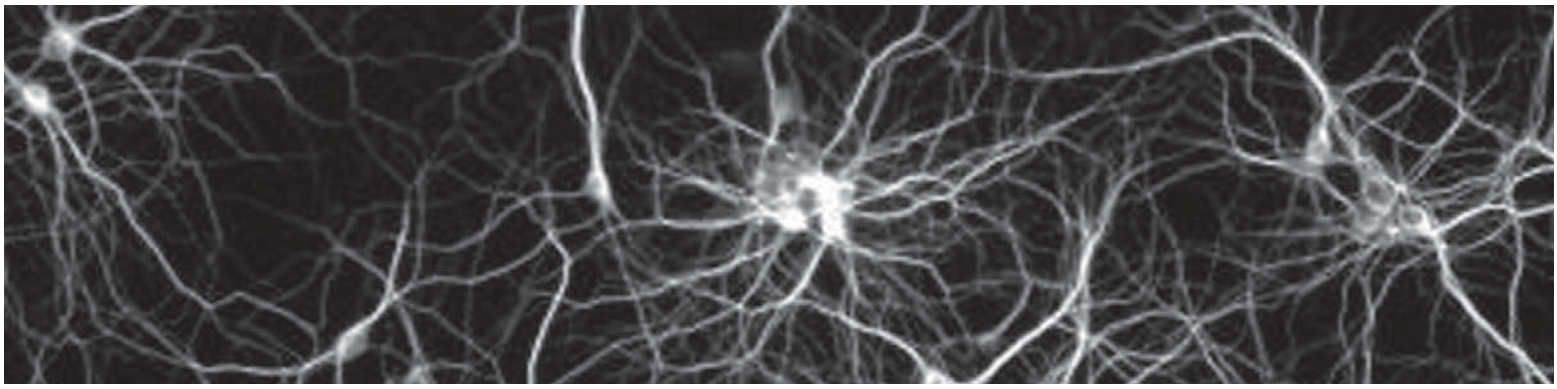

Bradycardia caused by accidental intake of high dose pramipexole

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ABSTRACT - A "treatment naïve" Parkinson's disease patient experienced an attack of bradycardia due to accidental intake of a high dose of pramipexole. The 83-year-old male patient with extrapyramidal symptoms and a history of high blood pressure, myocardiopathy and atrial fibrillation was accidentally administered 3 mg of pramipexole during hospital stay. Three hours later, he developed bradycardia and hypotension, but he recovered completely in one hour. Twenty-four-hour ECG showed basic fibrillation rhythm with an average heart rate of 55/min, minimal heart rate of 23/min and maximal heart rate of 102/min. Upon gradual introduction of levodopa and ropinirol extended-release formulation in therapy, the patient was free from cardiovascular symptoms. Twenty days later, repeat 24-hour ECG showed no evidence of bradycardia. Although bradycardia is described as a frequent side effect of dopamine agonists, pramipexole can rarely cause bradycardia as an adverse event. This patient report is important as a warning of this rare adverse event of pramipexole, while pointing again to the need of low and slow titration of dopamine agonists.

Key words: pramipexole; dopamine agonists; Parkinson's disease; bradycardia

INTRODUCTION

We report on a "treatment naïve" Parkinson's disease patient who experienced an attack of bradycardia and hypotension due to accidental intake of a high dose of pramipexole.

CASE REPORT

An 83-year-old male patient was admitted to University Department of Neurology, Osijek University Hospital Center for examination and treatment of rest tremor in his left hand. He had a history of high blood pressure, myocardiopathy and atrial fibrillation, and his regular therapy consisted of methyldigoxin 2x0.1 mg, warfarin sodium 3 mg, candesartan cilexetil 8 mg and carvedilol 2x6.25 mg *per* day. On day 2 of his hospital stay, before any treatment for Parkinson's disease was started, the patient was accidentally administered 3 mg of pramipexole instead of 3 mg of warfarin sodium. Three hours later, the patient complained of nau-

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sea, turned pale, and was covered with cold sweat, felt weak and vomited. He had no chest pain and was not losing consciousness. His blood pressure was 90/60 mm Hg and heart rate 42/min. ECG showed atrial fibrillation, frequency 45/min, without any other pathology. He was examined by a cardiologist and connected to 24-hour ECG immediately. Cardiac enzymes were all within the normal limits. He was administered an infusion of saline and antiemetics and carvedilol was removed from therapy permanently, while other drugs remained in the same dosage. After an hour, the patient recovered completely. His blood pressure was 130/70 mm Hg. Twenty-four-hour ECG showed basic fibrillation rhythm with an average heart rate of 55 beats *per* minute, minimum heart rate of 23 beats *per* minute and maximum heart rate of 102 beats *per* minute, with rare ventricular extrasystoles, without any ST changes and with maximum pause of up to 2.6 s.

After a week, he was started on levodopa at a dose of 100 mg/day with gradual titration to 200 mg/day, and subsequently he was administered ropinirole extended-release formulation in a dose of 2 mg/day.

During the rest of his hospital stay, his blood pressure values were normal and the patient was free from cardiovascular symptoms. Twenty days later, repeat 24-hour ECG showed no evidence of bradycardia.

DISCUSSION

Although bradycardia is described as a frequent side effect of dopamine agonists (1), pramipexole can rarely cause bradycardia as an adverse event (2). According to data available, bradycardia was described as a rare adverse event during phase II and III in clinical trials and listed in the group of adverse events that appear on at least two occasions in 2509 individuals exposed to pramipexole tablets. The reported events were included irrespective of determination of a causal relationship to pramipexole tablets (2). Apart from these clinical trials, there are no published case reports on such events (3). On the other hand, arterial hypotension as a pramipexole adverse event has been reported in more than 1% of patients in clinical trials (2).

The mechanism of bradycardia induced by the action of dopamine agonists includes stimulation of the peripheral nervous system (1). There are 5 subtypes of dopamine receptor agonists (D1, D2, D3, D4 and D5), and they are divided into two subpopulations of dopamine agonists: D1- and D2-like receptors. In D1 group, there are D1 and D5 receptors, while D2 group includes D2, D3 and D4 receptors (4). The antiparkinsonian effect of dopamine agonists is achieved by stimulating D2 receptor subpopulations. In D2 subpopulation, pramipexole has the highest binding affinity to D3 receptors with a high degree of stimulation as compared to other ergot and non-ergot dopamine agonists (4). In their experiments on rats, Polakowski *et al*. have demonstrated the effect of certain dopamine agonists depending on the binding affinity to particular receptor subtypes, cardiac contractility and regional hemodynamics. They found that a partial agonist at D3 receptor does not affect heart rate, but only a drop in blood pressure by reducing vascular resistance, while the D2 receptor agonist can cause change in the heart rate, vasodilation and decreased blood pressure (5). This would explain the low incidence of bradycardia caused by pramipexole in comparison to other dopamine agonists.

The cause of bradycardia in our "treatment naïve" patient was the high dose of pramipexole (3 mg) that exerted its influence on D3 receptors. The usual starting dose of pramipexole is 0.375 mg/day, which means that our patient started with a 10-fold initial dose. Bradycardia may also be the consequence of atrial fibrillation or concomitant drugs taken by the patient (6-8), however, it was excluded in our patient. There is temporal association between bradycardia and pramipexole intake, and our patient did not experience the same symptoms either before or after that, although he did take the same medications before. If hypotension was the only adverse event, there would be reactive tachycardia as a reflex cardiac action. So, hypotension in this case was probably the second adverse event of pramipexole.

CONCLUSION

The report of our patient is important as a warning of this rare adverse event of pramipexole, also pointing again to the need of low and slow titration of dopamine agonists.

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Bradikardija uzrokovana slučajnim uzimanjem visoke doze pramipeksola

SAŽETAK - U radu se prikazuje bolesnik s Parkinsonovom bolešću koji prethodno nije primao terapiju, kod kojega se razvila bradikardija nakon slučajnog uzimanja visoke doze pramipeksola. Muški bolesnik u dobi od 83 godine s ekstrapiramidnim simptomima i anamnezom povišenog krvnog tlaka, miokardiopatije i atrijske fibrilacije za vrijeme hospitalizacije pogreškom je dobio 3 mg pramipeksola. Tri sata nakon uzete doze lijeka u bolesnika se javila bradikardija i hipotenzija nakon čega se u potpunosti oporavio. Holter EKG pokazao je osnovni ritam atrijske fibrilacije s prosječnom frekvencijom od 55/min, minimalnom frekvencijom od 23/min i maksimalnom od 102/min. Nakon postupnog uvođenja levodope i ropinirola s produženim učinkom u terapiju bolesnik više nije imao kardiovaskularnih smetnji. Nakon 20 dana ponovljen je holter EKG koji nije pokazao znakova bradikardije. Iako se bradikardija opisuje kao česta nuspojava dopaminskih agonista pramipeksol ju rijetko može izazvati. Prikaz našega bolesnika bitan je kako bi upozorio na ovu rijetku, ali moguću nuspojavu pramipeksola i ponovno naglasio potrebu za postupnom titracijom što nižom djelotvornom dozom lijeka.

Ključne riječi: pramipeksol; dopaminski agonisti; Parkinsonova bolest; bradikardija