sciendo
10.2478/AMB-2025-0030

CASE REPORT

PERIOPERATIVE TREATMENT WITH HIGH DOSE ROTIGOTINE AND AMANTADINE COMBINATION IN A PATIENT WITH ADVANCED STAGE PARKINSON'S DISEASE AFTER ESOPHAGECTOMY

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Abstract: *Current treatment for Parkinson's disease (PD) includes: levodopa, dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, anticholinergics, clozapine and deep brain stimulation. A lot of patients with PD undergo surgery under general anesthesia for abdominal operations with a long fasting period. Interruption of antiparkinsonian drug therapy for long periods of time may worsen the PD symptoms. This is why parenteral substitution of antiparkinsonian medications during the complete fasting period is advised. Herein we present a case of a resistant to usual medication doses PD patient, who underwent total esophagectomy and was treated postoperatively with a combination of high dose rotigotine and amantadine.*

Key words: *esophagus, esophagectomy, Parkinson's disease, rotigotine, amantadine*

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Received: *30 September 2024;* ***Revised/Accepted:*** *28 October 2024*

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder, caused by dopamine deficiency in the basal ganglia, presenting with motor and non-motor symptoms [1]. Current treatment for PD includes: levodopa, dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, anticholinergics, clozapine and deep brain stimulation [2]. Treatment selection depends on the severity of symptoms and extrapyramidal side effects. In Bulgaria (the country where the case is originally from) the following PD treatment options exist: levodopa/benzerazide tablets, carbidopa/levodopa/entabapone intestinal gel, bromocriptine tablets, ropinirole tablets, rotigotine transdermal patches, pramipexole tablets, selegiline tablets, rasagiline tablets, amantadine tablets and infusion solution, clozapine tablets and deep brain stimulation (for highly selected patients only).

A lot of patients with PD undergo surgery – urological, ophthalmological and orthopedic procedures, but also abdominal operations that cause temporary postoperative ileus. Postoperative ileus is a primary ileus that is caused by surgical trauma. After abdominal surgery gastric motility recovers 24-48 hours postoperatively, small-bowel motility recovers almost

immediately or never seizes and the colon starts to function 48-72 hours after the operation [3].

Esophagectomy is an extensive thoraco-abdominal operation that causes massive tissue trauma. The postoperative recovery is prolonged and the postoperative strategy – complicated. There is still a debate upon institution of early enteral nutrition after esophagectomy and many surgical teams choose to advise on a long postoperative fasting for various reasons, including a fear of anastomotic leaks [4]. Moreover, malabsorption is a common significant postoperative complication after esophagectomy [5]. Therefore, we cannot rely on oral medication for PD symptom control after esophagectomy because of the significant postoperative changes in gastrointestinal motility and function.

The biggest problem that emerges for PD patients that need an esophagectomy is that interruption of antiparkinsonian drug therapy for longer than 6–12 h may worsen the PD symptoms, cause parkinsonism-hyperpyrexia syndrome or akinetic crisis [6]. This is why intensivists must consider using non-oral PD medication in order to avoid these complications.

There are only a few studies with limited number of patients that discuss abrupt change of medication from oral levodopa (or other oral medication) to a non-oral substitute during the postoperative period. Wüllner et al followed a group of 14 postoperative PD patients on levodopa that got substituted with an equivalent dose of rotigotine. 12 of them had no neurological complications and 1 suffered hallucinations [7]. Subcutaneous apomorphine infusion is also an option for levodopa substitution during postoperative fasting. Four patients with severe PD that were on levodopa were abruptly switched on continuous subcutaneous apomorphine infusion for 4-15 days and all of them did well [8]. Galvez-Jimenez and Lang report 2 more patients that were switched from levodopa to subcutaneous apomorphine (both not on continuous infusion but on a bolus regimen) after surgery and both suffered no severe complications [9]. Postoperative amantadine infusion as a substitute for oral antiparkinsonian medication was studied only in a small group of patients. They reported satisfactory control of their PD symptoms and did not experience any amantadine side effects [10]. Recent studies evaluate the role of subcutaneous and intravenous levodopa in severe PD cases but not as oral medication substitutes in the postoperative period [11–13].

Herein we present a case of a patient with severe PD, who underwent total esophagectomy and was managed postoperatively with a combination of high dose rotigotine and amantadine.

CLINICAL CASE DESCRIPTION

A 62-year-old male presented to our thoracic surgery department with complaints of dysphagia and weight reduction of 10 kg in the last 6 months. He was diagnosed with an esophageal stricture and was scheduled for elective esophagectomy. Eight years ago he was diagnosed with PD, which was treated with levodopa/ benzerazide 1000 mg/ 250 mg/d and pramipexole 2,5 mg/d. He complained of tremor, rigidity, loss of balance, slowness of movements and difficulty walking. He also experienced some on-off symptoms with worsening of the tremor and stiffness, making walking without assistance challenging. Physical examination showed cogwheeling in the knee, elbow and wrist joints.

The planned surgical procedure was complex, necessitating a long postoperative complete fasting period, during which the patient would not be able to take his oral antiparkinsonian medications.

In order to optimize his PD therapy for the perioperative period, he was admitted to a neurology department. There he was gradually weaned from oral levodopa/ benzerazide and pramipexole and was substituted with transdermal rotigotine 32 mg/d in combination with intravenous amantadine 400 mg/d.

Surgery was carried out on the 7-th day without oral antiparkinsonian therapy. We performed subtotal esophagectomy with an intrathoracic termino-lateral esophagogastroanastomosis and pyloroplasty.

During the first two postoperative days the patient received total parenteral nutrition and the prescribed doses of antiparkinsonian medications. On the third postoperative day he started to take 250/50 mg levodopa/ benzerazide via a nasoduodenal tube along with the high dose rotigotine and amantadine. In the next four days the levodopa/benzerazide and pramipexole doses were increased to the patient's usual preoperative intake, while the rotigotine and amantadine were gradually weaned. On the fourth postoperative day he showed signs of hypoactive delirium. In addition, he experienced mild stiffness in the lower extremities, which lead to difficulties in ambulation.

The patient was discharged on the twelfth postoperative day with recovered intestinal passage and on his usual oral antiparkinsonian medication regimen without any significant neurological complications.

DISCUSSION AND CONCLUSIONS

During the fasting period after abdominal surgery PD patients have to receive an alternative non-oral PD medication regimen, substituting their usual oral PD

medication. Experts suggest transition from levodopa to either transdermal rotigotine or subcutaneous apomorphine [6, 14]. Intravenous amantadine was also studied in a limited number of postsurgical patients and showed promising results [15].

In Bulgaria rotigotine transdermal patches, intravenous amantadine and subcutaneous apomorphine are available as non-oral PD medication. Rotigotine can be bought with a regular prescription directly from the pharmacy. On the other hand, apomorphine is prescribed via a special protocol for chronic PD treatment from our National Healthcare Fund and is reserved for patients that do not respond well to oral levodopa. In our case the patient was satisfied with his oral levodopa preoperative treatment and did not want to switch to an apomorphine pump permanently. Because of that he was not eligible for an apomorphine pump. Therefore, we decided to try a substitution regimen with transdermal rotigotine, which could be bought on the free market.

According to Mariscal et al. 8 mg of rotigotine are equivalent to 300 mg levodopa [6]. Our patient was taking 1000 mg levodopa/d, which had to be substituted for a rotigotine dose of more than 24 mg/d. Additionally, our patient was taking pramipexole, which necessitated an even higher rotigotine dose.

In a meta-analysis of Korczyn et al, which included 45 advanced stage PD patients, the rotigotine dose was 22.5 mg/d. According to these authors rotigotine doses up to 24 mg/d are considered as safe (outside of the perioperative context) [16]. In our case 24 mg/d rotigotine would have only substituted 90% of the patient's oral levodopa and none of the pramipexole. This is why we decided to titrate the rotigotine dose gradually to 32 mg/d.

There are two dopamine switching regimens – slow and rapid. In slow titration the dose is tapered over several weeks, while with the rapid titration, the two dopamine agonists are being switched safely overnight [17, 18]. We decided to undertake slow titration because: 1. The total dose of 32 mg/d rotigotine was very high and we did not know what kind of side effects it can induce; 2. If rapid titration the night before surgery had been unsuccessful, we would have discovered this after the esophagectomy and we would not have been able to switch back to oral or enteral levodopa because the patient would have been in a complete fasting period.

Despite the fact that no published clinical trial or even case report suggest a combination rotigotine with any other dopamine agonist, we decided to include 400 mg/d amantadine in the patient's treatment because we did not want to increase the rotigotine dose too much above the recommended safe dose. Furthermore, according to product specifications, amantadine is indicated for intensive care and first line treatment for akinetic crisis. While rotigotine is suitable for the chronic PD symptoms, amantadine will aid the prevention of an acute akinetic crisis – an event that will impair significantly the postoperative rehabilitation. Early ambulation of surgical patients is also a great contributing factor to restoration of gut passage and initiation of enteral nutrition.

On this dose regimen our patient experienced only mild PD symptoms (stiffness in the lower extremities) in the context of an ICU-induced hypoactive delirium.

High dose rotigotine regimen with addition of amantadine can be a feasible option for an alternative antiparkinsonian drug regimen for patients on high doses of oral levodopa and pramipexole during the early postoperative period after surgery of the gastrointestinal tract.

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

Funding: *The authors did not receive any financial support from any organization for this research work.*

Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

Informed Consent for a Clinical Case: *Written informed consent was obtained from the patient for the publication of this case report.*

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