Double-blind, Placebo Controlled Studies).[23]

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Name of the study</th>
<th>N</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrad and Langston (1969)</td>
<td>Pilot study for DATATOP</td>
<td>44</td>
<td>Endpoint (levodopa) Placebo 312.1 d Selegiline 548.9 d</td>
</tr>
<tr>
<td>Parkinson Study Group (1989a, b, 1993)</td>
<td>DATATOP</td>
<td>800</td>
<td>Endpoint (levodopa) After 12 months: Placebo 47% Selegiline 28%</td>
</tr>
<tr>
<td>Myllylä et al. (1992)</td>
<td>Finnish trial</td>
<td>47</td>
<td>Endpoint (levodopa) Placebo 372±28 d Selegiline 545±94 d</td>
</tr>
<tr>
<td>Allain et al. (1993)</td>
<td>French Selegiline multicenter trial</td>
<td>93</td>
<td>Endpoint (levodopa) After 3 months: Placebo 18.4% Selegiline 4.5%</td>
</tr>
<tr>
<td>Olanow et al. (1995)</td>
<td>SINDER</td>
<td>101</td>
<td>Deterioration in UPDRS between baseline and final visit (14 months) Placebo −5.8±1.4 points Selegiline −0.4±1.3 points</td>
</tr>
<tr>
<td>Puzuntok et al. (1999)</td>
<td>SELEDO</td>
<td>116</td>
<td>Primary and final: need for &gt;50% increase in levodopa dose Placebo 2.6 years Selegiline 4.9 years</td>
</tr>
<tr>
<td>Larsen et al. (1997, 1999)</td>
<td></td>
<td>183</td>
<td>Patients treated with levodopa+selegiline developed marked less severe parkinsonism (not statistically significant) and required lower doses of levodopa+placebo.</td>
</tr>
<tr>
<td>Myllylä et al. (1992)</td>
<td></td>
<td>52</td>
<td>Endpoint (levodopa) after two years Placebo 545±90 d Selegiline 372±28 d</td>
</tr>
<tr>
<td>Myllylä et al. (1997)</td>
<td></td>
<td>44</td>
<td>Levodopa dose (5 years): Placebo 725±78 mg/d Selegiline 405±59 mg/d</td>
</tr>
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</table>

RASAGILINE

In accordance with a preclinical experiment, neuroprotective effects of Rasagiline involved multifactorial mechanism. In Figure 9, the mechanism included in the setting of cellular antioxidant activity and anti-apoptosis factors was presented. Rasagiline’s propargyl part created antiapoptotic Bcl-2-inducing character and activated C kinase protein. In addition to that, the opening of mitochondrial permeability transition pore (MPTp) was restricted by Rasagiline and proapoptotic decline; including collapsed mitochondria membrane potency, released C cytochrome, and activated 3 caspases. Rasagiline prevented translocation of proapoptotic glyceraldehyde-3-phosphate dehydrogenase (GAPDH) into the core cell as well. Moreover, neuroprotection activities depended on antioxidant enzyme activation too; such as dismutase superoxide and catalase.[24]
Figure 9: Mechanism of Rasagiline’s neuroprotective action.\textsuperscript{[25]}

ROS = reactive oxygen species; PT = permeability transition

Table 2: Neuroprotection on Parkinson’s Disease by Rasagiline.\textsuperscript{[26]}

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased activities of SOD and catalase</td>
<td>Carrillo \textit{et al.} (2000)</td>
</tr>
<tr>
<td>Inhibition of prostaglandin E\textsubscript{2} release</td>
<td>Abu-Rayya \textit{et al.} (1999)</td>
</tr>
<tr>
<td>Stabilization of $\Delta Y$m; suppression of cytochrome c release, caspase 3 activation, and DNA fragmentation</td>
<td>Akao \textit{et al.} (2002a); Maruyama \textit{et al.} (2000c,a); Youdim \textit{et al.} (2001b); Maruyama \textit{et al.} (2002); Bar-Am \textit{et al.} (2005)</td>
</tr>
<tr>
<td>Prevention of nuclear GAPDH accumulation</td>
<td>Maruyama \textit{et al.} (2001); Ou \textit{et al.} (2009)</td>
</tr>
<tr>
<td>Up-regulation of GDNF and BDNF</td>
<td>Maruyama \textit{et al.} (2004); Weinreb \textit{et al.} (2004); Nači \textit{et al.} (2006); Weinreb \textit{et al.} (2009a)</td>
</tr>
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Rasagiline’s metabolite, 1(R)-aminoindane had an anti-apoptosis (on the higher concentration than the parent molecule) and showed similar biochemical mechanism spectrum to that explained for Rasagiline. The existence of propargyl cluster was important for neuroprotection, as propargylamine also had anti-apoptosis activities, although in a higher concentration than that required with Rasagiline or Selegiline.\textsuperscript{[9]}
An early postponed experiment of Rasagiline [ADAGIO] explained that in a daily normal clinical dosage of 1 mg, the disease growth was impeded, as shown by the UPDRS score. However, the effect was statistically insignificant on the higher dosage. There had been several interpretations about deficiency of Rasagiline effectiveness with a daily dosage of 2 mg to minimize the disease growth and potential disadvantageous such as the growth rate of disease in the population of research and higher symptomatic effects with a higher dosage.[9,26]

III. CONCLUSION

Parkinson’s disease was a neurodegenerative disease initiated by the loss of dopaminergic neuron in substantia nigra pars compacta located in basal ganglia. Dopamine deficiency caused motor disorder marked by classical motor symptoms (stiffness, bradykinesia, resting tremor, and postural instability) and non-motor symptoms. MAO-B inhibitors such as Selegiline and Rasagiline gave neuroprotective effects to MPTP toxicity. Selegiline had a metabolite, desmethylselegiline, an active neuroprotective molecule with an anti-apoptosis character. It significantly increased dismutase superoxide activities in striatum and protected neurons against various neurotoxic agents. Meanwhile, in Rasagiline, multifactorial mechanism was involved in the neuroprotective effect that was propargyl cluster and metabolite of Rasagilin 1(R)-aminoindane.

REFERENCES


