CONTINUOUS INFUSION OF APOMORPHINE IN A SERIES OF THIRTY PATIENTS WITH PARKINSON’S DISEASE

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Abstract
Apomorphine is a dopamine agonist primarily used for the treatment of motor fluctuations and severe dyskinesias in late – stage Parkinson’s Disease. We retrospectively studied medical records of 30 patients who were on continuous apomorphine infusion treatment. They were evaluated for their disease characteristics, satisfaction for the therapy and adverse events. Results showed that 17 patients were satisfied with the therapy. The main reason of cessation of therapy (15 patients) was subthalamic nucleus deep brain stimulation. Arrythmia and subcutaneous nodules were relatively rare (3 patients). Results were compared with similar studies. Apomorphine therapy appears as a safe option for patients with motor complications and cognitive or neuropsychiatric problems.

Key words: Apomorphine, Parkinson’s Disease

Introduction
Apomorphine (10-11 dihydroxyaporphine) is a non – selective dopamine agonist, activating D1 and D2 – like receptors. It is found in 1869 by Matthiessen and Wright heating morphine with hydrocloric acid [1] and is the first dopamine agonist used for the treatment of Parkinson’s Disease (PD). It is used as either intermittent or continuous subcutaneous therapy. Today the main employment of apomorphine is for advanced patients with long – term motor complications like dyskinesias, motor fluctuations or unexpected “off” states. It is prominently offered as a choice for patients who are no longer adequately controlled by oral medications but unlikely to receive surgical treatments due to conditions like cognitive disability, prominent axial symptoms, surgical contraindications or personal choice.

In late stages, most patients with PD may experience sudden, unexpected “off” states. Intermittent usage of apomorphine appears as a good choice for rescue injections with its fast acting but short lasting effect. Also, severe motor fluctuations and dyskinesias in advanced patients are major problems and can relieve with continuous subcutaneous therapy. It is well known that, oral dopaminergic treatments fail to mimic endogenic continuous dopamine release and in time the therapeutic window narrows causing severe peak dose dyskinesias and “wearing off” conditions. It is reported that up to 50 % of patients experience motor fluctuations in two years time [2], and 50 % of patients, who receive levodopa treatment face dyskinesias after five years in the disease course. This is a major problem especially in younger – onset patients [3]. Manson and colleagues reported that, patients, who were given 6 mg/hr continuous apomorphine treatment as monotherapy showed 56 % reduction in dyskinesias [4]. The reduction in dyskinesia was 30 % in group taking additional oral dopaminergic treatment. The reason behind this result may be the reduction of oral dopaminergic treatment or the direct effect of apomorphine in the receptor activity in striato – pallidal pathways with continuous tonic stimulation [5] or both.

Orientation to using an subcutaneous therapy, necessity of pretreatment education, neuropsychiatric problems, skin nodules, heart problems and other systemic reactions are the main reasons for noncompliance. All these adverse effects require a close doctor – patient relationship. Here in this report we share our experience of patients with advanced PD who receive continuous apomorphine infusion therapy.

Method
We investigated our patients’ documents retrospectively and enrolled those used subcutaneous continuous apomorphine treatment.
Patients are categorized for their “age”, “duration and severity of disease”, “dosage”, “duration of treatment”, “benefit”, “reason for cessation”, “degree of subjective satisfaction” and “adverse events”. All patients were asked for their feedback for the treatment as; Very Good, Good, Moderate, Bad or Very Bad. Results were analysed and compared with similar reports.

**Results**

A total of 30 patients that received continuous apomorphine treatment between 2007 and 2011 were enrolled in this study. Sixteen of the patients were women. The mean age was 57.9, and mean duration of disease was 13.3 years. Patients’ mean Hoehn & Yahr stage was 3.7. The mean duration of therapy was 10.5 months and the mean dosage of infusion therapy were 4.83 mg/hr. In half of the patients, treatment was stopped (15 patients, 50 %) due to various reasons. Seventeen of them (83.3 %) were generally satisfied with the treatment (Figure 1). Twelve patients (80 %) that continued apomorphine treatment gave feedback as “Very Good” or “Good” (Figure 2). The main reason for cessation of infusion were subthalamic nucleus deep brain stimulation (STN DBS) in 6 patients (40 %), ineffectiveness in 3 patients (20 %) and prolonged of QT in 2 patients (13.3 %) (Figure 3). The problems that did not require cessation of treatment were peak dose dyskinesia (2 patients – 13.3 %), subcutaneous nodules (1 patient – 6.6 %) and orthostatic hypotension (1 patient – 6.6 %). Other reasons were about compliance problems of patients.

Figure 1: Feedback of All Patients For The Treatment

<table>
<thead>
<tr>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Good</td>
</tr>
<tr>
<td>2</td>
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</table>

Figure 2: Feedback of Patients That Continue Therapy

<table>
<thead>
<tr>
<th>Number of Patients</th>
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</thead>
<tbody>
<tr>
<td>Very Good</td>
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<tr>
<td>12</td>
</tr>
</tbody>
</table>

Figure 3: Reasons For Discontinuation

<table>
<thead>
<tr>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>STN DBS</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

STN DBS: Subthalamic Nucleus Deep Brain Stimulation

Table 1: Studies That Evaluated Apomorphine Infusion in PD
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Patients</th>
<th>Duration of Disease (years)</th>
<th>Duration of Therapy (months)</th>
<th>Mean Dosage (mg/hr)</th>
<th>Sedation, Hallucinations</th>
<th>Subcutaneous Nodules</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drapier/2012</td>
<td>23</td>
<td>13.9</td>
<td>12</td>
<td>3.5</td>
<td>0</td>
<td>23</td>
<td>Prospective</td>
</tr>
<tr>
<td>Elia/2012</td>
<td>10</td>
<td>16.7</td>
<td>52.2</td>
<td>2.9</td>
<td>1</td>
<td>5</td>
<td>Prospective</td>
</tr>
<tr>
<td>Manson/2002</td>
<td>64</td>
<td>15.7</td>
<td>33.8</td>
<td>6.1</td>
<td>2</td>
<td>2</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Our Study</td>
<td>30</td>
<td>13.3</td>
<td>10.5</td>
<td>4.8</td>
<td>0</td>
<td>1</td>
<td>Retrospective</td>
</tr>
</tbody>
</table>

**Discussion**

The goal of this study was assessment of patient satisfaction, reasons for discontinuation and adverse events for patients refractory for medical treatment, receiving continuous apomorphine infusion. Some of the patients were not suitable for STN DBS, but some stopped therapy and undergone surgery. Although reduction in “off” episodes were given in a range of 50 – 80 % and mean reduction in levodopa dose was given % 49 (+16 % to -80 %) in reviews [6]; continuous apomorphine therapy is still considered as “Plan B” for advanced patients refractory to oral medication. The reasons for this may be less efficacy and maintainability of apomorphine treatment compared with STN DBS. When effect sizes and adverse effect profiles were compared, from separate studies, reports favor STN DBS over apomorphine infusion and duodenal infusion [7, 8].

There are no studies which blindly compared the three techniques mentioned above. Generally, it is accepted that STN DBS provides greater reduction in “off” time and it is harder to discontinue oral medication under continuous apomorphine treatment [9,10]. For this reason we chose STN DBS unless the patient was very satisfied with apomorphine treatment. Old age, dementia, systemic medical problems of the patient, and patient preference are other factors which make us prefer apomorphine infusion treatment over STN DBS.

On the contrary, continuous apomorphine treatment is found safer than STN DBS in terms of neuropsychological functions that may result behavioral complications [9]. In accordance with previously published data, we failed to recognize any neuropsychiatric problems in our patients. Likewise, cognition is another feature that is not expected to worsen under apomorphine treatment. Most of the time, cognitive status of the patient appears as a prominent factor for choosing between surgical or apomorphine therapy. Under apomorphine treatment, neuropsychiatric problems do not worsen but improve and rarely, if observed any, reduction in dose may be enough to handle [4]. To our knowledge there is only one case attempted suicide under apomorphine treatment [11].

Apart from STN DBS, the main reasons for dropping out from therapy were lack of efficacy and cardiac arrhythmia. Cardiac arrhythmia is relatively less reported [6]. The underlying mechanism is not known but piperidine moiety of apomorphine molecule may be responsible for this effect. Although rare, we do recommend cardiac monitoring during initiation of therapy since most of the patients are elderly. Additionally, haemolytic anemia or positive “Coombs test” results should be kept in mind with apomorphine therapy. Nausea and orthostatic hypotension are peripheral effects that can rarely cause discontinuation, domperidon is helpful most of the time.
As mentioned above, dyskinesia improves with continuous apomorphine treatment. This is seen especially in monotherapy indicating that, transition from pulsatile to continuous receptor stimulation is the key factor for reversing changes in basal ganglia [12]. Most of the time, the reason for failure of reduction of dyskinesia under continuous apomorphine treatment is continuation of oral theraphies [13].

Orientation to a subcutaneous therapy may be quite problematic especially in the beginning. Some patients simply do not like the idea of needle treatment. Some find more difficult to adjust the dosage and some of them find difficult to carry the equipment all day. Patient education for compliance at the start of the therapy may reduce these problems.

During the therapy, almost all patients experience skin reactions and subcutaneous nodules. Sometimes these nodules may cause panniculitis, necroses and abscesses. Different studies report different numbers; in our opinion, this is because there is not a unanimous agreement on the definition of nodule. From mild skin reactions to severe abscesses are reported, but serious abscesses leading to necroses or infections are quite rare [14]. Usually, improving hygiene, changing injection site may avoid fibrosis and solve the problem. In our study we saw only one patient with subcutaneous nodule, and she had to discontinue. Patient education and monitoring skin reactions from the beginning may help avoid serious dermatologic problems.

**Conclusion**
Continuous subcutaneous apomorphine therapy is a dopamine agonist that is suitable for patients with motor fluctuations and dyskinesias resistant to best oral medication. It is probably a good alternative to surgical treatment and better tolerated by patients with dementia, severe systemic and neuropsychiatric problems.

**Note:** This study was presented as a poster in 47th National Congress of Neurology, Turkey 2011.

**REFERENCES**


Резюме

Непрерывная инфузия апоморфина у тридцати пациентов с болезнью Паркинсона

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Апоморфин является агонистом допамина, в основном используется для лечения двигательных расстройств и тяжелой дискинезии в конечной стадии заболевания Паркинсона. Мы ретроспективно изучили медицинские карты 30 пациентов, которые находились на непрерывной инфузии апоморфина. Они были оценены по характеристике заболевания, эффекту лечения и побочных явлений. Результаты показали, что 17 пациентов были удовлетворены терапией. Основной причиной прекращения терапии (15 пациентов) была глубокая стимуляция субтalamических ядер мозга. Аритмии и подкожные узелки были относительно редки (3 больных). Результаты сравнились с аналогичными исследованиями. Апоморфинная терапия является безопасным вариантом для пациентов с двигательными, когнитивными и другими психоневрологическими осложнениями.

Ключевые слова: апоморфин, болезнь Паркинсона.

XÜLASƏ

ПАРКИНСОУ XƏSTƏLİYİ OLAN OTUZ PASİYENTDƏ DAVAMƏDİÇI AПОМОРФİN İNFÜZİYASI

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Açar sözlər: apomorfin, Parkinson xəstəliyi.