Published in final edited form as:

Pediatrics. 2009 August ; 124(2): e300–e304. doi:10.1542/peds.2009-0217.

Empiric use of Oral Potassium Citrate Reduces Symptomatic Kidney Stone Incidence with the Ketogenic Diet

Melanie A. McNally, BS,

Johns Hopkins University School of Medicine

Paula L. Pyzik, BS,

Department of Neurology and Pediatrics, Johns Hopkins Hospital

James E. Rubenstein, MD,

Department of Neurology and Pediatrics, Johns Hopkins Hospital

Rana F. Hamdy, MD, MPH, and

Department of Pediatrics, Johns Hopkins Hospital

Eric H. Kossoff, MD[†]

Department of Neurology and Pediatrics, Johns Hopkins Hospital

Abstract

OBJECTIVE—Kidney stones are an adverse event with the ketogenic diet (KD), occurring in approximately 6% of children who are started on this therapy for intractable epilepsy. Potassium citrate (Polycitra K®) is a daily oral supplement that alkalinizes the urine and solubilizes urine calcium, theoretically reducing the risk of kidney stones.

METHODS—Children at Johns Hopkins Hospital starting the KD from 2000–2008, with at least 1 month of follow-up, were evaluated (n=313). From 2000–2005, children were treated with daily Polycitra K® at 2 meq/kg/day only in the setting of identified hypercalciuria; whereas since 2006 it has been started in all children empirically at KD onset.

RESULTS—Polycitra K® was administered to 198 children preventatively overall, of whom 4 (2.0%) developed kidney stones, compared to 11 of 105 (10.5%) who did not receive Polycitra K®, $P=.003$. Two children since 2006 refused Polycitra K®, one of whom developed a kidney stone. Successful empiric administration of Polycitra K® at KD onset resulted in a kidney stone incidence of 0.9% (1 of 106) compared to administration only due to hypercalciuria, 6.7% (13 of 195), $P=.02$. Polycitra K® resulted in less acidic urine (mean pH 6.8 vs. 6.2, $P=.002$), but not reduced serum acidosis. No side effects of oral citrates were reported.

CONCLUSIONS—Oral potassium citrate is an effective preventative supplement against kidney stones in children receiving the KD, achieving its goal of urine alkalinization. Universal supplementation is warranted.

[†]Author for Correspondence: Suite 2158 – 200 North Wolfe Street, David M. Rubenstein Child Health Building, The John M. Freeman Pediatric Epilepsy Center, The Johns Hopkins Hospital, Baltimore, MD 21287-1000, Phone: (410) 955-4259, Fax: (410) 614-2297, ekossoff@jhmi.edu.

Keywords

ketogenic; diet; epilepsy; kidney stones; Polycitra

For nearly a century, the ketogenic diet (KD) has been recognized as an effective nonpharmacologic treatment for epilepsy.^{1,2} Despite positive effects on seizure frequency, repeated studies have shown that the KD is associated with an increased prevalence of kidney stones, ranging from 3–6% over a typical 2 year diet duration.^{3–7} Hypercalciuria, urine acidification, and hypocitraturia, all known risk factors for kidney stones,⁸ often occur in patients on the KD.³

In 2000, a study from our group identified that children with hypercalciuria (urine calcium to creatinine ratio typically > 0.2) on the KD were at highest risk for kidney stones.³ Past studies have shown that oral potassium citrate (Polycitra K®) effectively increases urinary pH, increases urinary citrate, and decreases incidence of kidney stones.^{9,10} From 2000–2005, our approach was to treat children on the KD at the time of laboratory-identified hypercalciuria with Polycitra K®. In this group, hypercalciuria occurred in 101 (52%) of 195 patients, usually after 3–6 months.⁷ Unfortunately, the incidence of kidney stones did not decrease with this strategy, with 13 (6.7%) developing stones over this time period.⁷ However, in 10 of these children hypercalciuria was either not noticed, treated, or the child refused treatment with Polycitra K®.⁷

In light of the results from this study, we began empirically giving all children, regardless of hypercalciuria, Polycitra K® at KD initiation. We believed the benefits outweighed any risks and universal use would avoid confusion and improve compliance. In this cohort study, we examined whether empiric Polycitra K® administration could reduce the 6.7% incidence of kidney stones in children started on the KD.⁷

PATIENTS AND METHODS

Medical records of all children started on the KD at Johns Hopkins Hospital from January 1, 2000 to December 31, 2008, with at least 1-month follow-up, were analyzed retrospectively. After an initial 24–48 hour fast, patients' caloric intake was gradually increased at either a 3:1 or 4:1 (fat to protein and carbohydrates) ketogenic ratio over a 3-day period.¹ Children were provided a fluid allotment of approximately 80–90% of their recommended daily requirements, but often increased to 100%.¹ Most children were rarely drinking their fluid requirements even before starting the KD and the fluid allotment is often an increase over their baseline. Children were typically seen in the clinic every 3 to 4 months for the first year, and every 6 months thereafter at which time all medications, including Polycitra K®, were confirmed with parents. The presence of a kidney stone was defined as (1) stones or stone fragments found to have been passed in urine or noted in the diaper, (2) gross or microscopic hematuria concurrent with lower flank pain, or (3) evidence on ultrasound or computed tomography scan of a stone or nephrolithiasis.

From January 2000 to December 2005, 195 children were administered the KD and treated with Polycitra K® as described previously, treating only for identified hypercalciuria.⁷ This

group is referred to as the 'reactive' group. From January 2006 to December 2008, all children started on the KD at our institution were started empirically on Polycitra K® at hospital discharge, and further described as the 'empiric' group.

Polycitra K® is available in a powdered packet of 30 meq (milliequivalents) that can be dissolved in fluid or sprinkled onto ketogenic foods such as heavy whipping cream or eggs, with a taste similar to lemons. The prescribed dose of Polycitra K®, 2 meq/kg/day divided twice daily, remained consistent in both groups. In general, most young children (<20 kilograms) received half a packet twice daily for ease of administration, and older patients (>20 kilograms) received approximately one packet twice daily. If a child refused, we recommended sodium citrate tablets (Bicitra®) instead.

Charts and electronic records were reviewed for patient age, gender, immobility (defined as spending the majority of their time in a wheelchair or stroller past age 2 years), carbonic anhydrase inhibitor (topiramate or zonisamide) use, kidney stone occurrence, and Polycitra K® use for both groups. Urine pH and serum CO₂ was analyzed after 3 months on the KD when available. Urine calcium and creatinine were obtained in the 'reactive' group approximately every 3–6 months but no longer monitored regularly in the 'empiric' group as it did not affect management, added cost, and our previous study showed no change in hypercalciuria with oral citrates.⁷ Baseline urine pH was examined for the 50 most recent subjects.

This study was approved by the Johns Hopkins Institutional Review Board and all families consented for their information to be included in a centralized database. Categorical data were analyzed using chi square test with Yates correction. Means were compared using a paired two-sample t test. Multiple regression analysis was used to adjust for carbonic anhydrate use and diet duration (in 12 month intervals) when examining for kidney stone occurrence. The significance level for all tests was $P = 0.05$.

RESULTS

Overall effects of receiving Polycitra K®

Between January 2000 and December 2008, 313 children with intractable epilepsy were started on the KD. Seven children discontinued the KD prior to 1 month and 3 children were lost to follow up; these cases were not included in the analysis. Polycitra K® was administered preventatively (either due to presence of hypercalciuria in the 'reactive' group (n=92) or at KD onset in the 'empiric' group (n=106)) to 198 children at some point during their KD care, of whom 4 (2.0%) developed kidney stones. In those children that did not receive Polycitra K®, 11 of 105 (10.5%) developed kidney stones. Between the two groups, preventative use of Polycitra K® decreased the incidence of kidney stones as compared to the group that did not receive Polycitra K® ($P = .003$).

Overall, the median time to kidney stone presentation was 6 months (range: 1–28 months). Only three stones were retrieved and analyzed; they were calcium oxalate, calcium carbonate, and uric acid in composition. Although there were sporadic reports about poor taste of the oral citrate powder, there were no side effects noted with its use.

Comparison of 'reactive' to 'empiric' Polycitra K® approach

From 2000–2005, 195 children were treated with the KD and are referred to as the 'reactive' group. Of this group, 161 (83%) were appropriately treated only when hypercalciuria occurred as planned. In those children not started on Polycitra K®, hypercalciuria was either never present, laboratory results were not available at clinic visits, or hypercalciuria not treated due to neurologist or parent decision. In total, 92 children (47%) received Polycitra K® in the 'reactive' group, 10 directly as a result of a symptomatic kidney stone.

From 2006–2008, 108 children were started on the KD and are referred to as the 'empiric' group. Of this group, 106 (98%) reported compliance with the recommended universal Polycitra K® use, $P < .001$. Two children in the 'empiric' group did not receive Polycitra K®. One of these children, a 9-month old male, was not given Polycitra K® due to parental confusion with provided prescriptions and developed hematuria and a kidney stone after 3 months. Symptoms resolved with extra fluids and Polycitra K®, and he remained on the KD for a total of 17 months. A second child, a 4-year-old female, has repeatedly refused Polycitra K® due to taste according to her parents. She has not developed a stone or hypercalciuria to date and has remained on the KD for the past 18 months.

Table 1 summarizes the comparison between the 'reactive' ($n=195$) and 'empiric' ($n=106$) approaches, excluding the two children in the 'empiric' group who were not given Polycitra K®. Empiric administration of Polycitra K® at KD onset resulted in a kidney stone prevalence of 0.9% compared to preventive administration (6.7%, $P=.02$). Only one child in the 'empiric' group who was receiving Polycitra K® developed a kidney stone. This 2-year-old female developed a stone and hematuria after 5 months on the KD. She was not receiving any carbonic anhydrase inhibitor and her parents reported daily use of Polycitra K® as prescribed. Urine pH was 6.0 and serum CO_2 13 mg/dl at the time of the stone. Lithotripsy was performed and she has remained on the KD (and Polycitra K®) 21 months to date without any further stones.

Both diet duration and use of carbonic anhydrase inhibitor showed slight differences between the 'empiric' and 'reactive' groups. Mean diet duration in the 'empiric' group was 13.3 months compared to a mean diet duration of 15.6 months in the 'reactive' group ($P=.11$). Use of carbonic anhydrase inhibitor was 53/106 (50%) in the 'empiric' group, while it was 82/195 (42%) in the 'reactive' group ($P=.19$). In a multivariate logistic regression adjusting for both diet duration and carbonic anhydrase inhibitor use, there was an odds ratio of 6.32 (95% CI: 0.79–50.67), $P=.08$. The mean urine pH in the empiric group was higher (6.8 vs. 6.2, $P=.002$), although there was not a similar increase in serum CO_2 . As a comparison, the baseline urine pH prior to starting the KD was 6.8 (SD=0.9).

DISCUSSION

Overall, these results confirm previous evidence that Polycitra K® administration is effective for kidney stone prevention in children receiving the KD.⁷ The results are perhaps more convincing now than in our previous study, with a 5-fold overall decrease in kidney stone incidence with its use overall, compared to a 3-fold reduction previously.⁷ Polycitra K® was well-tolerated as a supplement and no clear adverse effects were reported.

Comparing the two approaches of Polycitra K® administration at our center, there was a 7-fold drop in the incidence of kidney stones with an empiric, universal treatment approach since 2006 (0.9% vs. 6.7%). This approach is easier to follow as there is no longer any need for regular monitoring of the urine calcium to creatinine ratio. Additionally, the ketogenic diet team can simply confirm with parents that oral citrates are being administered, similarly to multivitamins and calcium. Using Polycitra K® from the start of the KD may also theoretically prevent stones from beginning to form, as no urine calcium to creatinine values were obtained until the 3 month clinic visit in the ‘reactive’ approach. We are now recommending Polycitra K® for all children in the ‘reactive’ cohort (started on the KD prior to 2006) who still remain on the KD to date.

Relative costs need to be considered for any treatment, and the average cost for Polycitra K® for the median 14 months in this study is approximately \$630 (www.drugstore.com). Using cost analysis to adjust for the overall 5-fold decrease in incidence with use, the number of children needed to treat to prevent one kidney stone is 11.7, hence \$7,371 worth of Polycitra K®. The cost for treatment of an individual child with a kidney stone, including pediatric urology clinic visits (2), renal/bladder ultrasounds, urinalysis, and analgesic medications is approximately \$2,100. If necessary, the costs of admission for intravenous fluids, pain management, as well as time off work and school, would then approach the combined cost of preventative oral potassium citrates. Although not always required, lithotripsy would cost an additional \$7,950 at our institution.

As would be predicted theoretically, urine pH within the ‘empiric’ group was significantly higher than the ‘reactive’ group and identical to baseline values before the KD. This was even higher than the median urine pH of 6.0 reported prior to 2000, before oral citrates were first prescribed.³ Alternatively, serum CO₂ was not different between the groups, suggesting that Polycitra K® may not affect serum acidosis and its therapeutic effects may be primarily due to urine alkalosis. A future potential method to monitor compliance with Polycitra K® might be to review urine pH data at KD clinic visits. Additionally, possibly increasing the dose if the urine pH is low (e.g. < 6.5) may be valuable in further avoiding kidney stones, as evident in the single child since 2006 with a stone despite Polycitra K® and a urine pH of 6.0.

CONCLUSIONS

We strongly believe that universal use of Polycitra K® is warranted in all children starting the KD, with clear benefits outweighing risks. We advise initial education about the importance of regular Polycitra K® use at the time of KD onset and subsequent reinforcement at each follow-up clinic. Further studies may help determine if higher doses of Polycitra K® would be completely preventative or could perhaps be combined with other supplements such as multivitamins to aid compliance.

Acknowledgments

Financial disclosure and conflict of interest: This study was supported in part at Johns Hopkins by the Pediatric Clinical Research Unit, NIH/National Center for Research Resources grant M01-RR00052 and The Carson Harris Foundation. The authors acknowledge the support of Dr. Lori Jordan with the relative cost analysis.

Abbreviations

KD	ketogenic diet
meq	milliequivalents

References

1. Freeman JM, Kossoff EH, Hartman AL. The ketogenic diet: One Decade Later. *Pediatrics*. 2007; 119(3):535–543. [PubMed: 17332207]
2. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol*. 2008; 7(6):500–506. [PubMed: 18456557]
3. Furth SL, Casey JC, Pyzik PL, et al. Risk factors for urolithiasis in children on the ketogenic diet. *Pediatr Nephrol*. 2000; 15(1–2):125–128. [PubMed: 11095028]
4. Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EPG. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. *Epilepsia*. 2002; 43(10):1168–1171. [PubMed: 12366731]
5. Kielb S, Koo HP, Bloom DA, Faerber GJ. Nephrolithiasis associated with the ketogenic diet. *J Urology*. 2000; 164(2):464–466.
6. Kang HC, Kim YJ, Kim DW, Kim HD. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. *Epilepsia*. 2005; 46(2):272–279. [PubMed: 15679508]
7. Sampath A, Kossoff EH, Furth SL, Pyzik PL, Vining EPG. Kidney stones and the ketogenic diet: risk factors and prevention. *J Child Neurol*. 2007; 22(4):375–378. [PubMed: 17621514]
8. Pak CY, Sakhaee K, Fuller CJ. Physiological and physiochemical correction and prevention of calcium stone formation by potassium citrate therapy. *Trans Assoc Am Physicians*. 1983; 96:294–305. [PubMed: 6679957]
9. Pak CY, Sakhaee K, Fuller CJ. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int*. 1986; 30(3):422–428. [PubMed: 3784284]
10. Bushinsky DA. Nephrolithiasis. *J Am Soc Nephrol*. 1998; 9(5):917–924. [PubMed: 9596092]

TABLE 1

Demographics, kidney stone prevalence, and laboratory values as based on the two treatment approaches.

	'Reactive' approach, 2000–2005 (n=195)	'Empiric' approach, 2006–2008 (n=106)	P value
<i>Baseline demographics</i>			
Age, years (mean, SD)	4.3 (3.4)	4.1 (3.6)	.50
Diet duration, months (mean, SD)	15.6 (13.1)	13.3 (9.4)	.11
Gender, female (%)	90 (46%)	56 (52%)	.57
Immobile (%)	47 (24%)	28 (26%)	.76
Carbonic anhydrase use (%)	82 (42%)	53 (50%)	.19
Seizure reduction >50% (%)	128 (66%)	72 (67%)	.78
<i>Results</i>			
Stones, overall (%)	13 (6.7%)	1 (0.9%)	.02
Urine pH (mean, SD)	6.2 (0.7)	6.8 (0.9)	.002
Serum CO ₂ (mean, SD)	20.5 (3.8)	20.1 (3.7)	.61