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

Eun Young Choi ☆, Youngouk Ro ☆, Jong-Wook Choi, Chong Myung Kang, Gheun-Ho Kim *

Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea

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

* Corresponding author. Department of Internal Medicine, Hanyang University College of Medicine, 222-1, Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea.
E-mail address: kimgh@hanyang.ac.kr (G-H Kim).
☆ Drs. Eun Young Choi and Youngouk Ro contributed equally to this work.

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.

Table 2. Number of patients with and without electrolyte disturbances

	Hyponatremia	No hyponatremia	Total
Hypokalemia	3	5	8
No hypokalemia	8	52	60
Total	11	57	68

When patient characteristics were compared between those with and without cicletanine-induced hyponatremia, there were no significant differences in age, sex, body mass index (BMI), comorbidities, concurrent antihypertensives, serum creatinine, serum uric acid, and daily dose of cicletanine. However, patients with hyponatremia had significantly lower levels of serum total protein and albumin than those without hyponatremia (Table 3). The duration of cicletanine administration was significantly longer in patients with hyponatremia than in those without hyponatremia (943 ± 958 vs. 74 ± 166 days, $P < 0.05$).

Cicletanine-induced hypokalemia

Cicletanine-induced hypokalemia occurred in 8 patients (11.8%), and all these patients had mild hypokalemia (≥ 3.0 mmol/L); the serum potassium level was decreased to 3.2 ± 0.1 mmol/L. All 3 patients who had hypokalemia and hyponatremia simultaneously recovered after cicletanine withdrawal, and 5 patients with only hypokalemia improved without discontinuing cicletanine. However, 4 of these 5 patients had recurrent hypokalemia and had to discontinue cicletanine for complete recovery.

When patient characteristics were compared between those with and without cicletanine-induced hypokalemia, there were no significant differences in age, sex, body mass index, comorbidities, concurrent antihypertensives, serum creatinine, serum albumin, serum uric acid, and daily dose of cicletanine (Table 4). Although serum chloride was significantly lower in patients with hypokalemia than in those without hypokalemia (99 ± 6 vs. 105 ± 6 mmol/L, $P < 0.05$), the increase in serum total CO_2 was not statistically significant (24 ± 4 vs. 21 ± 6 mmol/L).

Table 3. Data comparison between patients with and without cicletanine-induced hyponatremia

	Hyponatremia ($n = 11$)	No hyponatremia ($n = 57$)	P
Age (y)	50.3 ± 13.7	49.9 ± 10.6	0.677
Sex (M/F, n)	6/5	38/19	0.441
Body mass index (kg/m^2)	24.0 ± 6.2	23.2 ± 3.3	0.848
Serum sodium (mmol/L)	129 ± 4	139 ± 2	< 0.001
Serum potassium (mmol/L)	3.9 ± 0.5	4.0 ± 0.6	0.484
Serum chloride (mmol/L)	98 ± 8	106 ± 4	< 0.001
Total CO_2 (mmol/L)	18.2 ± 4.3	22.3 ± 5.4	0.019
BUN (mg/dL)	35.5 ± 17.5	33.1 ± 18.4	0.583
Serum creatinine (mg/dL)	2.4 ± 1.5	1.9 ± 1.2	0.594
Serum uric acid (mg/dL)	6.8 ± 4.7	7.7 ± 2.8	0.128
Serum total protein (g/dL)	5.9 ± 0.9	6.8 ± 0.7	0.005
Serum albumin (g/dL)	3.6 ± 0.5	4.0 ± 0.5	0.028
Serum glucose (mg/dL)	87 ± 12	89 ± 15	0.784
Daily dose of cicletanine (mg)	172.7 ± 46.7	170.2 ± 46.2	0.894
Duration of cicletanine use (d)	943 ± 958	74 ± 166	< 0.001

Data are presented as mean ± SD.
BUN, blood urea nitrogen.

Table 4. Data comparison between patients with and without cicletanine-induced hypokalemia

	Hypokalemia ($n = 8$)	No hypokalemia ($n = 60$)	P
Age (y)	56.6 ± 13.1	49.2 ± 10.5	0.116
Sex (M/F, n)	5/3	39/21	0.890
Body mass index (kg/m^2)	21.9 ± 2.3	23.6 ± 4.0	0.261
Serum sodium (mmol/L)	134 ± 6	138 ± 4	0.100
Serum potassium (mmol/L)	3.2 ± 0.1	4.1 ± 0.5	< 0.001
Serum chloride (mmol/L)	99 ± 6	105 ± 6	< 0.001
Total CO_2 (mmol/L)	23.6 ± 4.0	21.4 ± 5.5	0.336
BUN (mg/dL)	30.5 ± 15.5	33.9 ± 18.5	0.682
Serum creatinine (mg/dL)	2.1 ± 1.5	2.0 ± 1.2	0.864
Serum uric acid (mg/dL)	7.1 ± 3.3	7.6 ± 1.5	0.594
Serum total protein (g/dL)	6.3 ± 0.8	6.6 ± 0.8	0.291
Serum albumin (g/dL)	3.7 ± 0.6	4.0 ± 0.5	0.309
Serum glucose (mg/dL)	84.5 ± 11.1	89.3 ± 15.3	0.511
Daily dose (mg)	200.0 ± 0.0	166.7 ± 47.5	0.128
Duration of administration (d)	375 ± 523	193 ± 513	0.435

Data are presented as mean ± SD.
BUN, blood urea nitrogen.

Discussion

In this study, we demonstrated that cicletanine induced hyponatremia and hypokalemia while it was used for the treatment of hypertension in kidney transplant patients. Hyponatremia was more frequently associated with cicletanine than hypokalemia, and extended use of cicletanine may increase the risk of hyponatremia.

The mechanisms of action by which cicletanine exerts antihypertensive effects are unclear. However, one possibility is a direct action on the vascular wall because cicletanine, a furopyridine-derivative drug, is believed to stimulate the synthesis of prostaglandin I_2 (also called prostacyclin) [5] and inhibit sympathetic nerve activity [10]. Another possibility is the natriuretic activity of the drug, resulting from the action of the sulfoconjugated metabolite of cicletanine [4].

Whether cicletanine acts like thiazide diuretics in the distal convoluted tubule is controversial. According to Greven [11], cicletanine has a tubular site of action similar to thiazide diuretics, so despite the disparity in chemical structure between these drugs, there is speculation that cicletanine has adverse effects similar to thiazides. However, Monroy et al [12] demonstrated that the natriuretic metabolite of cicletanine (cicletanine sulfate) was unable to inhibit thiazide-sensitive NaCl cotransporters in the distal convoluted tubule. Cicletanine may act on different transporters than those targeted by thiazides, such as the apical Na^+-dependent Cl^-/HCO_3^- anion exchanger in the distal convoluted tubule [4]. Thus, cicletanine may not act like thiazide diuretics.

Despite these pharmacologic clues, clinical studies on electrolyte disorders induced by cicletanine were not previously reported. According to Tarrade et al [6], hematologic and biochemical values are not affected by cicletanine. Adverse effects reported during the use of cicletanine were gastrointestinal disorders, fatigue, pruritus, headache, vertigo, and lower limb edema, so it was concluded that cicletanine had no toxic or serious adverse effects. Passa [13] reported that cicletanine administered at 150–200 mg/d did not significantly influence serum sodium and potassium levels.

However, the ability to concentrate or dilute urine is diminished in CKD, ultimately leading to changes in the serum

sodium concentration [14]. As a result, KT recipients can be susceptible to hyponatremia, especially when thiazide-like diuretics are administered.

In this study, hyponatremia occurred in 11 patients (16.2%) among 68 kidney transplant recipients who used cicletanine for the treatment of hypertension. We believe that a causative relationship was present between hyponatremia and use of cicletanine because hyponatremia appeared after using cicletanine and was relieved by the discontinuance of the drug. The incidence of cicletanine-induced hyponatremia that we observed appears to be similar to that of thiazide-induced hyponatremia, although previous studies have shown variable incidences of thiazide-induced hyponatremia. Gross et al [15] reported an estimated incidence of 11% in 114 elderly patients. According to Clayton et al [16], the incidence was 13.7% in 951 adult patients. Interestingly, a population-based study reported a higher prevalence (32.4%) of thiazide-associated hyponatremia [17].

In comparison with hyponatremia, cicletanine-induced hypokalemia in our patients was less frequent (11.8%) and milder in severity. The association between hypokalemia and use of cicletanine was also clear. The simultaneous occurrence of hyponatremia and hypokalemia suggests that the diuretic property of cicletanine induces natriuresis and kaliuresis. Consistently, Wagner et al [8] reported that both hydrochlorothiazide and cicletanine had more natriuretic, diuretic, and kaliuretic effects than placebo. However, they showed that 150 mg of cicletanine had less kaliuresis than 25 mg of hydrochlorothiazide, a finding that is compatible with our results. According to Singer et al [9], cicletanine has milder natriuretic effects than thiazides and is relatively safer than thiazides with lower risk of developing hypokalemia. These findings suggest that cicletanine is a favorable and well-tolerated option for the treatment of hypertension, compared to hydrochlorothiazide [8,9].

Advanced age, female gender, and low body weight were known to be risk factors of thiazide-induced hyponatremia [16,18]. However, these factors were not significantly associated with cicletanine-induced hyponatremia in our study. As expected, patients with hyponatremia had a longer duration of cicletanine administration. It is not clear why patients with cicletanine-induced hyponatremia had lower levels of serum protein than those without hyponatremia. In patients with cicletanine-induced hypokalemia, the serum chloride level was decreased, most likely due to hypokalemic metabolic alkalosis. However, we did not find that the serum total CO_2 level was significantly different between patients with and without hypokalemia.

This study has limitations because it involved clinical data from a small number of patients that were retrospectively analyzed. The chance of observation may increase in parallel with the duration of medication. Only some of the patients had urine electrolyte data, but they were all compatible with diuretic-induced hyponatremia and hypokalemia [19,20]. We excluded patients who had histories of electrolyte imbalance before cicletanine administration. Importantly, most of our patients with cicletanine-induced hyponatremia and hypokalemia recovered within 2 weeks of discontinuation of the drug (17 of 19 patients, 89.5%).

In conclusion, we documented cicletanine-induced hyponatremia and hypokalemia in kidney transplant patients. To the best of our knowledge, there have been no clinical studies on cicletanine-associated electrolyte disorders. It may be emphasized that patients using cicletanine need to be monitored for electrolyte disturbance as in cases with thiazide diuretic use. Further studies are required to determine conclusively whether cicletanine induces hyponatremia or hypokalemia in other scenarios of CKD and in a population with normal kidney function.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

[1] Weir MR, Burgess ED, Cooper JE, Fenves AZ, Goldsmith D, McKay D, Mehrotra A, Mitsnefes MM, Sica DA, Taler SJ: Assessment and management of hypertension in transplant patients. *J Am Soc Nephrol* 26:1248–1260, 2015

[2] Meng L, Fu B, Zhang T, Han Z, Yang M: Salt sensitivity of blood pressure in non-dialysis patients with chronic kidney disease. *Ren Fail* 36:345–350, 2014

[3] Moes AD, Hesselink DA, Zietse R, van Schaik RH, van Gelder T, Hoorn EJ: Calcineurin inhibitors and hypertension: a role for pharmacogenetics? *Pharmacogenomics* 15:1243–1251, 2014

[4] Kalinowski L, Szczepańska-Konkel M, Jankowski M, Angielski S: Cicletanine: new insights into its pharmacological actions. *Gen Pharmacol* 33:7–16, 1999

[5] Yasu T, Imanishi M: Effects of cicletanine on prostaglandin I_2 and E_2 levels in patients with essential hypertension. *Am J Hypertens* 10: 750–755, 1997

[6] Tarrade T, Berthet P, Paillasseur JL, Bosquet D, Allard M: Antihypertensive effectiveness and tolerance of cicletanine. Results obtained with monotherapy in a large population. *Arch Mal Coeur Vaiss* 82:91–97, 1989

[7] Tarrade T, Guinot P: Efficacy and tolerance of cicletanine, a new antihypertensive agent: overview of 1226 treated patients. *Drugs Exp Clin Res* 14:205–214, 1988

[8] Wagner F, Malice MP, Wiegert E, McGrath HE, Gildea J, Mitta S, Van Dyck K, De Lepeleire I, Johnson-Levonas AO, Sisk CM, Fernandez R, Greenwalt DM, Beals C, Carey RM, Nunes I: A comparison of the natriuretic and kaliuretic effects of cicletanine and hydrochlorothiazide in prehypertensive and hypertensive human. *J Hypertens* 30:819–827, 2012

[9] Singer DR, Markandu ND, Sugden AL, MacGregor GA: A comparison of the acute effects of cicletanine and bendrofluazide on urinary electrolytes and plasma potassium in essential hypertension. *Eur J Clin Pharmacol* 39:227–232, 1990

[10] Ando K, Ono A, Sato Y, Asano S, Fujita T: Involvement of the sympathetic nervous system in antihypertensive effect of cicletanine in salt-loaded young spontaneously hypertensive rats. *Am J Hypertens* 7:550–554, 1994

[11] Greven J: Effects of cicletanine on kidney function. 1. Clearance and micropuncture studies in anesthetized rats. *J Pharmacol Exp Ther* 273:1190–1196, 1995

[12] Monroy A, Plata C, Gamba G, Droy-Lefaix MT, Garay RP: Lack of effect of cicletanine and its sulfoconjugated metabolite on the thiazide receptor expressed in Xenopus oocytes. *Arch Mal Coeur Vaiss* 92:1001–1004, 1999

[13] Passa P: Cicletanine tolerance in hypertensive patients with metabolic disorders. *Arch Mal Coeur Vaiss* 82:135–138, 1989

[14] Combs S, Berl T: Dysnatremias in patients with kidney disease. *Am J Kidney Dis* 63:294–303, 2014

[15] Gross P, Ketteler M, Hausmann C, Reinhard C, Schömig A, Hackenthal E, Ritz E, Rascher W: Role of diuretics, hormonal derangements, and clinical setting of hyponatremia in medical patients. *Klin Wochenschr* 66:662–669, 1988

[16] Clayton JA, Rodgers S, Blakey J, Avery A, Hall IP: Thiazide diuretic prescription and electrolyte abnormalities in primary care. *Br J Clin Pharmacol* 61:87–95, 2006

[17] Rodenburg EM, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, Stricker BH, Visser LE: Thiazide-associated hyponatremia: a population-based study. *Am J Kidney Dis* 62: 67–72, 2013

[18] Glover M, Clayton J: Thiazide-induced hyponatraemia: epidemiology and clues to pathogenesis. *Cardiovasc Ther* 30:e219–e226, 2012

[19] Reynolds RM, Padfield PL, Seckl JR: Disorders of sodium balance. *BMJ* 332:702–705, 2006

[20] Weiner ID, Wingo CS: Hypokalemia—consequences, causes, and correction. *J Am Soc Nephrol* 8:1179–1188, 1997