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Nicorandil Induced Symptomatic Bradycardia in A Normokalemic Patient

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Abstract

Nicorandil is an antianginal agent having both nitrate-like and ATP-sensitive potassium (KATP) channel activator properties. Potassium channel activation causes expulsion of potassium ions (K+) out of cells leading to membrane hyperpolarization, closure of voltage gated calcium channels (Ca++) and finally vasodilatation. Nicorandil induced hyperkalemia and bradycardia have been reported in patients with abnormal kidney function. We present a case of chronic stable angina on multiple drugs developing symptomatic junctional bradycardia. After detailed evaluation, nicorandil was suspected to be the cause. This case reminds us that physicians should be aware of this potential complication in patients receiving ATPsensitive potassium channel activator.

Keywords: Nicorandil, ATP-sensitive potassium channel, Junctional bradycardia

INTRODUCTION

Nicorandil is commonly used for treating angina pectoris. It has nitrate-like as well as ATP-sensitive potassium channel activator properties. Excessive activation of K_{ATP} channels can cause overt K+ efflux which could result in hyperkalemia. Lee et al. have reported a case of life-threatening bradycardia due to nicorandil induced hyperkalemia in a uremic patient [1]. Chowdhary et al reported a case of nicorandil induced hyperkalemia in a patient with diabetic nephropathy [2]. To our best knowledge, only a few cases of symptomatic junctional bradycardia due to nicorandil in normokalemic patients with normal kidney function have been reported till date. Here, we present a patient with normal kidney function and normal serum potassium level who developed symptomatic junctional bradycardia after taking nicorandil.

CASE PRESENTATION: A 77-year-old man with a past medical history of Type 2 Diabetes Mellitus, Hypertension and Coronary artery disease was admitted with dyspnea on exertion. Patient had undergone coronary artery bypass graft (CABG) surgery 10 years ago. Since then, he had been on aspirin 75 mg OD, bisoprolol 5 mg OD, amlodipine 5 mg OD, ramipril 2.5 mg OD, hydrocholorothiazide 12.5 mg OD, teneligliptin 20mg OD, metformin 500 mg OD, atorvastatin 10 mg OD. During his first visit in our outpatient department 15 days back, the patient had dyspnea on exertion for which he was prescribed glyceryl trinitrate 2.6 mg BID. Three days after addition of glyceryl trinitrate, the patient visited us with complaints of headache and dizziness. His vitals were within normal limits. Electrocardiography (ECG) showed sinus rhythm. Echocardiography showed normal biventricular function. Laboratory

data did not show any significant abnormality. Glyceryl trinitrate was suspected to be the cause of his symptoms and was stopped. Nicorandil 10 mg BID was started.

A few days after starting nicorandil, patient started experiencing worsening of dyspnea for which he was admitted. His blood pressure was 90/60 mm of Hg, pulse rate was 50/min. ECG showed junctional bradycardia. Echocardiography showed normal biventricular function with no regional wall motion abnormality at rest. There was no significant mitral regurgitation. Laboratory data showed: serum urea 75.7 mg/dl, serum creatinine 1.35 mg/dl, serum calcium 8.75 mg/dl, sodium 133.4 meq/l, potassium 4.03 meq/l, BNP 903.38 pg/ml, haemoglobin 11.3 gm/dl, troponin I and CK-MB were normal. Blood glucose was 106 mg/dl and blood pH was 7.38.

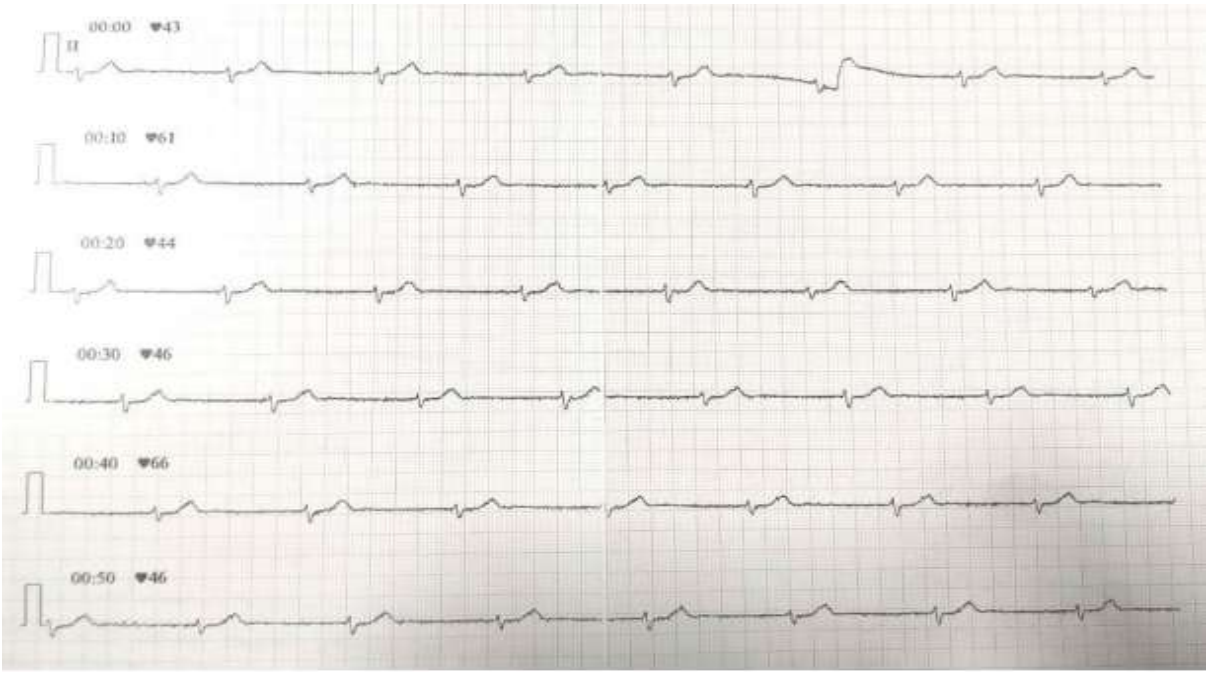

Figure 1: Electrocardiography on admission showed junctional bradycardia

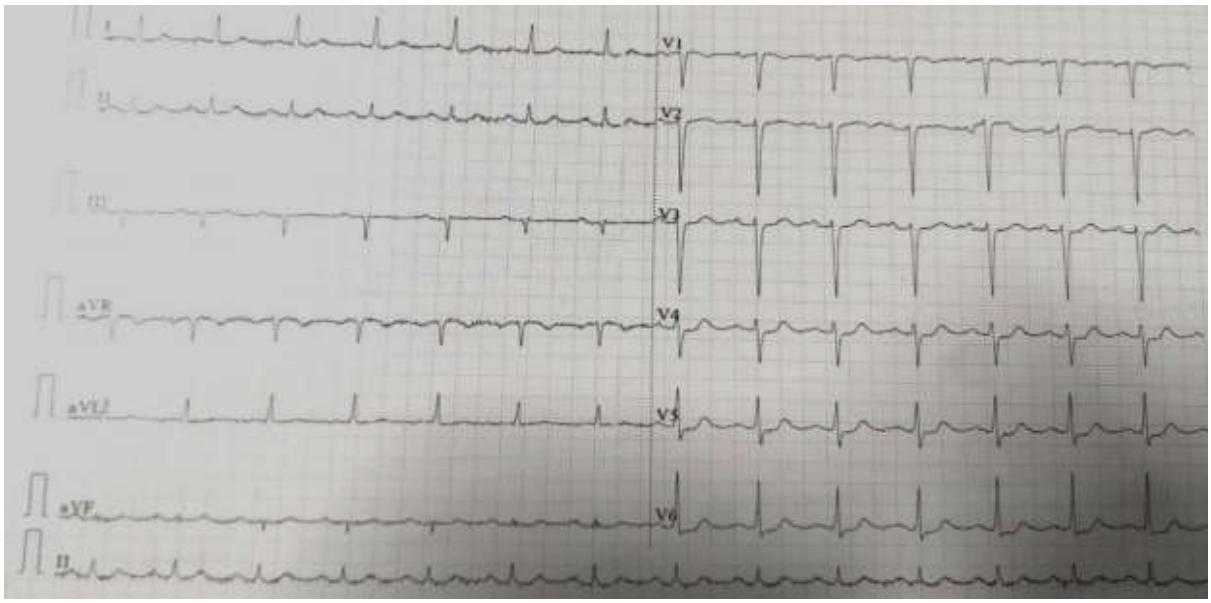

Figure 2: Electrocardiography showing sinus rhythm two days after stopping nicorandil

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Because the patient was taking bisoprolol and amlodipine for a long time they were not considered to be the primary cause of his symptomatic bradycardia and were continued. In review of his medications, he only took nicorandil recently. After reviewing adverse effects of his medications, nicorandil was suspected to be the cause of his bradycardia. Nicorandil was stopped and trimetazidine 35mg BID was started. After cessation of nicorandil use, his rhythm reverted to sinus rhythm. His dyspnea improved and he was discharged uneventfully. On follow up visits, patient remained in sinus rhythm and his symptoms improved.

Discussion: Nicorandil is an antianginal agent with dual mechanism of K_{ATP} channel activator and nitrate-like effect which causes both arterial and venous vasodilatation [2].

At antianginal doses, nicorandil has a coronary vasodilating effect as well as a balanced peripheral action that decreases both preload and afterload . It also has strong spasmolytic activity which is beneficial in dynamic coronary obstruction [2].

Besides decrease in preload and afterload nicorandil has several favorable effects on cardiovascular system like improvement of myocardial perfusion, protection of cardiac muscles from ischemic damage, prevention of Ca++ overload by opening ATP sensitive K+ channels, as an anti-inflammatory and anti-proliferative effects, anti-apoptosis, anti-arrhythmic effects, endothelial protection and preservation of kidney [3].

Nicorandil improves coronary microcirculation and is found to be effective in patients with stable angina and acute coronary syndrome [4].

Nicorandil stimulates guanylate cyclase which increases the formation of cyclic GMP which in turn activates protein kinase G (PKG). PKG phosphorylates and inhibit guanosine triphosphatase and decreases Rho-kinase activity that leads to an increase in myosin phosphatase activity and this ultimately leads to a decrease in calcium sensitivity of the smooth muscle. PKG also activates the calcium pump of sarcolemma to remove calcium as well as it acts on K+ channels causing K+ efflux and membrane hyperpolarization [5]. This causes closure of L-type voltage gated Ca ++ channels and finally coronary vasodilation [6].

ATP sensitive K+ channels were first known in the sarcolemma of cardiac myocytes [7]. The K_{ATP} channels are composed of two subunits, an inwardly rectifying potassium channel pores (Kir6.2) and regulatory sulfonylurea receptor (SUR2A and SUR2B) [8]. Nicorandil is known to activate the receptors, Kir6.2/ SUR2A and Kir6.2/ SUR2B, which confirms its specificity for K_{ATP} channels of cardiac and smooth muscles [9]. The ATP binds to Kir6.2 that causes inhibition of channel activity and SUR is the primary target for sulfonylureas, K+ channel openers and nucleoside diphosphates [2]. ATP binds to both the open and closed state of the K_{ATP} channel and this reduces the mean open time and mean burst duration, which increases the frequency and duration of the inter-burst closed states [10].

Nicorandil shows no observable effect on insulin secretion due to its lack of its effect on Kir6.2/SUR 1 currents, which shows its good tolerability in diabetic patients [9].

The K_{ATP} channels are present in cardiomyocytes, skeletal muscle cells, vascular smooth muscle cells, pancreatic beta cells, intestines, kidney, neurons and mitochondria [11].

The K_{ATP} channels could open in response to physical stress like hypoxia, hypercapnia, acidosis, ATP depletion or by K_{ATP} channel opening drugs. In vascular smooth muscle cells, the K_{ATP} channels causes vasodilatation by increasing the release of nitric oxide from the endothelium as well as due to the closure of voltage gated Ca++ channels. The vasodilatation occurred mostly in coronary, mesenteric, renal and skeletal muscle beds [2].

The opening of K_{ATP} channel mainly dilates peripheral and coronary resistance arterioles using low doses of nicorandil whereas it's NO dilating property mainly dilates epicardial coronary arteries and veins using high doses of nicorandil [9]. Opening of K_{ATP} channel causes reduction of electrical activities, thereby decreases cardiac stress and has an important role in ischemic preconditioning [7]. Singer et al. reported three cases with severe hyperkalemia, bradycardia and hypotension after use of various K_{ATP} channel activators including nicorandil, ciclosporin and isoflurane. In all these cases glibenclamide promptly reversed these abnormalities. Glibenclamide binds to SUR receptor which inhibits K_{ATP} channels. This condition is known as "potassium channel syndrome"

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which is associated with drug related, excessive K_{ATP} channel activation [1].

The safety of nicorandil was proved in various studies. Arnold et al reported three patients out of 42, who developed transient symptomatic hypotension and bradycardia. In the Safety Profile of Nicorandil Prescription Event Monitoring (PEM) cohort study, only 6 possible cases of bradycardia among 13,260 patients were reported from Dec 1994 to Oct 1996. In these studies, no cases of hyperkalemia were reported [1].

Chowdhry et al reported a case of Nicorandil induced potassium channel syndrome with intractable hyperkalemia in a patient with diabetic nephropathy. There was no bradycardia or hypertension in that patient [2].

We report a post CABG patient with type 2 diabetes mellitus and hypertension who developed hypotension and bradycardia without developing hyperkalemia after taking nicorandil. After detailed evaluation and exclusion of other causes of hypotension and bradycardia like myocardial ischemia, electrolyte imbalance, acidbase disorder, nicorandil was suspected to be the cause. After stopping nicorandil, hypotension and bradycardia improved. The entity was finally assumed to be "Nicorandil-induced potassium channel syndrome".

We recommend that in addition to its anti-ischemic benefits physicians should be aware of this potential complication of nicorandil.

References:

1. Lee H-H, Hsu P-C, Lin T-H, Lai W-T, Sheu S-H. Nicorandil-Induced Hyperkalemia in a Uremic Patient. Case Rep Med. 2012; 2012:812178.
2. Chowdhry V, Mohanty BB. Intractable hyperkalemia due to nicorandil induced potassium channel syndrome. Ann Card Anaesth. 2015;18(1):101–3.
3. Decreased cardiac mortality with nicorandil in patients with ischemic heart failure [Internet]. [cited 2021 Jul 6]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5452293/
4. Sato S, Takahashi M, Mikamo H, Kawazoe M, Iizuka T, Shimizu K, et al. Effect of nicorandil administration on cardiac burden and cardio-ankle vascular index after coronary intervention. Heart Vessels. 2020;35(12):1664–71.
5. Tarkin JM, Kaski JC. Vasodilator Therapy: Nitrates and Nicorandil. Cardiovasc Drugs Ther. 2016;30(4):367–78.
6. George M, Joseph L, John C, George JM, Alex R. Effect Of Nicorandil On Serum Potassium Levels In Patients With Coronary Artery Disease. 2017; 4(03):3.
7. Yamada M. Mitochondrial ATP-sensitive K+ channels, protectors of the heart. J Physiol. 2010 Jan 15;588(Pt 2):283–6.
8. Ashcroft FM. ATP-sensitive potassium channelopathies: focus on insulin secretion. J Clin Invest. 2005 Aug 1;115(8):2047–58.
9. Ahmed LA. Nicorandil: A drug with ongoing benefits and different mechanisms in various diseased conditions. Indian J Pharmacol. 2019;51(5):296–301.
10. Craig TJ, Ashcroft FM, Proks P. How ATP Inhibits the Open KATP Channel. J Gen Physiol. 2008 Jul;132(1):131–44.
11. Gross GJ, Peart JN. K ATP channels and myocardial preconditioning: an update. Am J Physiol-Heart Circ Physiol. 2003 Sep;285(3):H921–30.

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