Kidney Res Clin Pract 35 (2016) 142–146

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Original Article

Cicletanine-induced hyponatremia and hypokalemia in kidney transplant patients

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Article history:
Received 11 April 2016
Received in revised form
17 May 2016
Accepted 18 May 2016
Available online 25 May 2016

Keywords:
Cicletanine
Hypokalemia
Hyponatremia
Kidney transplantation

Abstract

Background: Cicletanine is an antihypertensive agent with vasorelaxant and diuretic properties. It has been widely used in European countries; however, cicletanine-associated electrolyte disturbances have yet to be defined. We investigated cicletanine-induced hyponatremia and hypokalemia in kidney transplant patients.

Methods: Data from a total of 68 kidney transplant recipients who were treated for hypertension with cicletanine were retrospectively analyzed. Cicletanine-induced hyponatremia and hypokalemia were defined as serum sodium < 135 mmol/L and potassium < 3.5 mmol/L, respectively, after the use of cicletanine.

Results: The average patient age was 50 (±11) years, and 44 (65%) were male. The daily dose of cicletanine was 171 ± 46 mg, and the duration of drug use was 215 ± 514 days. Hyponatremia occurred in 11 patients (16.2%), and hypokalemia occurred in 8 patients (11.8%). Three patients (4.4%) had hyponatremia and hypokalemia simultaneously. The duration of cicletanine administration was significantly longer in patients with hyponatremia than in those without hyponatremia (943 ± 958 vs. 74 ± 166 days, $P < 0.05$). The occurrence of hypokalemia was not affected by either daily dose or duration of drug use. Among 11 patients with hyponatremia, 10 were corrected within 2 weeks after withdrawal of the drug and 1 was spontaneously corrected. Among 8 cases of hypokalemia, 7 were corrected after withdrawal of the drug and 1 was spontaneously corrected.

Conclusion: We demonstrate that cicletanine may induce hyponatremia or hypokalemia in kidney transplant patients. Hyponatremia is more frequently associated with cicletanine than hypokalemia, and extended use of cicletanine may increase the risk of hyponatremia.

Introduction

Kidney transplant patients frequently have hypertension irrespective of their native kidney diseases. It is important to control blood pressure after kidney transplantation (KT) because uncontrolled hypertension is associated with earlier graft failure and higher cardiovascular mortality in the recipients [1]. Notably, salt sensitivity has a role in the pathogenesis of hypertension associated with chronic kidney disease (CKD) [2] and the use of calcineurin inhibitors [3]. Thus, diuretic

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http://dx.doi.org/10.1016/j.krcp.2016.05.004

therapy would be helpful to control hypertension in kidney transplant recipients.

Cicletanine (Tenstaten; Daewoong, Seoul, Korea) is an antihypertensive agent, synthetized by Esanu et al in 1986, and has been widely used in European countries [4]. It has been commercially available in Korea since 1992 and is used for the treatment of hypertension because it has effects of natriuresis and vasodilation without reflex tachycardia [5]. Although previous studies reported on the efficacy and safety of cicletanine in the treatment of hypertension [6,7], adverse effects of electrolyte imbalance induced by cicletanine have yet to be investigated.

Considering that the action of cicletanine is associated with natriuresis and kaliuresis [8], we postulated that cicletanine may produce side effects of hyponatremia and hypokalemia similar to those of thiazide diuretics. A few previous studies have shown that cicletanine has a milder natriuretic effect [9] and less kaliuresis [8] than thiazide diuretics in a small number of patients with essential hypertension. However, whether hyponatremia and hypokalemia are induced by cicletanine has not been investigated in patients with CKD. This study was undertaken to characterize cicletanine-induced hyponatremia and hypokalemia in kidney transplant patients.

Methods

We conducted a retrospective analysis of adult patients who underwent KT in Hanyang University Seoul Hospital and were prescribed cicletanine >2 weeks for the treatment of hypertension from January 2001 to April 2008. The patients who returned to hemodialysis or peritoneal dialysis after KT were excluded. We also excluded patients whose serum sodium and potassium levels were previously lower than 135 and 3.5 mmol/L, respectively.

Laboratory data, including serum electrolytes, blood urea nitrogen (BUN), and serum creatinine before and after cicletanine administration, were reviewed. To evaluate patient characteristics, demographic data including comorbidities and concurrent medications were also collected. The dose and duration of cicletanine use were estimated. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Cicletanine-induced hyponatremia and hypokalemia were defined as having follow-up serum sodium concentration of < 135 mmol/L and serum potassium concentration of < 3.5 mmol/L. Accordingly, the incidence of cicletanine-induced hyponatremia and hypokalemia was estimated. To compare patient characteristics, patients were divided into those with and without cicletanine-induced hyponatremia or hypokalemia.

Data are expressed as mean ± standard deviation or frequency (and proportion). Two groups were compared using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using StatView software (version 5.0 for Windows; SAS Institute Inc., Cary, USA).

Results

General characteristics of patients prescribed cicletanine

A total of 68 patients were included in this study: 44 men (65%) and 24 women (35%). The mean age was 50 ± 11 years, and KT duration before cicletanine administration was 157 ± 57 months. Concurrent antihypertensives comprised angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, beta antagonists, loop diuretics, and potassium-sparing diuretics. Forty-nine patients (72%) were concurrently medicated, with calcium channel blockers being the most common medication ($n = 28$, 41%).

The laboratory data obtained before cicletanine administration are shown in Table 1; the serum sodium level was 142 ± 2 mmol/L, and the serum potassium level was 4.3 ± 0.5 mmol/L. The serum creatinine level ranged from 0.8 to 5.6 mg/dL. The average daily prescribed dose of cicletanine was 171 ± 46 mg, and the duration of cicletanine administration was 215 ± 514 days, leading to a mean cumulative dose of 33 ± 68 g·days.

Cicletanine-induced hyponatremia

Table 2 summarizes the number of patients with and without electrolyte disturbances. Eleven patients (16.2%) had cicletanine-induced hyponatremia; the serum sodium level was decreased to 129 ± 4 mmol/L. Among them, 3 patients (4.4%) had hyponatremia and hypokalemia simultaneously. Hyponatremia was mild in 9 patients (82%, 126–134 mmol/L) and severe in 2 patients (18%, ≤125 mmol/L). Two severe hyponatremia patients and 6 of 9 mild hyponatremia patients had their serum sodium concentration improved by discontinuation of cicletanine. In contrast, hyponatremia was spontaneously corrected in 3 patients whose hyponatremia was relatively mild (132–133 mmol/L) despite continued use of cicletanine. Among them, however, hyponatremia recurred in 2 patients (66%).

Table 1. General characteristics of patients ($n = 68$)

Demographic profile	
Age (y)	50.0 ± 11.0
Sex (male)	44 (65)
Body mass index (kg/m^2)	23.4 ± 3.9
Period after kidney transplantation (mo)	157 ± 57
Comorbidities	
Diabetes mellitus	6 (8.8)
Dyslipidemia	25 (36.8)
Malignancy	6 (8.8)
Concurrent medications (n)	
ACE inhibitors	18
ARBs	16
Beta blockers	6
Calcium channel blockers	28
Loop diuretics	6
Baseline laboratory data	
Serum sodium (mmol/L)	142 ± 2
Serum potassium (mmol/L)	4.3 ± 0.5
Serum chloride (mmol/L)	105 ± 4
Total CO_2 (mmol/L)	24.5 ± 4.2
BUN (mg/dL)	30.7 ± 14.6
Serum creatinine (mg/dL)	2.0 ± 1.3
eGFR* (mL/min/1.73 m^2)	44.7 ± 21.7
Uric acid (mg/dL)	7.6 ± 1.7

Data are presented as mean ± SD or n (%).
* eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.