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

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INTRODUCTION

Drug-induced hyperkalemia is a common event in clinical practice, accounting for 35%-75% of hyperkalemia in hospitalized patients. 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. In particular, medications related to transcellular potassium shifts often lead to severe hyperkalemia. Nicorandil is an anti-angina drug that acts as ATP-sensitive potassium channel activators. Hyperkalemia attributable to drugs with potassium channel-opening properties, such as nicorandil, has been described as a potassium channel syndrome. In real-world settings, nicorandil has favorable safety profiles, and nicorandil-induced hyperkalemia has rarely been reported. 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,
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°C. His initial laboratory findings were as follows: white blood cells, 15,720/mm³; hemoglobin, 8.9 g/dL; platelets, 242 K/mm³; 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, PaCO₂ 40.2 mmHg, PaO₂ 84.0 mmHg, and HCO₃⁻ 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-
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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