

Intractable hyperkalemia due to nicorandil induced potassium channel syndrome

Vivek Chowdhry, B. B. Mohanty¹

Departments of Cardiac Anaesthesiology and ¹CTVS, Care Hospital, Bhubaneswar, Odisha, India

ABSTRACT

Nicorandil is a commonly used antianginal agent, which has both nitrate-like and ATP-sensitive potassium (K_{ATP}) channel activator properties. Activation of potassium channels by nicorandil causes expulsion of potassium ions into the extracellular space leading to membrane hyperpolarization, closure of voltage-gated calcium channels and finally vasodilatation. However, on the other hand, being an activator of K_{ATP} channel, it can expel K^+ ions out of the cells and can cause hyperkalemia. Here, we report a case of nicorandil induced hyperkalemia unresponsive to medical treatment in a patient with diabetic nephropathy.

Received: 23-09-14
Accepted: 02-12-14

Key words: ATP-sensitive potassium channels; channelopathy; hyperkalemia; nicorandil

INTRODUCTION

Nicorandil is an arterial vasodilator having cardioprotective properties via activation of ATP-sensitive potassium (K_{ATP}) channels. It is used as an antianginal agent and coronary vasodilator due to its nitrate-like and K_{ATP} channel activator properties. However, excessive activation of K_{ATP} channels may cause overt potassium efflux, which could result in hyperkalemia. Singer *et al.*^[1] have reported a few cases of life-threatening hyperkalemia and hemodynamic disturbance due to K_{ATP} channels activation. Lee *et al.*^[2] have also reported a case of life-threatening bradycardia due to nicorandil induced hyperkalemia. Besides these few case reports, the literature has no mention of this potential problem. Till date, hyperkalemia has not been recognized as a side effect of nicorandil.

Here, we highlight the case of nicorandil induced hyperkalemia in a patient with diabetic nephropathy, which was difficult to control by the conventional treatment of hyperkalemia and could only be managed by stopping nicorandil.

CASE REPORT

A 68-year-old male patient with unstable angina, diabetic nephropathy with serum creatinine of 1.6 mg/dL was admitted with coronary artery disease. He had a history of persistently high serum creatinine of 2.8 mg/dL 4 months back. Urine analysis showed microalbuminuria and serum potassium was high around 5.1–5.3 mEq/L. The patient was taking tablet cilnidipine 10 mg once daily and nicorandil twice daily orally and was kept on the heparin infusion. Coronary angiography revealed distal left main 70% stenosis and diffused triple vessel disease with bad target vessels. The preanesthetic assessment was done the day before surgery and heparin infusion was stopped 6 h prior to surgery. The patient underwent off-pump coronary artery bypass surgery, and three vein grafts were anastomosed. The surgery was uneventful, and the patient was shifted to the Intensive Care Unit (ICU) for postoperative recovery with stable hemodynamics and minimal inotropic support. In the ICU, nicorandil infusion was started to prevent spasm of the small caliber and diffusely diseased native coronary

Access this article online

Website: www.annals.in

DOI:

10.4103/0971-9784.148331

Quick Response Code:



Address for correspondence: Dr. Vivek Chowdhry, Department of Cardiac Anaesthesiology, Care Hospital, Chandrasekharpur, Bhubaneswar - 751 015, Odisha, India. E-mail: vivek.chowdhry@gmail.com

arteries, and low dose aspirin was administered. In the postoperative period, the urine output was good, extremities were warm, blood gases were normal and the patient remained hemodynamically stable. Despite no sign of low cardiac output, the serum potassium was high around 5.2–5.5 mEq/L. Patient was extubated uneventfully after 6 h of shifting to ICU. Serial serum potassium estimation had a rising trend and remained persistently high. In order to lower down the serum potassium level, dextrose insulin solution, inter-mittent furosemide and potassium binding resins were repeatedly tried. Despite all the efforts, serum potassium was persistently high and gradually rose to 6.4 mEq. Finally, trying to find out the cause of this intractable hyperkalemia we reviewed the patient's drug chart and after thorough discussion, the nicorandil infusion was stopped.

After stopping the nicorandil infusion, the serum potassium started decreasing. After 2 h of stopping nicorandil infusion, serum potassium decreased to 5.3 mEq/L and after 24 h it became 4.8 mEq/L and remained at a safer level thereafter. Rest of the course was uneventful.

DISCUSSION

Efficacy and safety of nicorandil in the treatment of angina pectoris have been evaluated extensively.^[3] At antianginal doses, nicorandil has a coronary vasodilating effect as well as a balanced peripheral action that leads to decreases in both preload and afterload. Therefore, nicorandil affects two main determinants of oxygen demand without impairing myocardial contractility or atrioventricular conduction. Further, its strong spasmolytic activity is beneficial when dynamic coronary obstruction is considered. The vasodilator effect of nicorandil is mainly due to its nitrate-like property. However, nicorandil is effective in cases where nitrates are not effective due to its K^+_{ATP} channel opening effect providing pharmacological preconditioning and cardio-protection against ischemia.^[4]

Mechanism of action of nicorandil

Nicorandil stimulates guanylate cyclase to increase the formation of cGMP. cGMP activates protein kinase G (PKG) which phosphorylates and inhibits guanosine triphosphatase and decreases Rho-kinase activity. Reduced Rho-kinase activity leads to an increase in myosin phosphatase activity which decreases the calcium sensitivity of the smooth muscle. PKG also

activates the sarcolemma calcium pump to remove calcium as well as act on K^+ channels to promote K^+ efflux and the ensuing hyperpolarization inhibits voltage-gated calcium channels.^[5]

As a K^+_{ATP} channel opener, nicorandil activates K^+_{ATP} channel, causing K^+ efflux. This hyperpolarizes the cell, which inactivates voltage-gated calcium channels and reduces free intracellular Ca^{2+} . Overall, via this dual mechanism of action nicorandil causes relaxation of the vascular smooth muscle and coronary vasodilatation.

The K^+_{ATP} channels are composed of two subunits; inwardly rectifying potassium channel pores (Kir6.2) and regulatory sulfonylurea-receptor (SUR). The ATP binds to Kir6.2, which leads to inhibition of channel activity and SUR is the primary target for potassium channel openers as well as the sulfonylurea, e.g. glibenclamide. ATP binds to both the open and closed states of the channel and reduces the mean open time and mean burst duration, which increases the frequency and duration of the inter-burst closed states.^[6]

The K^+_{ATP} channels are present in the pancreas, cardiomyocytes, vascular smooth muscle cells, skeletal muscle, neurons and mitochondria. In pancreas, they contribute to glucose homeostasis by regulating both insulin and glucagon secretion. Under resting conditions, the channels remain largely in a closed state. Opening of these channels result in a reduction of electrical activities, thereby decreasing cardiac stress and help in ischemic preconditioning, also protect the brain from seizures.^[7]

The K^+_{ATP} channels could open in response to physical stress like hypoxia, hypercapnia, acidosis, ATP depletion or by drugs with K^+_{ATP} channel opening effect.^[8] In vascular smooth muscle cells, the K^+_{ATP} channels after activation cause potassium efflux, which results in membrane hyperpolarization, closure of voltage-gated calcium channels, and finally, vasodilatation. Beside this, they may also cause vasodilatation by enhancing release of nitric oxide from the endothelium. The vasodilatation occurred predominantly in coronary, mesenteric, renal, and skeletal muscle beds, which improves the blood supply matching the demand. K^+_{ATP} channel also plays an important role in ischemic preconditioning and exert its cardioprotective effects against various stresses, like ischemia and hypoxia.^[9]

According to the impact of nicorandil in angina study, nicorandil has proved to be a safe and useful antianginal drug and its use can significantly improve the cardiovascular outcome in patients with stable angina.^[10,11] The hemodynamic side effects are dose dependent and include transient symptomatic hypotension and bradycardia. Singer *et al.* reported three cases with severe hyperkalemia after use of various K_{ATP} channel activators including; nicorandil. In all those cases, there was a poor response to conventional potassium lowering treatments. However, administration of glibenclamide promptly reversed these abnormalities as glibenclamide by acting on SUR inhibit the K_{ATP} channels. This condition of drug-induced, excessive K_{ATP} channel activation was described as “potassium channel syndrome,” which was managed by glibenclamide.

There are frequent incidences of hyperkalemia after nicorandil use in patients with renal insufficiency or uremia. The components of energy balance like; energy intake, energy expended for physical activity and resting energy expenditure are disrupted by a number of disorders commonly present in chronic kidney disease and end-stage renal disease. This disruption of energy balance leads to a significant decrease of ATP, total adenine nucleotides and phosphocreatine.^[12] Thus, ATP depleted patients with simultaneous use of potassium channel openers can cause channel dysfunction for a prolonged period leading to intractable hyperkalemia.^[13]

CONCLUSION

We report a patient having coronary artery disease with diabetic nephropathy who developed hyperkalemia after taking nicorandil. This hyperkalemia was very much resistant to the potassium lowering measures. As there is no method or test to prove that the hyperkalemia was due to nicorandil, but after detailed evaluation and exclusion of other potential causes of hyperkalemia like low cardiac output, acidosis, potassium containing medications and drugs causing hyperkalemia, nicorandil was suspected to be the

cause. After stopping the nicorandil infusion, the serum potassium level begins to decrease and within a few hours came down to became absolutely normal. The entity was finally assumed to be “nicorandil-induced potassium channel syndrome.”

Here, we would like to recommend that, while prescribing nicorandil for its antiischemic benefits, physicians should also be aware of this potential complication and hyperkalemia should be recognized as one of the rare but potential side effects of the nicorandil.

REFERENCES

1. Singer M, Coluzzi F, O'Brien A, Clapp LH. Reversal of life-threatening, drug-related potassium-channel syndrome by glibenclamide. *Lancet* 2005;365:1873-5.
2. Lee HH, Hsu PC, Lin TH, Lai WT, Sheu SH. Nicorandil-induced hyperkalemia in a uremic patient. *Case Rep Med* 2012;2012:812178.
3. Krumenacker M, Roland E. Clinical profile of nicorandil: An overview of its hemodynamic properties and therapeutic efficacy. *J Cardiovasc Pharmacol* 1992;20 Suppl 3:S93-102.
4. Markham A, Plosker GL, Goa KL. Nicorandil. An updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. *Drugs* 2000;60:955-74.
5. Kukovetz WR, Holzmann S, Pösch G. Molecular mechanism of action of nicorandil. *J Cardiovasc Pharmacol* 1992;20 Suppl 3:S1-7.
6. Craig TJ, Ashcroft FM, Proks P. How ATP inhibits the open K (ATP) channel. *J Gen Physiol* 2008;132:131-44.
7. Ashcroft FM. ATP-sensitive potassium channelopathies: Focus on insulin secretion. *J Clin Invest* 2005;115:2047-58.
8. Yamada M. Mitochondrial ATP-sensitive K⁺ channels, protectors of the heart. *J Physiol* 2010;588:283-6.
9. Gross GJ, Peart JN. KATP channels and myocardial preconditioning: An update. *Am J Physiol Heart Circ Physiol* 2003;285:H921-30.
10. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: The impact of nicorandil in angina (IONA) randomised trial. *Lancet* 2002;359:1269-75.
11. Roland E. Safety profile of an anti-anginal agent with potassium channel opening activity: An overview. *Eur Heart J* 1993;14 Suppl B: 48-52.
12. Cuppari L, Ikizler TA. Energy balance in advanced chronic kidney disease and end-stage renal disease. *Semin Dial* 2010;23:373-7.
13. Del Canale S, Fiaccadori E, Ronda N, Söderlund K, Antonucci C, Guariglia A. Muscle energy metabolism in uremia. *Metabolism* 1986;35:981-3.

Cite this article as: Chowdhry V, Mohanty BB. Intractable hyperkalemia due to nicorandil induced potassium channel syndrome. *Ann Card Anaesth* 2015;18:101-3.

Source of Support: Nil, **Conflict of Interest:** None declared.