Improvement of Disability and Akinesia of Patients With Parkinson’s Disease by Intravenous Iron Substitution

JOERG G. D. BIRKMAYER, M.D., Ph.D.*
and WALTHER BIRKMAYER, M.D.†

*Department of Medical Chemistry, University of Graz, 8010 Graz, Austria
†Evangelic Hospital, 1090 Vienna, Austria

ABSTRACT

Akinetic crises are one of the problems arising in patients with Parkinson’s disease in particular after long term treatment with levo-dihydroxyphenylalanine (L-DOPA). They are characterized by severe disability to move. Increasing dosages of L-DOPA and decarboxylase or monoaminoxidase inhibitors do not improve these symptoms. Intravenously applied iron in the form of a ferri-ferro-complex exhibits a considerable benefit for all patients treated so far. They regained a remarkable mobility. Their disability score dropped from up to 90 percent down to 30 percent. The effect is dosage-dependent, and withdrawal of iron will lead again to akinetic crises.

Introduction

Parkinson disease is characterized by the symptoms trias of rigor, tremor, and akinesia.

Histopathologically, a degeneration of nigrostriatal neurons occurs which leads to a deficit in dopamine. The biochemical bases for L-DOPA treatment of Parkinson-disease was elucidated by Carls­son and co-workers in the late 1950s. They injected reserpine into mice and evoked akinesia and catalepsy, symptoms which are characteristic for Parkinson disease. By administering L-DOPA, they were able to reverse the effect of reserpine. As consequence of these findings, L-DOPA was successfully applied in substituting the dopamine deficit in Parkinson patients. The effect of DOPA with regard to akinesia was remarkable but of short-time. In order to prolong the L-DOPA effect, decarboxylase inhibitors and selective monoaminoxidase inhibitors were added to the therapeutic medication in order to block its degradation. By this combination, an increased duration of L-DOPA action was achieved.

One of the problems clinicians are faced in treating Parkinson patients is the so called “off-effect”. Suddenly, the patients are unable to move. Off-effects lead to longer lasting akinetic crises. Predominantly, they occur in patients with advanced disease and after long term treatment. Akinetic crises are accompanied by a labile respiration and circulation and other vital functions; thus, any
additional stress such as infection or surgical intervention cause a fatality. To overcome these crises, an effective medication is urgently needed. Attempts with higher dosages of L-DOPA or decarboxylase inhibitors did not work nor did any of the therapeutic additives such as amantadine, bromocryptine, or monoamineoxidase (MAO)-B inhibitors.

Another possibility to elevate the dopamine concentration in the brain is the stimulation of its synthesis. The rate limiting step in catecholamine-synthesis is the oxidation of the amino-acid tyrosine to DOPA. This step is catalyzed by tyrosine-hydroxylase, an iron containing enzyme with pteridine as co-enzyme.8

It has been recently shown that the tyrosine-hydroxylase activity in brain tissue of Parkinson patients is considerably reduced, for example, in substantia nigra to about 75 percent.5 Another interesting finding is that tyrosine-hydroxylase from brain tissue can be stimulated up to 20-fold by iron. Tyrosine-hydroxylase from brain tissue of patients with Parkinson's disease is stimulable by iron but to a lesser extent as that of normal brain tissue.9 As a logical consequence of the stimulation capacity of iron it was applied in a special complex to patients with Parkinson's disease in akinetic crises.

Materials and Methods Diagnosis

Diagnosis and disability scores of the Parkinson patients where established (table 1) according to scale of Birkmayer and Neumayer.3

Iron was applied in the form of a complex composed of sodium-ferrico-ferroso ascorbic acid and sodium-ferrico aloxanic acid.* Thirty mg of oxiferriscorbone were dissolved in 100 ml of 0.9 percent sodium chloride, pH 7.4, and intravenously infused in 30 minutes. Disability scores were determined before and two hours after the infusion.

Results

In general terms, all patients treated so far exhibited a considerable drop of their disability score. Details of the individual patients, their disability, and their previous as well as their present therapy are summarized on table II. In particular, the walking and pushing ability improved remarkably as so did the posture and mimic. The action of iron lasted between 24 and 48 hours. At withdrawal of iron from the usual medication, a worsening of the patients' disability was observed. This indicates the improvement of the patients' symptoms to be based on the iron applied. In addition to the improvement of disability, another effect of iron was observed. The dosage of the usual Parkinson therapy Madopar® could be decreased by half in four patients and omitted totally in three patients. On the basis of our clinical findings, it is suspected that a lack of iron in the particular brain stem area is the cause of the reduced tyrosine-hydroxy-

---

* Reg. trade name: Oxiferriscorbone.
TABLE IX

Exposure of 10 Cases of Patients with Parkinson's Disease Treated with Iron

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Previous Therapy (Year Started)</th>
<th>New Therapy</th>
<th>Percent Disability Before New Therapy</th>
<th>Percent Disability After New Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.H.</td>
<td>72</td>
<td>M</td>
<td>Sinemet/2 (since 1975)</td>
<td>O.F.S. 15 mg Deprenyl/20 mg</td>
<td>80 (8/11/86)</td>
<td>50 (8/25/86)</td>
</tr>
<tr>
<td>H.W.</td>
<td>61</td>
<td>F</td>
<td>Madopar 125 mg/2 Deprenyl/20 mg Noostril 1 g (since 1960)</td>
<td>O.F.S. 22.5 mg</td>
<td>90 (9/30/86)</td>
<td>80 (8/15/86)</td>
</tr>
<tr>
<td>F.B.</td>
<td>56</td>
<td>M</td>
<td>Madopar 250 mg/3 Deprenyl/20 mg Parlodel 10 mg (since 1970)</td>
<td>O.F.S. 15 mg</td>
<td>40 (8/1/86)</td>
<td>30 (8/14/86)</td>
</tr>
<tr>
<td>A.H.</td>
<td>54</td>
<td>M</td>
<td>Madopar 125 mg/6 Lisuride/3 (since 1965)</td>
<td>O.F.S. 15 mg</td>
<td>70 (8/4/86)</td>
<td>30 (8/31/86)</td>
</tr>
<tr>
<td>K.F.</td>
<td>63</td>
<td>N</td>
<td>Madopar 125 mg/3 Deprenyl/20 mg Lisuride/3 (since 1960)</td>
<td>O.F.S. 15 mg</td>
<td>75 (8/4/86)</td>
<td>30 (9/9/86)</td>
</tr>
<tr>
<td>N.R.</td>
<td>77</td>
<td>M</td>
<td>Madopar 250 mg/3 Deprenyl/20 mg</td>
<td>O.F.S. 15 mg Deprenyl/1</td>
<td>75 (2/13/76)</td>
<td>50 (9/25/86)</td>
</tr>
<tr>
<td>A.R.</td>
<td>75</td>
<td>M</td>
<td>Madopar 125 mg/3 Deprenyl/20 mg (since 1981)</td>
<td>O.F.S. 15 mg Deprenyl/1</td>
<td>75 (2/13/76)</td>
<td>50 (9/25/86)</td>
</tr>
<tr>
<td>K.E.</td>
<td>70</td>
<td>M</td>
<td>Madopar 125 mg/3 Deprenyl/20 mg Kemadrin 5 mg/2 (since 1976)</td>
<td>O.F.S. 15 mg Deprenyl/1</td>
<td>50 (9/10/86)</td>
<td>20 (9/25/86)</td>
</tr>
<tr>
<td>R.W.</td>
<td>76</td>
<td>M</td>
<td>Madopar 125 mg/5 Deprenyl/20 mg Noostril 400 mg/3 (since 1982)</td>
<td>O.F.S. 15 mg phys. NA CL 250 Madopar 125 mg/3</td>
<td>70 (7/23/85)</td>
<td>30 (9/20/86)</td>
</tr>
<tr>
<td>G.W.</td>
<td>73</td>
<td>F</td>
<td>Madopar 125 mg/6 Deprenyl/20 mg Saroten 20 mg/3 (since 1978)</td>
<td>O.F.S. 15 mg Deprenyl/1</td>
<td>75 (7/8/86)</td>
<td>50 (9/20/86)</td>
</tr>
</tbody>
</table>

O.F.S. = Oxiferriscorbone (reg. Trade mark)

lase and the DOPA deficiency. This explanation appears oversimplified, because Riederer et al9 found that the iron content of various brain stem nuclei, such as substantia nigra, in patients with Parkinson's disease does not differ from that of the normal brain. Therefore, other reasons might be responsible for the action of iron.

At present, speculation can be made on the possible mechanism of action. It is very likely that the galenic formulation of the iron compound is one of the reasons of its action. The usual iron medication is in form of ferrousulfate or ferrocarbonate. From this, iron dissociates readily into the blood, where it is captured by transferrine. Owing to this transferrin-binding, iron does not reach site of its action. The iron which was used by the present authors represents a special compound of a mixture of ferri- and ferro-complex with ascorbic acid. In this complex, the binding seems to be rather tight, because a certain percentage of iron reaches the target cells and
expresses its action there. In addition to the galenic formulation, the effect may be based also on the different saturation kinetic of iron and tyrosine-hydroxylase. From the iron dependency of the stimulation of tyrosine-hydroxylase activity, it is possible to estimate an apparent association constant of tyrosine-hydroxylase with iron (Fe 3+).

According to this, only a small part of the enzyme is actually active. Under normal level of brain iron, less than 50 percent of the enzyme is associated with Fe 3+ and is active. In the normal brain, this amount of tyrosine-hydroxylase is sufficient for synthesis of normal levels of DOPA. In patients with Parkinson’s disease, however, this is not the case. As found by Riederer et al., tyrosine-hydroxylase of patients with Parkinson’s disease is approximately 30 percent of that of the normal brain. However, in the brain of patients with Parkinson’s disease, an increase in the amount of active enzyme almost to the normal level can be achieved by increasing the level of Fe 3+. If this mechanism actually is responsible for this phenomenon, then iron therapy should work in all cases of tyrosine-hydroxylase deficiencies. As tyrosine-hydroxylase deficiencies are reflected by low levels of DOPA clinical syndromes associated with DOPA deficiency, such as presenile dementia of Alzheimer-type, non-Parkinson movement disabilities and depression should benefit from iron therapy. Clinical work is in progress in this direction.

References