Case Report

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Potassium Channel Syndrome Caused by Nicorandil in Chronic Kidney Disease: A Case Report and Literature Review

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Nicorandil is an anti-anginal drug that is commonly used in the treatment of ischemic heart disease. Nicorandil acts as a nitrate donor and ATP-sensitive potassium channel agonist, inducing coronary artery vasodilation. Potassium efflux through ATP-sensitive potassium channels activated by nicorandil can cause refractory hyperkalemia, particularly in patients with chronic kidney disease (CKD). Here, we report the case of an 85-year-old man who presented with severe refractory hyperkalemia, despite proper medical management. His serum potassium level increased from 4.96 to 7.21 mEq/L 7 days after restarting nicorandil. Hyperkalemia resolved shortly after discontinuation of nicorandil, which was presumed to be the offending drug. Previously, a few cases reported nicorandil-induced hyperkalemia called potassium channel syndrome in patients with CKD, and hyperkalemia can be reversed by ceasing nicorandil or using sulfonyl urea drugs. Given that CKD patients may have several contributing factors to this adverse event, clinicians should be aware of the risk of nicorandil-induced hyperkalemia, and medication review and drug discontinuation should be considered.

Key Words: Nicorandil, Hyperkalemia, Chronic kidney disease, Potassium channel syndrome

INTRODUCTION

Drug-induced hyperkalemia is a common event in clinical practice, accounting for 35%-75% of hyperkalemia in hospitalized patients[1]. Clinicians usually pay careful attention to the use of ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARB) in relation to hyperkalemia. Nevertheless, other frequently used drugs that induce hyperkalemia have been relatively overlooked[2,3]. In particular, medications related to transcellular potassium shifts often lead to severe hyperkalemia[1]. Nicorandil is an anti-angina drug that acts as ATP-sensitive potassium channel activators[4]. Hyperkalemia attributable to drugs with potassium channel-opening properties, such as nicorandil, has been described as a potassium channel syndrome[5]. In real-world settings, nicorandil has favorable safety profiles, and nicorandil-induced hyperkalemia has rarely been reported[6]. Therefore, abrupt refractory hyperkalemia related to nicorandil could pose a challenge to clinicians. Here, we report medically refractory hyperkalemia caused by nicorandil in a patient with non-dialysis chronic kidney disease (CKD).

CASE REPORT

An 85-year-old man was admitted to the Inha University Hospital with dyspnea. He had a history of CKD, hypertension, dementia, cerebral infarction, and ischemic heart disease. He had been in a nursing home for 2 years due to dementia and was nearly bedridden for his medical conditions. His medications before admission included 8 mg of candesartan daily, 5 mg of nicorandil three times daily, 10 mg of atorvastatin daily, and 75 mg of clopidogrel daily. On admission,

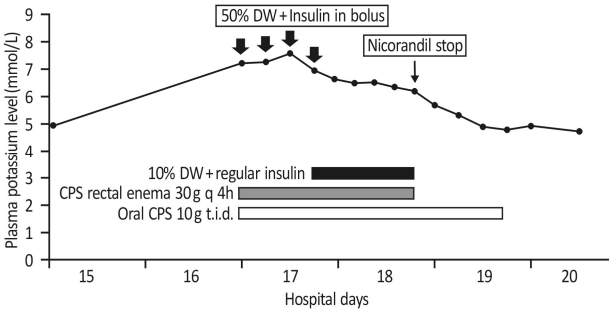

Fig. 1. Clinical course of the case. CPS, calcium polystyrene sulfonate; DW, dextrose water.

the patient presented with productive cough and sputum. Lung auscultation revealed coarse crackles in the lower right lung field. His blood pressure was 113/59 mmHg, pulse rate was 76/min, respiratory rate was 22/min, and body temperature was 37.0℃. His initial laboratory findings were as follows: white blood cells, 15,720/mm^3; hemoglobin, 8.9 g/dL; platelets, 242 K/mm^3; blood urea nitrogen, 50.4 mg/dL; serum creatinine, 2.31 mg/dL; sodium, 134.9 mEq/L; potassium, 4.75 mEq/L; chloride, 99.7 mEq/L; and C-reactive protein, 3.37 mg/dL. He was diagnosed with aspiration pneumonia, and his symptoms improved after 2 weeks of antibiotic treatment. He was presumed to have acute kidney injury superimposed on CKD at the time of admission. Therefore, candesartan was discontinued during the admission. Other medications including nicorandil were stopped at admission and restarted after his respiratory symptoms improved. The pneumonia was treated with a broad-spectrum antibiotic (piperacillin/tazobactam). Other drugs related to hyperkalemia such non-steroidal anti-inflammatory drugs, trimethoprim/sulfamethoxazole, heparin, and beta-blocker were not used. The patient was given oxygen by nasal cannula (1-2 L/min) during the initial phase of admission, but there were no signs of dehydration. However, 7 days after resuming medication, the serum potassium level increased from 4.96 to 7.21 mEq/L. Other laboratory findings were as follows: sodium, 132.2 mEq/L; chloride, 97.7 mEq/L; blood urea nitrogen, 45.4 mg/dL; and serum creatinine, 2.64 mg/dL. Arterial blood gas analysis revealed pH 7.40, $PaCO_2$ 40.2 mmHg, PaO_2 84.0 mmHg, and HCO_3 24 mmol/L. Urine potassium-to-creatinine ratio was 92.16 mEq/g. Fractional excretion of sodium was 6.8%. Electrocardiography revealed tall-peaked T waves in V3-V5. Acute hyperkalemia was managed with conventional treatment, including calcium gluconate, insulin-mixed dextrose water, calcium polystyrene sulfonate, and a low-potassium diet (Fig. 1). Despite repeated management, the potassium level remained at >6 mEq/L for >48 h. After thorough medication review, we decided to stop nicorandil. Immediately after discontinuation of nicorandil, the serum potassium level rapidly decreased without further management. Thereafter, the patient was discharged without any adverse events, and nicorandil was not readministered after discharge.

DISCUSSION

Nicorandil has now been incorporated into clinical practice for the treatment of ischemic heart disease, showing improved outcomes, such as length of stay, morbidity, and mortality in patients with angina[7]. Furthermore, the Japanese Coronary Artery Disease Study of patients with acute myocardial infarction or unstable angina showed significantly lower cardiovascular death in the nicorandil group than in the control group[8]. Nicorandil is being increasingly prescribed because of its cardioprotective effects seen in the trials.

Nicorandil causes vasodilatation through two mechanisms. First, nicorandil activates the ATP-sensitive channel, leading to membrane hyperpolarization through the efflux of potassium. Then, voltage-gated calcium channels are closed, which finally induces vasodilation in the vascular smooth muscle[9]. Second, nicorandil activates guanylate cyclase by acting as a nitrate oxide donor, increasing intracellular cyclic GMP levels, which results in vasodilatation[10]. Coronary vasodilation mediated by the cGMP pathway is considered a major mechanism underlying its clinical efficacy in angina[11]. Given its mechanism of action, nicorandil may cause hyperkalemia. However, currently, only a few cases have been reported. Most cases occur in patients with CKD, including end-stage renal disease (ESRD). Two case reports described nicorandil-induced recurrent hyperkalemia in ESRD patients despite repeated hemodialysis[12,13]. Chowdhry et al. reported intractable hyperkalemia caused by nicorandil in patients with non-dialysis CKD with a serum creatinine of 1.6 mg/dL[14]. In only one case, hyperkalemia developed in a patient with normal kidney function[5], in which case refractory hyper-

Table 1. Summary of all reported cases related to nicorandil-induced hyperkalemia

References	Age	Dose of nicorandil	Baseline creatinine	Onset (fromnicorandilinitiation)	Comorbidities	Coadministered medications
Singer et al.[5]	58	NA	normal	Unknown (after CABG)	Coronary artery disease	Beta-blocker, nitrate, aspirin
Chen et al.[12]	83	5 mg tid	ESRD	Unknown	Coronary artery disease, diabetes mellitus, ESRD	NA
Lee et al.[13]	51	5 mg tid	ESRD	1 month	Coronary artery disease, hypertension, ESRD	Aspirin
Chowdry et al.[14]	68	NA (iv)	1.6mg/dL	Unknown (after CABG)	Coronary artery disease, diabetes mellitus	Clinidipine
Wei et al.[17]	78	6mg iv x 2	NA	Immediately (during PCI)	Coronary artery disease (STEMI), hypertension	Amlodipine
Montgomery et al.[18]	78	15 mg/day	NA	Unknown (after CABG)	Coronary artery disease	Isorbide mononitrate, atenolol
The present study	85	5 mg tid	2.31mg/dL	A few days (<7 days)	Coronary artery disease, hypertension, cerebral infarct, dyslipidemia	Candesartan, atorvastatin, clopidogrel

NA, not available; ESRD, End-stage renal disease; iv, intravenous; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; STEMI, ST- elevation myocardial infarction.

kalemia was noticeably reversed by glibenamide administration. Mechanistically, sulfonyl urea drugs, including glibenamide, inhibit the action of nicorandil on ATP-sensitive potassium channels. ATP-sensitive potassium channels consist of an inwardly rectifying k-channel subunit (Kir) and sulfonylurea-receptor subunit (SUR)[15]. Both ATP binding to Kir and sulfonyl urea binding to SUR induce potassium channel closure and subsequent vasodilation[16]. The closure of ATP-sensitive potassium channels by sulfonyl urea drugs attenuates the potassium channel agonistic effect of nicorandil. In addition, there were cases of nicorandil-induced hyperkalemia and cardiac arrest during coronary angiography[17] and coronary artery bypass surgery[18]. Table 1 summarizes a few cases of nicorandil-induced hyperkalemia.

There are some common features in reported cases of nicorandil-induced hyperkalemia, including ours. First, nicorandil-induced hyperkalemia was mostly observed in patients with advanced CKD. Patients with CKD frequently experience hyperkalemia due to decreased potassium excretion and ATP depletion by the uremic milieu[19]. ATP-sensitive potassium channels open as cellular ATP levels decreases[20]; thus, uremic conditions could be a contributing factor to nicorandil-induced hyperkalemia. Second, nicorandil-treated patients are usually older and at a high risk of cardiovascular disease, and they often use other medications related to hyperkalemia, such as ACEi, ARB, and aldosterone antagonists. Third, hyperkalemia is usually seen in patients who have recently started (or resumed) nicorandil rather than in those who have continued to take it. In this case, there was no information about hyperkalemia during nicorandil administration before admission. However, because various physical stress, including hypoxia, ischemia, and ATP depletion, can open ATP-sensitive potassium channels[9,20], acute medical conditions such as pneumonia, hypoxia, and deconditioning possibly augment nicorandil-induced hyperkalemia. Finally, nicorandil could lead to a severe form of hyperkalemia that is sustained despite adequate medical management until the discontinuation of nicorandil.

Nicorandil, an ATP-sensitive potassium channel agonist, can cause medically refractory hyperkalemia. Particularly, in the setting of renal impairment, nicorandil administration could be a potential contributor to severe hyperkalemia. We suggest that potassium levels should be carefully monitored in patients with CKD starting treatment with nicorandil, and clinicians should consider nicorandil as a possible cause of unexplained refractory hyperkalemia. Although sulfonyl urea drugs can antagonize this adverse event, prompt discontinuation of the offending drug should be prioritized over other measures.

Conflict of interest

The authors declare no relevant financial interests. This article is not published previously, and will not be submitted for publication elsewhere.

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