The Optimal Dose of Potassium Citrate in the Treatment of Children with Distal Renal Tubular Acidosis

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Abstract

Background : Distal renal tubular acidosis (RTA) is a common cause of intractable calcium nephrolithiasis. In adults, the use of potassium citrate (PC) in distal RTA effectively decreases metabolic acidosis and the risk of calcium oxalate stone but it cannot decrease the risk of calcium phosphate stone. However, there is no report for the optimal dose of PC and the risk of calcium stone in distal RTA in children.

Objective : To evaluate the optimal dose of PC that minimizes the risk of calcium nephrolithiasis in children with distal RTA.

Method : Prospective study

Patients : Children who have distal RTA and were followed-up for 4 months. Patients were studied in a control phase, 1 month of PC 2 mEq/kg/day, 2 months of PC 3 mEq/kg/day and 1 month of PC 4 mEq/kg/day. The urine specimens of 41 normal children were measured for the reference value of the parameters determining the risk of calcium stone.

Results : Eight children (mean age of 10 $\pm$ 3.7 years, female : male = 6 : 2) with distal RTA were studied during the control phase and after receiving PC 2 mEq/kg/day for 1 month. Treatment with PC 2 mEq/kg/day was not able to normalize serum bicarbonate and caused no significant change in the urine citrate/creatinine ratio, and activity production of calcium phosphate stone but it caused a significant decrease in the urine calcium/citrate ratio.

Although PC 3 mEq/kg/day for 1 month normalized plasma bicarbonate, only this dose given for 2 months caused a significant increase in the urine citrate/creatinine ratio and urine calcium/citrate ratio to values that were not different from normal children, while the activity production of calcium phosphate stone did not decrease to normal level. The effect of PC 4 mEq/kg/day was similar to that of 3 mEq/kg/day.

Conclusion : Potassium citrate 3 mEq/kg/day for 2 months effectively normalized serum bicarbonate and decreased the risk of calcium oxalate stone but this treatment was theoretically unable to reduce the risk of calcium phosphate stone in children with distal RTA.

Key word : Potassium Citrate, Distal Renal Tubular Acidosis

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Distal renal tubular acidosis (RTA) is a common cause of intractable nephrocalcinosis(1). This defect is associated with high urinary pH, hypercalciuria and low urinary citrate, which leads to the formation of calcium oxalate and calcium phosphate stones by increasing urinary saturation and lowering inhibitor activity.

Therapy aims at correction of acidosis at a rate commensurate with risks of electrolyte and acid base abnormalities and improved growth velocity(2). Prevention of nephrocalcinosis, which may lead to chronic interstitial nephritis with scarring and glomerulosclerosis is also important. In adult patients, clinical use of potassium citrate can decrease the risk of calcium oxalate stone formation, but it can not decrease calcium phosphate stone formation(3). In children with distal RTA, potassium citrate or bicarbonate at doses of 2-3 mEq/kg/day maintain normal growth(2,4). There is no known study in children showing the optimal dose of potassium citrate which decreases the risk of calcium nephrolithiasis. This study reports the appropriate doses of potassium citrate therapy in children with distal renal tubular acidosis in order to minimize the risk of calcium nephrolithiasis.

METHOD

Patient selection

The patients selected for this study were 16 years old or younger who were treated at Ramathibodi Hospital from 1987 to 1999 and met the following criteria: 1) had persistent metabolic acidosis and plasma total carbon dioxide content <17.5 mmol/L, 2) had urine pH >5.5 during metabolic acidosis, and 3) had normal glomerular filtration rate (GFR) by estimating creatinine clearance.

After informed written consent was obtained, the patients stopped previous medication for 2-4 weeks until they had metabolic acidosis. They were hospitalized and venous blood was obtained for determination of blood gas, sodium, potassium, chloride, total carbon dioxide content, calcium, phosphorus, magnesium, and creatinine. Urine was collected in 8-hour pools for determination of total volume, pH, calcium, phosphorus, magnesium, sodium, potassium, chloride, creatinine, and citrate and in 24-hour pools for determination of titratable acid, ammonia, and bicarbonate to calculate net acid excretion (NAE). Pre-treatment nephrocalcinosis was identified by plain X-ray KUB.

After the initial evaluation, all patients began treatment with 2 mEq/kg/day of potassium citrate daily in 3 divided doses for 1 month. The blood and overnight 8-hour urine pools of patients were re-evaluated according to the same initial procedure. The patients were further instructed to take 3 mEq/kg/day of potassium citrate for 2 months and 4 mEq/kg/day for 1 month, successively. After finishing each period, they were re-evaluated according to the same initial protocol.

Compliance of medication regimen was confirmed by counting the potassium citrate packages. Adverse events and gastrointestinal symptoms were assessed at each follow-up visit.

Forty one healthy children, aged 5-15 years, were evaluated using laboratory protocol which included overnight 8-hour urine pools for determination of volume, urine citrate, creatinine, magnesium, calcium, oxalate, and phosphate.

By using a blood gas analyzer, venous blood gas was evaluated for pH and pCO_2. Serum electrolytes, and ionized magnesium were determined by the ion selective exchange method, serum calcium by the O-cresolphthalein method, serum phosphate by the phosphomolybdate method, and serum creatinine by the Jaffe method.

Eight-hour urine specimens were collected and refrigerated at 2-8°C for less than 1 day and then evaluated for volume, pH by pH meter, urine calcium by the O-cresolphthalein method, urine phosphate by the phosphomolybdate method, urine magnesium by colori method, urine sodium and potassium by Quik Lyte method, creatinine by the Jaffe method, and urine citrate by citrate lyase technique.

The creatinine clearance was calculated to estimate the glomerular filtration rate (GFR) and the activity production (AP) of calcium phosphate stone was calculated by using the formular[5].

$$\text{AP (CaP) index} = \frac{B \times \text{calcium}^{1.07} \times \text{phosphate}^{0.7} \times (\text{pH} - 4.5)^{6.8}}{\text{citrate}^{0.2} \times \text{volume}^{1.31}}$$

$$\text{Factor } B = 3.2 \times 10^{-3}$$

Statistical analysis

The data of citrate/creatinine, calcium/citrate and AP (CaP) index of patients were analysed among different doses of potassium citrate by Kruskal-Wallis test. A p-value of less than 0.05 was considered significant.

RESULTS

Normal children

Twenty healthy children (14 males and 6 females) aged 5-10 years and twenty-one children (12 males and 9 females) aged 10-15 years were evaluated and their 8-hour urine specimens were collected. Mean urinary citrate/creatinine, calcium/citrate and AP (CaP) were evaluated according to age groups and sex (Table 1).

Patient population

Eight patients (6 females and 2 males) with a mean age of 10 ± 3.7 years were included in the study. The patients were previously diagnosed with primary distal RTA since age 1 month to 10 years. Failure to thrive, weakness, polyuria and polydipsia were predominant symptoms. All patients received $NaHCO_3$, and KCl before starting the study and some had poor compliance.

After discontinuing previous medication, the patients had hypokalemic hyperchloremic metabolic acidosis (Table 2). Mean urinary net acid excretion was 57.41 (25-65) $\mu Eq/m^2/min$ and urine pH were above 5.5. Nephrocalcinosis was visualized on plain X-ray KUB of all patients. Mean urinary calcium, calcium/citrate ratio, and AP (CaP) were significantly higher than those of normal children, while citrate/creatinine ratio were significantly lower (Table 3). The initial enrollment included 8 patients receiving different doses and durations of potassium citrate administration. Six patients completed the study while two patients lost follow-up after taking potassium citrate of 3 mEq/kg/day for 1 month. However, one of them continued to receive potassium citrate of 4 mEq/kg/day.

After the patients received 2 mEq/kg/day of potassium citrate for 1 month, the serum bicarbonate were not normalized and urine citrate/creatinine ratio, and AP (CaP) were not significantly changed, whereas, calcium/citrate ratio was significantly decreased ($p<0.05$) (Table 3). Although potassium citrate 3 mEq/kg/day for 1 month normalized plasma bicarbonate (Table 2), it increased urine pH, potassium and citrate but decreased urine calcium. There was no significant change in urine citrate/creatinine ratio and AP (CaP) (Table 3). When patients received 3 mEq/kg/day of potassium citrate for 2 months, urine citrate/creatinine ratio was significantly

Table 1. The mean ± SD of urinary chemistries of normal children.

Sex	Age (yr)	Total	Mean age (yr)	Citrate/Cr	Ca/citrate	AP (CaP)
Male	5-10 yr	14	7.86 ± 1.45	0.18 ± 0.12	0.44 ± 0.31	34.63 ± 64.82
	10-15 yr	12	12.1 ± 1.45	0.19 ± 0.12	0.39 ± 0.26	11.13 ± 9.55
Female	5-10 yr	6	7.66 ± 1.50	0.21 ± 0.11	0.34 ± 0.26	48.76 ± 40.86
	10-15 yr	9	12.4 ± 1.71	0.19 ± 0.06	0.31 ± 0.14	20.35 ± 31.33

Table 2. The mean ± SD of serum chemistries of the studied patients after treatment with potassium citrate.

Value	Potassium citrate (mEq/kg/day)				
	0 (n = 8)	2 (n = 8)	3* (n = 8)	3**(n = 6)	4 (n = 7)
Sodium (mmol/L)	142 ± 2.43	139 ± 2.50	141 ± 4.26	141 ± 2.80	139.57 ± 2.64
Potassium (mmol/L)	3.4 ± 0.53	3.9 ± 0.51	4.2 ± 0.57	4.1 ± 0.44	4.23 ± 0.49
Chloride (mmol/L)	113 ± 3.5	109 ± 3.9	107 ± 3.8	107 ± 4.00	106.57 ± 3.50
Carbonate (mmol/L)	15.5 ± 1.7	17.4 ± 3.8	23.1 ± 1.3	22.5 ± 5.5	20.41 ± 3.17
Calcium (mmol/L)	2.2 ± 0.16	2.2 ± 0.17	2.4 ± 0.1	2.35 ± 0.12	2.35 ± 0.19
Phosphorus (mmol/L)	1.3 ± 0.33	1.33 ± 0.30	1.4 ± 0.31	1.47 ± 0.22	1.36 ± 0.29

* one month after treatment
** two months after treatment

Table 3. Effect of potassium citrate on urine chemistries of the studied patients with distal RTA expressed as median and quartile.

Value (8 h)	Control	Potassium citrate (mEq/kg/day)					
		0	2	3*	3**	4	P value
PH		7.84 (7.09-8.17)	8.28 (7.83-8.43)	8.31 (8.15-8.81)	8.03 (7.52-8.04)	8.07 (7.78-8.40)	
Potassium (mmol/L)		8.22 (4.41-14.23)	7.10 (4.6-15.16)	21.77 (11.12-32.0)	30.59 (11.4432.12)	14.83 (11.70-49.23)	
Calcium (mmol/L)	0.6 (0.44-0.99)	0.98 (0.78-2.0)	0.38 (0.26-0.86)	0.69 (0.29-0.93)	0.41 (0.30-0.82)	0.39 (0.23-0.82)	
Phosphorus (mmol/L)	6.7 (4.7-10.7)	4.83 (1.72-5.98)	4.18 (1.79-5.8)	3.76 (1.61-6.47)	4.02 (3.58-7.44)	3.90 (3.00-7.11)	
Citrate/creatinine	0.1680 (0.13-0.22)	0.0098 (0.0024-0.0157)	0.0215 (0.012-0.059)	0.0390 (0.0180-0.1790)	0.2150+ (0.064-0.294)	0.1354+ (0.09-0.38)	0.02
Calcium/citrate	0.33 (0.20-0.45)	178.43 (56.87-893.61)	22.73 (7.94-43.33)	16.24 (3.93-30.13)	1.86+ (0.72-4.73)	0.392+ (0.311-0.44)	0.0001
AP (CaP)	8.85 (2.94-24.00)	736.84 (477.72-946.09)	822.57 (394.81-2531.64)	1,477 (784.91-2528.81)	274.24+ (203.99-289.74)	250+ (92.03-730.71)	0.0001

* one month after treatment
** two month after treatment
+ $p<0.05$

increased from 0.009 to 0.215 ($p<0.005$) and was normal when compared to the healthy children (Table 3). In addition, urine calcium/citrate ratio was significantly increased to 1.86 (0.72-4.73) ($p<0.005$) and was normal when compared to the healthy children. Although mean AP (CaP) was significantly decreased from 736.84 to 274.24 ($p<0.005$), but it was not in the normal range (2.94-24.00).

The effects of 4 mEq/kg/day and 3 mEq/kg/day of potassium citrate were similar. There were normal urine citrate/creatinine and calcium/citrate ratios (Table 3). One patient lost follow-up after

receiving 4 mEq/kg/day of potassium citrate. There was an abnormally high level of urine citrate in one patient, no matter how much potassium citrate he received.

This study shows that treatment with short-term potassium citrate is unable to normalize urine AP (CaP) to normal level.

There was no adverse effect of potassium citrate in the present study. All patients had medication compliance of more than 95 per cent.

DISCUSSION

Distal RTA is characterized by the failure to establish a significant hydrogen ion in urine, causing chronic metabolic acidosis and negative calcium balance, consequently lead to failure to thrive and kidney stone[6]. Correction of metabolic acidosis by alkali therapy can improve growth[3,4,6].

Chronic metabolic acidosis increased bone resorption, renal wastage of sodium, potassium, calcium and phosphate, resulting in supersaturation of calcium and phosphate in urine[7]. Citrate is a powerful inhibitor of aggregation of calcium oxalate crystals. A previous study has shown that hypokalemia and acidosis contribute to the hypocitraturia found in distal RTA[8]. The combination of supersaturation, alkaline urine and low citrate excretion favors precipitation of calcium phosphate and calcium oxalate stones. The present study also showed high calcium and calcium/citrate ratio in urine of untreated patients.

Previous studies in children treated with alkali therapy showed favorable results in decreasing stone formation[3,9,10].

Potassium citrate was used in the present study because citrate is a good alkali and it not only restores the serum potassium, but also decreases urine calcium more effectively than sodium alkali[11,12]. Urine calcium/citrate ratio which has strong correlation with calcium oxalate stone formation was used to evaluate the risk of this stone formation[13]. According to the correlation between AP (CaP) with EQUIL 2 program, AP (CaP) was used to evaluate the risk of calcium phosphate stone formation[14,15].

This study has demonstrated that 3 mEq/kg/day and 4 mEq/kg/day of potassium citrate maintained serum potassium, bicarbonate within normal limit, increased urinary citrate and citrate/creatinine ratio but significantly diminished the urinary calcium excretion. Such changes in the urinary environment produced by these doses of potassium citrate could significantly decrease urine calcium/citrate ratio and consequently reduce the risk of calcium oxalate stone formation. There was an abnormally high urine citrate/creatinine ratio in one patient who did not have nephrocalcinosis on the plain KUB X-ray. He was diagnosed with distal RTA at aged 4 months, and his net acid excretion was quite low (25 $\mu Eq/m^2/min$). The reason for high urine citrate/creatinine ratio in this boy is not clear. However, the risk of calcium oxalate and calcium phosphate stone formation in this patient was similar to other patients.

The significant elevation in urinary pH seen with potassium citrate therapy caused a decrease in urine AP (CaP), and increased the risk of calcium phosphate stone formation. However, the hypocalciuric action of potassium citrate apparently negated the effect of the increased phosphate dissociation and, therefore in the present study, the AP (CaP) reduced, but remained much higher than normal level.

A previous study by Preminger et al also showed that the saturation of calcium phosphate stone was not changed after potassium citrate therapy for 3 years. However, there was no new stone formation in that study[3].

The present study had several limitations. The number of subjects was too small to allow definitive assessment of dose effectiveness of potassium citrate. Moreover, this study had limited time for evaluating the effective dosage.

A large number of patients and long-term evaluation would be required to determine whether there are differences between 3mEq/kg/day and 4 mEq/kg/day of potassium citrate therapy. However, the present study shows 4 mEq/kg/day of potassium citrate has no more benefit over 2 months than 3 mEq/kg/day of potassium citrate in terms of reducing the risk of calcium stone in distal RTA patients.

SUMMARY

In distal RTA patients, treatment with potassium citrate 3 mEq/kg/day for 2 months can normalize metabolic acidosis and substantially reduce the risk of calcium oxalate stone formation, but cannot normalize the risk of calcium phosphate stone formation.

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ขนาดของโปแทสเซียม ซิเตรตที่เหมาะสมในการรักษาภาวะร่างกายเป็นกรดจากความผิดปกติของทิวบูลส่วนปลายของไตในเด็ก

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ภาวะร่างกายเป็นกรดจากความผิดปกติของทิวบูลส่วนปลายของไตเป็นสาเหตุสำคัญทำให้เกิดนิ่วในระบบทางเดินปัสสาวะ ในผู้ใหญ่การใช้ยาโปแทสเซียม ซิเตรตสามารถแก้ไขภาวะร่างกายเป็นกรดและลดความเสี่ยงของการเกิดนิ่วชนิดแคลเซียมออกซาเลต แต่ไม่สามารถลดความเสี่ยงของการเกิดนิ่วชนิดแคลเซียมฟอสเฟตได้ อย่างไรก็ดียังไม่มีรายงานขนาดของโปแทสเซียม ซิเตรตที่เหมาะสมและโอกาสเสี่ยงต่อการเกิดนิ่วในผู้ป่วยเด็ก

จุดประสงค์ : หาขนาดที่เหมาะสมของโปแทสเซียม ซิเตรตที่สามารถลดโอกาสเกิดนิ่วชนิดแคลเซียมในเด็กที่เป็นโรคภาวะเป็นกรดจากทิวบูลส่วนปลายของไตผิดปกติ

วิธีการ : Prospective study

ผู้ป่วย : ผู้ป่วยเด็กที่เป็นโรคภาวะเป็นกรดจากทิวบูลส่วนปลายของไตผิดปกติจะได้รับการติดตามนาน 4 เดือน โดยเก็บข้อมูลในระยะควบคุม ระยะที่ได้รับโปแทสเซียม ซิเตรตขนาด 2 mEq/กก/วัน นาน 1 เดือน ระยะที่ได้รับโปแทสเซียม ซิเตรตขนาด 3 mEq/กก/วัน นาน 2 เดือน และระยะที่ได้รับโปแทสเซียม ซิเตรตขนาด 4 mEq/กก/วัน นาน 1 เดือน ได้เก็บปัสสาวะเด็กปกติ 41 ราย เพื่อหาค่าเปรียบเทียบในการคำนวณโอกาสเสี่ยงของการเกิดนิ่วจากแคลเซียม

ผลการรักษา : การศึกษาผู้ป่วย 8 ราย (อายุ 10 $\pm$ 3.7 ปี, ชาย : หญิง = 6 : 2) พบว่าการให้โปแทสเซียม ซิเตรตขนาด 2 mEq/กก/วัน ไม่สามารถทำให้ค่าไบคาร์บอเนตในเลือดปกติ, ไม่พบการเปลี่ยนแปลงอย่างมีนัยสำคัญ ในค่า citrate : creatinine ในปัสสาวะและค่า activity production ของนิ่วชนิดแคลเซียมฟอสเฟต แต่พบว่า calcium : citrate ในปัสสาวะมีการลดลงอย่างมีนัยสำคัญ การให้โปแทสเซียม ซิเตรตขนาด 3 mEq/กก/วัน สามารถทำให้ค่าไบคาร์บอเนตในเลือดมีค่าปกติได้แต่ต้องให้ขนาดนี้นาน 2 เดือน จึงจะทำให้ citrate : creatinine และ calcium : creatinine ในปัสสาวะมีค่าไม่แตกต่างจากเด็กปกติ ขณะที่ไม่สามารถทำให้ค่า activity production ของการเกิดนิ่วแคลเซียมฟอสเฟตลดลงเป็นปกติได้ การใช้โปแทสเซียม ซิเตรตขนาด 4 mEq/กก/วัน ได้ผลไม่แตกต่างจากขนาด 3 mEq/กก/วัน

สรุป : โปแทสเซียม ซิเตรตขนาด 3 mEq/กก/วัน นาน 2 เดือน ได้ผลดีทำให้ค่าไบคาร์บอเนตในเลือดปกติและลดความเสี่ยงในการเกิดนิ่วชนิดแคลเซียมออกซาเลต แต่ไม่สามารถลดความเสี่ยงจากการเกิดนิ่วชนิดแคลเซียมฟอสเฟตในเด็กที่มีภาวะร่างกายเป็นกรดจากความผิดปกติของทิวบูลส่วนปลายของไตได้

คำสำคัญ : โปแทสเซียม ซิเตรต, ภาวะร่างกายเป็นกรดจากความผิดปกติของทิวบูลส่วนปลาย

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