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Review / Derleme

Apomorphine in the Treatment of Parkinson's Disease

Parkinson Hastalığı Tedavisinde Apomorfin

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Abstract

Apomorphine is a dopamine agonist used in the treatment of some motor and non-motor complications during Parkinson's disease, which could be administered as an intermittent or continuous infusion. Although apomorphine treatment has been shown to be effective on motor fluctuations and dyskinesias, there is no sufficient consensus regarding the administration of apomorphine test or infusion, and the management of the treatment. In this review, our aim is to create a "treatment management guideline," which includes recommendations for the use of apomorphine in the clinical practice, and to discuss the problems encountered in both intermittent and continuous infusion applications, in the light of the literature.

Keywords: Apomorphine, Parkinson's disease, treatment

Öz

Apomorfin, Parkinson hastalığı seyrinde görülen bazı motor ve non-motor komplikasyonların tedavisinde kullanılan, intermitan ya da sürekli infüzyon şeklinde uygulanabilen bir dopamin agonistidir. Apomorfin tedavisinin, motor dalgalanmalar ve diskineziler üzerine etkisi gösterilmiş olmasına rağmen, apomorfin testi ya da infüzyon uygulamaları ve tedavinin yönetimi ile ilgili yeterli fikir birliği yoktur. Bu derlemede amacımız, klinik pratikte apomorfinin kullanımı ile ilgili önerilerin yer aldığı "tedavi yönetim rehberi" oluşturmak ve gerek intermitan gerekse de sürekli infüzyon uygulamalarında karşılaşılan sorunları literatür bilgileri eşliğinde tartışmaktır.

Anahtar Kelimeler: Apomorfin, Parkinson hastalığı, tedavi

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease that is widespread in the entire nervous system which causes many non-motor clinical symptoms together with bradykinesia, rigidity, and tremor, mainly because of a progressive loss of monoaminergic neurons, especially in the substantia nigra. Although there are effective oral treatments (levodopa, etc.) especially for motor symptoms, because of the progression of neurodegeneration and the pulsatile effects of these oral treatments, most of the patients shift into the motor complication stage where motor fluctuations (end-of-dose worsening, on/off phenomenon, and dyskinesias) occur. Even in the fifth year of its onset, motor fluctuations could be observed at a rate of approximately 50% and dyskinesias at 40% (1). At this stage, one of the treatment options is to make dopaminergic stimulation as more continuous. For this purpose, although arrangements such as increasing the frequency of administration by adjusting the doses of the oral treatments and adding new oral treatments are recommended, invasive treatment is used as a good complementary treatment due to the limited effectiveness of those approaches (2). Apomorphine is an effective treatment for the control of both "off" periods and dyskinesias (3). The drug, which has been approved to use in the advanced stage of PH in many countries (also in our country since 2002), is administered as an intermittent or continuous infusion to control the motor complications. Although its effect on motor fluctuations and dyskinesia has been demonstrated in many of the open-label studies, little consensus has been established regarding the treatment management during the administration (4). In these reports, some recommendations made in the treatment management may differ from our clinical practice, and there are still unexplained areas (e.g., apomorphine test, dose adjustment of oral drugs during the infusion therapy, etc.). To assist clinicians in the practice of apomorphine treatment, this treatment management guideline was created in the view of our nearly 20 years of experience in the clinical use and literature information in both intermittent and continuous infusion therapy. In addition, we think that these guidelines will reduce the rate of frequently encountered discontinuation of the apomorphine treatment.

In the first phase of the guideline a task group was created including the eight movement disorder specialists from neurology departments from different universities who were the members of the Movement Disorders Working Group of the Turkish Neurological Society (B.E., Si.Ö., R.Ç., C.A., H.H., O.D., S.Ö., S.E.). At first, four main topics were determined for the apomorphine treatment management (patient selection, apomorphine test, initiation of intermittent and infusion therapy, treatment management and management of side effects), and task distribution was made within the group (two faculty members for each topic). The titles, which were prepared by considering the necessary literature review and experience in the clinical practice, were discussed in five consecutive meetings with the participation of other faculty members and the report was prepared. At the last stage, it was presented in writing to the Movement Disorders Working Group of the Turkish Neurological Society, and their suggestions were received, later the report was finalized by making the necessary changes.

Apomorphine Treatment in Parkinson's Disease

Apomorphine is a non-ergo-derived dopamine agonist with high lipophilicity, capable of producing short-term agonistic effects on D1 and D2 receptors. It was first obtained by Matthiessen and Wright in 1869 by heating the morphine in an acidic environment (5). It is emetic property, which was initially detected, attracted attention and it was recommended in the acute treatment of poisoning (6). The first studies examining the effect of the drug, which was subjected to unsuccessful trials in the various psychiatric and neurological diseases in the following years, where PD has begun in the 1950s (5,7). Although clinical efficacy was clearly demonstrated with a subcutaneous injection in subsequent studies, even at a level comparable to levodopa, the side effects of nausea and vomiting limited the use of the drug (8,9). However, with the demonstration that this temporary side effect could be controlled with peripherally acting anti-dopaminergic drugs (especially domperidone), and the development of technologies used in the form of drug administration (pump technologies), clinical use has started to increase since the early 90s, and it has become an option in routine clinical treatment with the approval of its' use in many countries (10,11,12).

With an intermittent use, an improvement of >90% in the motor scores of the patients and an average of 60% decrease in the daily "off" times could be achieved with the injection administered during the "off" periods (13,14,15). The onset of a significant clinical effect after the injection is 5-10 mins, and the duration of effect is between 1 and 2 hrs. After the first effective dose adjustment, it does not require dose adjustments in long-term use. Because of these features, intermittent injection is considered a good "off" period rescue treatment. However, it may cause an increase in the duration and severity of dyskinesia, especially in the patients with "on" period dyskinesias. Continuous subcutaneous infusion is the preferred method of administration in the patients with "off" periods (long-term or frequent) that are difficult to control with intermittent injection and in the presence of severe dyskinesia (13).

Continuous infusion of apomorphine as monotherapy or along with the existing oral treatments in patients at the stage of motor complications was shown in open-label studies to provide approximately 60% reduction in the daily "off" times and approximately 33% reduction in the dyskinesia scores (16,17,18). In a recent placebo-controlled, double-blinded multicenter study (TOLEDO study), consistent with these data, the infusion reduced the total "off" times in a day by 2.47 hrs, which was more significantly different from the placebo. It was determined that the "on" periods were extended by 2.77 hrs. In addition to this effect, there was a significant decrease in the doses of oral drugs of the patients, and no serious side effects were reported (19). These results show that continuous infusion therapy is comparable to other invasive treatments (e.g., Deep Brain Stimulation and Levodopa Intestinal Gel Injection) in reducing both daily "off" times and dyskinesias (20).

The clinical recommendations of our group (patient selection, apomorphine test, initiation of intermittent and infusion therapy, treatment management, and management of side effects) in the treatment of apomorphine, which is effective in controlling the motor complications are as follows:

1. Patient Selection

Selection of an appropriate patient is crucial for the success of apomorphine therapy. The responsibilities of the patient and caregiver are high, as the form of treatment requires an invasive

administration method minimally (continuous infusion with a pump or intermittent injection). For this reason, before starting the treatment, the responsibilities of the patient, caregiver, and the things to be done during the application should be explained in detail, and it should be ensured that they could apply the treatment. Ideally, the patient should be motivated for the treatment and have good caregiver support. Suitable candidates are the patients with an idiopathic PD who respond to levodopa and experience motor fluctuations and/or dyskinesias that cannot be controlled by the oral therapy. Patients with "Parkinsonism plus" syndromes may have a partial response to levodopa in the early stages of the diseases should be excluded, and the diagnosis of PD should be ensured. Otherwise, the effectiveness of the treatment will be weak.

Intermittent apomorphine therapy is a preferable agent for the patients' experiencing periods of motor fluctuation such as end-of-dose worsening or morning problems (akinesia/dystonia) despite the appropriate oral treatments, patients with a delayed onset of drug effect due to an impaired absorption of oral levodopa or problems of gastric emptying, and the patients with unpredictable motor or non-motor closures.

Continuous infusion therapy is indicated in all the patients in whom intermittent administration is indicated and who need a daily dose of >4-6 injections, or whose off periods last longer than the effect of the intermittent injection, or who have uncontrollable severe dyskinesia that adversely affect the daily life, or who cannot take oral medication and require an immediate dopaminergic drug administration (perioperative periods, Parkinsonism hyperpyrexia syndrome) (Table 1).

Conditions to be careful about because of the side effects that may occur in the apomorphine treatment are AV block and long QT syndrome, hemolytic anemia, orthostatic hypotension, severe systemic diseases (e.g., liver, kidney, or heart failure), history of severe psychosis, and the use of anticoagulants.

Table 1. Indications for apomorphine treatment (not improving enough with oral treatments)

Apomorphine rescue injections:
• Predictable "OFF"s (end-of-dose worsening, etc.)
• Unpredictable "OFF"s ('ON-OFF' phenomenon)
• Presence of disabling non-motor complications (such as pain, mood disorders) associated with "OFF" periods
• Delayed gastric emptying (gastroparesis)
• Early morning akinesia or dystonia
Apomorphine infusion:
• Very frequent need for rescue doses of apomorphine injection (≥5 administrations/day)
• "OFF" periods longer than the duration of the effect of intermittent therapy
• Severe dyskinesias that cannot be controlled and negatively affect the daily life
• When levodopa-carbidopa intestinal gel infusion or deep brain stimulation (DBS) is contraindicated, or these invasive interventions are not accepted by the patient
• In the pre-DBS or perioperative period, which requires immediate dopaminergic drug administration, where no oral medication could be taken
• Nocturnal symptoms that cannot be controlled by oral therapy

Although there was no strong evidence that apomorphine could cause QT interval prolongation, it was reported especially during the apomorphine test, and a warning letter was published by the manufacturer in the later period (21,22). Although this effect was not observed in later studies, the warning to be careful about the QT interval continued (21).

Hemolytic anemia is a relative contraindication. Drug-induced autoimmune hemolysis has been reported very rarely in the literature, as case reports with the dopaminergic drugs including levodopa (23). There are only a few case reports involving the patients receiving the apomorphine infusion therapy (24,25). Therefore, we do not recommend the apomorphine test and the Coombs test as a necessary preliminary examination to examine the presence of hemolytic anemia before the intermittent use. However, if continuous infusion therapy is to be preferred and the patient does not receive an intermittent therapy, the Coombs test could be performed. In the transition from the intermittent to infusion therapy, the Coombs test is not mandatory in our opinion.

Neuropsychiatric findings due to the advanced age or dopaminergic treatments, mild hallucinations and moderate cognitive impairment do not create a contraindication for the apomorphine treatment. However, the presence of advanced dementia and psychosis constitutes a contraindication.

2. Apomorphine Test

The purpose of testing when starting apomorphine treatment is to find the effective dose of apomorphine for the treatment in the patient, to observe the possible side effects and sometimes to evaluate the dopaminergic response. Evaluation of dopaminergic response may be used for diagnostic purposes.

During the test, side effects such as temporary nausea-vomiting, orthostatic hypotension, and fatigue may occur. To prevent the side effects such as nausea, 3x10 mg domperidone tablets are started three days before. Domperidone 20 mg should be used in the morning of the test day.

Before testing, a consent form describing the possible side effects should be obtained from the patients. In this form, treatable side effects that may occur during the test (e.g., nausea, vomiting, hypotension, arrythmia, fatigue) should be explained and it should be stated that the patient will be followed up by the doctor and nurse during the test.

Suggested tests before the procedure are electrocardiography (ECG), routine blood tests (complete blood count, liver function tests, electrolytes), and evaluation of orthostatic hypotension.

In addition, domperidone, which is used to prevent the nausea and vomiting, is a drug that may cause conduction block. Domperidone was a drug of which parenteral use was discontinued due to arrhythmias, sudden death, and cardiac arrests observed with its intravenous high-dose administration in the 1980s. However, its oral use continues in the following years.

More recently, in two case-control studies, a mild increase in ventricular arrhythmia and cardiac arrest rates was reported in patients >60 years of age, when used for > one week and at doses >60 mg, in patients with hepatic failure and concomitant use of the drugs that were degraded by the cytochrome P_{450} enzyme system, and in the presence of severe electrolyte imbalance. Since

2014, the European Medicines Agency Pharmacovigilance Risk Assessment Committee has issued recommendations restricting the use of domperidone to the patients younger than 60 years, at doses <30 mg/day, and only for a short time (up to 7 days) (26). In a recently published population-based study based on at least 10 years of screening, the risk of ventricular arrhythmia was found to be increased with the use of domperidone. In the study, it was shown that this risk was significantly lower compared to the other prokinetic agents, and it was reported that it could be used safely in the patients for this reason (27). In the light of these data and our observations during its long-term clinical use, ECG should be done before the procedure in patients and caution should be taken in patients with long QT intervals. We think that domperidone at a dose of 10 mg/three times a day could be used for one month with a clinical observation, and ECG monitoring is required when it is necessary to use it for longer periods. In addition, caution should be exercised when using drugs that act on cytochrome P_{450} enzyme, and in cases of liver failure or electrolyte imbalance.

The apomorphine test could be used both to find the appropriate dose of apomorphine to which patients will respond, and to test the dopaminergic response. When used for diagnostic purposes in PD, its predictive value is approximately 85% (28). Testing should be performed in a clinic or medical office to monitor the blood pressure, determine the effective dose, monitor the side effects and, if necessary, provide an appropriate intervention, and train the patient or family member. All PD treatments should be discontinued at least 12 hrs before the test, as patients must be in the "off" phase. As this may cause discomfort in patients, it is recommended to perform the test in the morning. Motor examinations should be performed immediately prior to the procedure, which will be used to assess the response. For this, the 30-second finger tapping test (the number of finger tapping is evaluated during the period) or the walking test (the time the patient gets up from his/her seat and walks 6 meters forward and sits back down, and the number of freezes during the test) may be used. In the numerical values of these tests, 25% or more improvement will be considered as a positive response. If testing is performed for more specific symptoms (tremor, non-motor, etc.), related items of the Unified PD Rating Scale could be used. A 30% improvement in this score means a positive response. However, these rates only show the presence of dopaminergic response in the patient. For adequate control of the "off" periods, the patient's motor response must be maintained at a sufficient level and for a sufficient period for functionality. For this reason, the dose may be increased until the desired functionality is achieved, and observations are made if the patient's "off" periods.

Although there are different recommendations in the test application, our recommendation is to start the test with 1.5 mg SC injection to shorten the test time, to observe for at least 30 mins after the injection, to continue by increasing the dose for 40 mins after the injection if the patient does not respod or at least 60 mins after the injection if there is an insufficient response (Figure 1) (29). The injection site should be changed with each new dose to avoid the irritation. If adequate response is not seen, the doses are increased to 3 mg, 5 mg, and 7 mg, respectively. If there is no response with a 7 mg injection, it means no response. However, if there is a response with 7 mg but it is insufficient, the 10 mg dose also could be tested. If side affects such as mild nausea, etc.

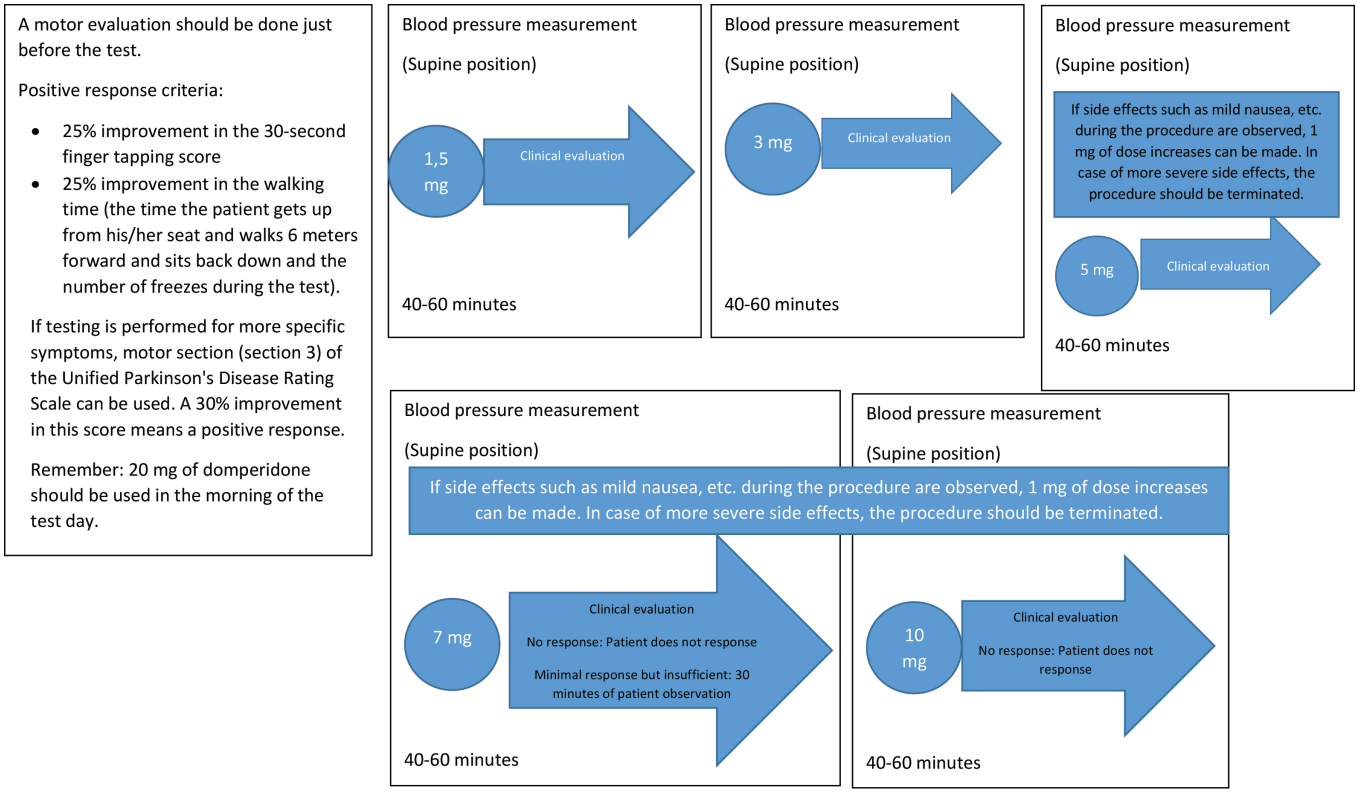

Figure 1. Apomorphine test

during the procedure are observed, 1 mg of dose increases could be made. In case of more severe side effects, the procedure should be terminated. After the appropriate dose is found, the necessary education could be given to the patient and his/her relatives and further treatment could be started (Figure 1).

3. Intermittent Treatment

Intermittent injection is a suitable form of administration for the patients with "off" periods, each lasting approximately 1-1.5 hours, at most 4-5 times a day. However, if the patient has dyskinesias in the "on" period along with these "off" periods, it should be noted that there may be an increase in these dyskinesias, and in this case, it is a better to start a treatment with continuous infusion (29).

In the apomorphine injections used for the patient's "off" periods in an intermittent therapy, no dose adjustment is required for the patient's other oral medications. If the complaint of nausea occurs, domperidone 10 mg three times a day may be continued for one month, paying attention to the above recommendations. To increase the patient's compliance with the treatment, at discharge, the patient should be given a phone (support nurse and the center where the application is made) that he/she may constantly reach for any problems (side effects, lack of material, drug supply, etc.). Making a phone or telemedicine call about 10 days later for the first control will increase the patient's sustainability for the treatment.

4. Infusion Therapy

Continuous infusion therapy is the preferred method of administration in the presence of the need for an average of five or more intermittent injections during the day (wake-up hours), long-term "off" periods (where the duration of action of the intermittent therapy is insufficient), and/or in the presence of dyskinesia that is disabling the daily life activities. When starting the treatment, it is more convenient to follow the patient by hospitalization, manage side effects, provide an appropriate education to the patient and their relatives, and make the dose adjustments faster.

If the patient is not under intermittent apomorphine treatment and infusion therapy is started directly, to reveal similar risk of side effects and contraindications as in the apomorphine test and intermittent administration, ECG examination, routine blood tests (complete blood count, liver function tests, electrolytes), and evaluation for orthostatic hypotension should be performed before the procedure. Risky situations that may occur are same as those specified in the apomorphine test. However, we recommend performing the Coombs test to reduce the risk of hemolytic anemia in the patients who will start treatment with infusion for the first time. This examination is not required for transitions from an intermittent therapy to continuous infusion.

When starting treatment, it is recommended to connect the infusion pump preferably in the morning and infuse for a maximum of 16 hours. It is important to use the treatment during the daytime when the patient is awake, not to infuse at nighttime except for very severe nighttime symptoms, and to avoid 24-hour infusion in terms of decreasing the side effects.

From the beginning, the patient and his/her relatives are provided with a practical training supported by the visuals, and the support for the procedure is continued until the patient or his/her relative may perform this procedure alone. There should be communication channels (support nurse, movement disorders nurse, doctor, etc.) that the practitioner and the patient may reach at any time.

The dose of levodopa is reviewed from the first day according to the indication of the started infusion (it may not be changed if it has been started for long "off" periods, the dose could be reduced from the first day in the indication of severe dyskinesia). Dosage of dopamine agonists should be reduced as soon as the infusion is started, as this may increase the incidence of side effects. Dopamine agonists may be given at nighttime, at the end of low-dose infusion therapy. Since withdrawal symptoms may occur, if oral dopamine agonists are to be discontinued, they should be reduced gradually over the weeks. Monoamine oxidase-B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, anticholinergics may be gradually discontinued within the days, starting from the first day.

It is preferred that the treatment be done in the hospital, but if there is a support from the treatment nurse, the treatment could be started by making the longer interval of dose adjustments at home with a close follow-up. In this case, observation of the therapeutic nurse and close contact with the doctor are important. The infusion may be started in the morning at a dose of 1.5 or 3 mg/hr. If the patient has a severe "off" complaints, a dose of 3 mg/s may be preferred, and if there are milder complaints and dyskinesia, a dose of 1.5 mg/h may be preferred. If the transition to continuous infusion is made after the intermittent use, the effective bolus dose may be adjusted as an hourly starting dose in the patients. Dose increases may be made at 1-to-4-hour intervals in hospital, or with 1 mg/h weekly increments in the home settings, depending on the clinical effect. If the effect starts late, "morning bolus" dose; and in patients with daytime stiffness, "intermediate bolus" doses should be defined. Doses of long-acting levodopa should be added to the control nocturnal symptoms at the end of the infusion.

In a comparative study, a 64% reduction in the dyskinesia severity in patients who could receive monotherapy was reported to be 30% in polytherapy (infusion in addition to oral treatments) (30). These findings suggest that monotherapy is more effective when it is aimed to reduce dyskinesias. Our clinical observation is that monotherapy may be used in patients in whom there is difficulty in controlling the dyskinesia.

5. Side Effects and Management

The most common side effects that occur during apomorphine therapy, either intermittently or as a continuous infusion, are injection site-related nodule formation and other skin reactions. In addition, nausea-vomiting, sedation, neuropsychiatric side effects, ineffectiveness, and compliance problems with pump application are may be encountered.

- **Nodules**

Although subcutaneous nodule formation is a very common side effect at any time of the treatment in patients with apomorphine therapy, it is rarely a reason for discontinuation of the treatment, and it may also rarely cause necrotic ulceration and abscess formation. Although it is seen less frequently in the intermittent treatment, a frequency of 40-70% has been reported in continuous infusion (19,31). Possible cause is allergic panniculitis against the product ingredients. Although rare, it may cause serious skin

problems, so preventing its occurrence is the primary approach. Inspecting the injection sites at each control of the patient will ensure that nodules that are not complained of are detected, that the patient and their relatives are re-informed about the necessary precautions about the application, and that any deficiencies are to be corrected. Cleaning the area with soapy water before the injection is a good preventative approach. Injection sites should also be changed constantly. The most suitable injection sites is the abdomen, the areas below the umbilicus, at least 2 cms from the midline, and up to the thigh region (Figure 1). It is necessary to change the side of the area to be injected (right-left/bottom-upper), and when it is the turn of the same area, it should be applied at least 2 cms away from the previous injection site in that area. In addition, if there is nodule formation, injection should not be made over the nodule. This situation both reduces the effectiveness of the drug and increases the risk of ulceration. Especially the patients receiving an infusion therapy, if there is a swelling at the injection site after the infusion set is removed, squeezing the area slightly to make it bleed, cleaning the infusion sites with a soapy cloth and applying massage with massage balls, and applying creams to increase the blood supply to these areas (Hamamelis virginiana) (witch hazel) containing Hametan® and equivalents, ruscogenin/trimebutin containing cream etc.) will reduce the nodule formation. If a nodule occurs, steroid pomades may be applied to this area, if there is no open wound. In dense nodule formations, therapeutic ultrasound doses (3-5 Hz, 0.5 W/cm^2, 3-7 mins, continuous or pulsed mode, 3 times a week) could be used (32,33).

- **Sedation**

Although it has been reported as a side effect seen at a high rate (~40%) especially in long-term infusion therapy studies, our clinical experience shows that it is not a side effect encountered with this frequency (18). There are other conditions that may cause this side effects, which is usually considered to be temporary. Hypothyroidism and metabolic causes should be investigated, and concomitant medications that may have sedative effects should be questioned. If daily life is adversely affected, the dose may be reduced. Modafinil and similar stimulant treatment agents are generally ineffective (34,35).

- **Neuropsychiatric Side Effects**

Impulse control disorder and psychosis may occur during the treatment with dopamine agonists. These side effects are probably due to the D3 receptor agonistic effect (36). However, these side effects are seen less frequently during the apomorphine treatment (37). Despite the non-selective agonistic effect of apomorphine on dopamine receptors (like dopamine), its much lower affinity for D3 receptors and 5-hydroxytryptamine 2A receptors, which may be responsible for hallucinations, probably explains this situation (38,39). Therefore, apomorphine treatment may be tried in patients who experience these problems under the treatment of other dopamine agonists (40). Even if the incidence is low, the patient should be questioned for these complaints (hallucination, impulse control disorder, psychosis, etc.) during the treatment. When neuropsychiatric problems are seen; examination of the possible structural and metabolic causes (intracranial space-occupying formations, thyroid dysfunction, electrolyte imbalance, infection, etc.), questioning of concomitant drugs (another dopamine agonist, anticholinergic, amantadine, etc.), and if detected, it should be discontinuated, questioning of dementia and if detected initiation of an appropriate cholinesterase inhibitor therapy, and if improvement is not achieved, a reduction in the dose of apomorphine may be recommended.

- **Loss of Efficacy**

It is the decrease or disappearance of a long-lasting positive efficacy. It is one of the most common reasons for leaving the treatment (41). If it occurs in the early phase of the treatment, the dose adjustment of the PD drugs that the patient is taking may be done quickly, and dose adjustment may be required. Under the normal conditions, the dose of apomorphine that the patient responds to does not change for many years during the treatment (42). The most common causes of loss of efficacy over a time are disease progression and decreased dopaminergic response. However, when unresponsiveness develops, the diagnosis of the patient should be re-questioned. The early, albeit temporary, dopaminergic treatment response in Parkinsonism plus syndromes may sometimes lead to misdiagnosis (43). However, in such cases of sudden loss of efficacy, technical problems (expiration date of the drug, injection into the nodule, etc.) must be questioned.

- **Compatibility Issues**

As in all interventional treatments, patient and caregiver compliance is very important in apomorphine treatment, especially in continuous infusion treatment. The process of installing and dismounting the pump is a situation that requires responsibility and is one of the reasons for leaving the treatment. To avoid these problems, the patient and his/her relatives should be discussed in detail, and the responsibilities and side effects should be fully explained while deciding on the appropriate patient for the treatment. In addition, during the treatment, patients and their relatives should be able to share their problems and reach the physicians or responsible nurses easily. In this process, the patient support nurse program is very useful and increases the ease and compliance of the process for both the physician and the patient (44).

In conclusion, although the efficacy of apomorphine therapy on motor complications in PD is known, a guideline on treatment management during and after the administration has not been established. We have created a guide that may be used in both intermittent and continuous infusion therapy to assist the clinicians in the practice of apomorphine administration in view of our 20 years of experience in the clinical use and literature information, and we think that with these guidelines applications, a decrease in the rates of discontinuation, which is frequently encountered in clinical practice, will also be achieved.

Ethics

Peer-review: Internally peer-reviewed.

Concept: S.Ö., S.E., B.E., S.S.Ö., R.Ç., M.C.A., H.H., O.D., Design: S.Ö., S.E., B.E., S.S.Ö., R.Ç., M.C.A., H.H., O.D., Data Collection or Processing: S.Ö., S.E., B.E., S.S.Ö., R.Ç., M.C.A., H.H., O.D., Analysis or Interpretation: S.Ö., S.E., B.E., S.S.Ö., R.Ç., M.C.A., H.H., O.D., Literature Search: S.Ö., S.E., B.E., S.S.Ö., R.Ç., M.C.A., H.H., O.D., Writing: S.Ö., S.E., B.E., S.S.Ö., R.Ç., M.C.A., H.H., O.D.

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