Lisuride Combined with Levodopa in the Treatment of Advanced Parkinson’s Disease

İLERİ DÖNEM PARKİNSON HASTALIĞININ TEDAVİSİNDE LEVODOPAYA EK OLARAK VERİLEN LİSİRİDİN ETKİLERİ

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SUMMARY

22 patients with advanced Parkinson’s disease were studied, all having a deteriorating response to levodopa and suffering from daily fluctuations in disability. An open study was performed. Lisuride was added 0.1 mg, daily and increased in four weeks period. After reaching the optimal dose, it is given at fixed dose in two /three weeks period. Optimal daily lisuride dose was 1.2 mg. (Range 0.8-1.2 mg). Mean Levodopa dose was reduced from 650 mg. to 520 mg.

16 patients completed the 6-8 weeks trial. The addition of lisuride resulted significant improvement of parkinsonian disability. Among the patients with “on-off” phenomena, there was an increase in “on” period from 8 hours to 11 hours and end of dose deterioration was delayed from 2 hours to 3 hours. All of these changes were significant (p< 0.01). It seems that Lisuride was effective on parkinsonian disability and fluctuations in advanced Parkinson’s disease.

Key Words: Lisuride, advanced parkinson’s disease


ÖZET

Bu çalışmada, Levodopaya yanıt azalan ve flütüasyonları ortaya çıkan 22 ileri dönem parkinson hastası araştırıldı. Lisürüdünde 0.1 mg olarak tedaviye eklendi ve 4 haftalık periyoda dozu arttırdı. Ideal doza ulaşıldıkta sonra 2-3 hafta aynı dozda verildi. Ortalama günülük Lisürüdüşu 1.2 mg (0.8-1.2 mg) idi. Ortalama günülük Levodopa dozu 650 mgdan 520 mg’a düşürildü.

On altı hasta 6-8 haftalık çalışmayı tamamladı. Lisüründen eklendikten sonra parkinson hastalarında “On” dönemi 8 saattan 11 saate uzakken, doz sonu kötüleşmesi 2 saatten 3 saat gecekti. Bu değişimler istatistiksel olarak anlamlı bulundu (p< 0.001). İleri dönem parkinson hastalarında, parkinsoniyanın yetersizlik ve flütüasyonlarda Lisürid efektif olabilir.

Anahtar Kelimeler: İleri dönem parkinson hastalığı, lisürid

Levodopa is the most effective drug for the treatment of Parkinson’s disease (1,2,3). The salutary response of patients with idiopathic Parkinson’s disease to levodopa, generally does not last. Within a few years, a majority will begin to experience a shortening in their duration of antiparkinsonian action, a narrowing of their optimal dose range and fluctuations in their motor response (4). The dimished response may result from continued degeneration of the nigrostriatal neurons (5).

In early mild Parkinson’s disease, there is still sufficient storage capacity present to buffer the patient against fluctuations in the plasma levodopa level, but as the disease progresses, that storage capacity is gradually lost and the patient’s clinical state reflects the rising and falling plasma levodopa levels (1). These patients might benefit from drugs that bypass the nigrostriatal neurons and stimulate dopamine receptors directly (5).

We investigated the usefulness of the combination of lisuride with levodopa in patients with more advanced disease.
PATIENTS AND METHODS

22 patients with Idiopathic Parkinson’s disease were included. All patients had had long term levodopa treatment and they suffered from a deteriorating response to levodopa and different kind of fluctuations in disability.

The mean age was 58.7 years (range, 47 to 70). Duration of Parkinson’s disease was 9.4 years (range, 2 to 27). All patients had been treated with levodopa. Mean duration of treatment with levodopa was 7.7 years (range 2 to 17) and mean dose was 625 mg. (range 375-1250).

14 patients have taken anticholinergic drugs, 3 patients have taken bromocriptine, one amantadine, another privedil. Bromocriptine and Privedil were discontinued before the trial.

Patients disability states according to Hoehn and Yahr stage (6) are shown Table 1. the mean stage was 2.9.

Patients clinical states for UPDRS (Unified Parkinson’s Disease Rating Scale. Version 3.0 1987) was between 5 and 84 and mean rate was 44.27 (UPDRS’s maximum ratio was 108).

The daily begining dose of lisuride was 0.1 mg. p. o. The dose was increased 0.1 mg every three days until an optimal therapeutical effect was reached or until side effects appeared. The dose increment period of 4 weeks followed by a 2-3 weeks treatment with a fixed dose. Mean lisuride dose was 1.2 mg (range 0.8-1.6 mg.).

Patients were examined at 0, 9, 18, 24 and 42 to 49th days by the same Neurologist who experienced on movement disorders. The severity of Parkinson’s disease was assessed according to Hoehn&Yahr scale and UPDRS. Blood pressure values on lying down and standing positions and heart rates were measured. Motor complications were assessed by the patients’ and/or their relatives’ diaries.

Laboratory evaluations included haemogram, fasting glucose levels, tests of liver and renal functions and eletrocardiogram. Wilcoxon signed ranks test was performed for nominal data.

RESULTS

16 of the 22 patients completed 7 week trial. 6 patients were dropped from the study because of adverse effects. The addition of lisuride to levodopa treatment resulted in a significant further improvement in the total parkinsonian disability of the patients with a deteriorating levodopa response (Table-2).

Among the 16 patients who completed 7 week trial, 11 achieved one stage reduction in Hoehn & Yahr scale. Among the parkinsonian symptoms the improvement in tremor was less significant than the response of other parkinsonian symptoms.

14 patients had end of dose deterioration. Before the trial, end of dose deterioration had been seen in one hour and 55 minutes (1/2 hour-3.5 hours) after the last levodopa dose. After the trial it was delayed to 3 hours (1.5-4.5 hours).

Among the 16 patients, 7 were with dyskinesias. After the trial two of them experienced a decrease in duration and frequency of involuntary movements, while two of them having an increase in involuntary movements. There was no change in dyskinesias in the rest of three patients.

Among the patients who completed the trial 8 were with “on-off” phenomena. Lisuride therapy resulted in an increase in the duration of “on” periods from 8 hours and 15 minutes to 11 hours and 7 minutes. Six of eight patients’ daily “on” hours were protracted in between one to eight hours (Table-3) Another

Table 1. Stages of the patients.

<table>
<thead>
<tr>
<th>Stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Improvement in parkinsonian disability on UPDRS in 16 patients who completed 7 week clinical trial

<table>
<thead>
<tr>
<th>Dose Lisuride (mg)</th>
<th>Dose Levodopa (mg)</th>
<th>Rig.</th>
<th>Tr.</th>
<th>Brad</th>
<th>UPDRS MP</th>
<th>Total</th>
<th>HOEHN&amp; Yahr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-</td>
<td>10.8</td>
<td>7</td>
<td>2.1</td>
<td>14.9</td>
<td>44.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Range</td>
<td>-</td>
<td>3-19</td>
<td>0-22</td>
<td>0</td>
<td>0-32</td>
<td>5-84</td>
<td>1-4</td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.2</td>
<td>4.9</td>
<td>4.2</td>
<td>1.1</td>
<td>6.25</td>
<td>21.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Range</td>
<td>0.8-1.6</td>
<td>1-10</td>
<td>0-19</td>
<td>0-3</td>
<td>0-19</td>
<td>1-52</td>
<td>1-3</td>
</tr>
</tbody>
</table>

Rig : Rigidity
Tr : Tremor
Brad : Bradykinesia
MP : Motor performance (Speech, Rapid alternating movements of hand and leg and gait assessed)
two patients show no change in the duration of “on” periods.

Brief freezing episodes had been seen on two patients. After lisuride administration one patient’s episodes completely resolved and other’s episodes decreased from 5-6 times a day to once in 2-3 days.

**Adverse Effects**

Lisuride was discontinued in 6 of 22 patients because of adverse effects (%27). All adverse effects disappeared within several days of discontinuing lisuride.

Nausea and vertigo developed in 7 of the 16 patients that completed the trial. Within first days of lisuride administration these patients’ complaints resolved spontaneously and lisuride therapy was continued. All the 6 patients that lisuride was discontinued had developed severe nausea and vomiting between 2th and 15th days of treatment, and did not resolve with antiemetic drugs.

For two patients the drug was discontinued, because their dyskinesias increased in addition to nausea and vomiting.

There were no abnormalities in any of the tests of ECG, liver or kidney function.

But in two patients there was significant rises in blood glucose levels. One patient was an old diabetic and before the trial his blood glucose level was 158 mg/dl. After the trial it was 233 mg/dl. Other patient did not know that he was diabetic and basal glucose level was 240 mg/dl. After the trial it was 361 mg/dl.

There was no change in blood pressure values on standing or decubitus positions. There was no mental changes, hallucinations, mood elevations, drowsiness, digital vasospasm, weight gain or edema.

**DISCUSSION**

Levodopa is the most effective drug for the treatment of Parkinson’s disease (7,8,9). Levodopa therapy often produces fluctuating short duration responses in addition to dyskinesias as Parkinson’s disease persists beyond a few years. The short duration of responses to therapy with levodopa probably reflects, a progressive reduction of dopaminergic nigrostriatal terminals with diminished capacity to concentrate and decarboxylate levodopa and provide a storage pool of levodopa (10). Striatal stimulation would thus become directly dependent on fluctuating levels of dopaminergic substances in plasma, resulting in the marked fluctuations in the clinical picture (dyskinesias, on-off syndrome) (11). Pharmacologically these adverse effects are characterized by a gradual shortening of the antiparkinsonian response to levodopa and a progressive narrowing of its therapeutic window (11).

Dopamine agonists are a diverse group of drugs with differing chemical and physical properties. They have been developed in order to compensate the deficit of endogenous dopamine in the basal ganglia of Parkinsonian patients by direct stimulation of central dopamine receptors (7,12). The advantages of direct dopamine agonists are, their independence of the degenerating presynaptic neuron and do not depend on a pool of decarboxylase enzyme for converting into the active product, since during the course of the Parkinson’s disease the number of neurons projecting to the striatum declines and the activity of dopa decarboxylase diminishes. Most importantly they do not undergo oxidation and avoid the toxic byproducts of levodopa metabolism (7,12,13). Theoretically they reduce dopamine turnover and oxidative stress on surviving cells, thus decrease nigral cell death (13,12).

Lisuride has both dopamine D2 agonist and serotonin agonist effects. It’s dopaminergic effects were potansialised by recurrent take ins (14-16). For advanced Parkinson’s patients and the ones who have developed fluctuations, lisuride can be used either alone or with levodopa (17).

Some of the studies about lisuride’s effects when given levodopa have stated that, tremor improved more than the other parkinsonian symptoms (17,18). In another study tremor was less improved than the others (19). They also pointed out that all parkinsonian symptoms improved significantly (5,15,18).

In our study, we found significant improvement in all symptoms. Among them, tremor was less improved than the others. Total improvement in UPDRS was %21 and Hoehn & Yahr stage reduced from 3.0 to 2.3.

Among the patients that were with “on-off” phenomena, “on” periods were prolonged in a ratio of %37. All of the complications apart from dyskinetic movements has improved.

Among the side effects, we met more frequently with nausea and vomiting compared to similar studies and this was the main cause for discontinuing the drug. organic confusion syndrome is caused by serotonin agonist effect of lisuride and is seen at dosages higher than 2 mg. per day (17,15). Since we used lisuride in

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**Table 3. Results of treatment of lisuride combined with levodopa on the “on-off” effects in 8 patients.**

<table>
<thead>
<tr>
<th></th>
<th>Hours “on”</th>
<th>Total hours awake</th>
<th>% “on”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8’, 15”</td>
<td>16’, 22”</td>
<td>50.3</td>
</tr>
<tr>
<td>Range</td>
<td>5’-13’</td>
<td>14’-20’</td>
<td></td>
</tr>
<tr>
<td><strong>After</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11’, 7”</td>
<td>16’, 7”</td>
<td>68.9</td>
</tr>
<tr>
<td>Range</td>
<td>7’-14’</td>
<td>14’-20’</td>
<td></td>
</tr>
</tbody>
</table>

p<0.1
dosages below this level we did not meet with this side
effect.

Two of our patients’ blood glucose levels have
showed significant increase compared to basal levels.
The number of the patients in our group is not enough to
certain definitive terms on this issue. We don’t know if
this is related to lisuride and we couldn’t found any pa-
per, that drew attention to this issue. Anyhow it’s an
important effect and it must be investigated in wider
groups.

CONCLUSION

Lisuride is effective when given with levodopa to
advanced parkinsonian patients whose response to
levodopa have decreased. In addition to lessening park-
insonian disability, lisuride increased the number of “on”
hours and delayed the end of dose deterioration. Nau-
sea and vomiting are the frequent side effects.

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