7-16-2022

Over-the-Counter Alkali Agents to Raise Urine pH and Citrate Excretion: A Prospective Crossover Study in Healthy Adults

Noah E. Canvasser

Marcelino Rivera

Seth K. Bechis

Johann Ingimarsson

John Knoedler

See next page for additional authors

Authors

Noah E. Canvasser, Marcelino Rivera, Seth K. Bechis, Johann Ingimarsson, John Knoedler, Karen Stern, Christa L. Stoughton, Daniel Wollin, Michael Borofsky, Naeem Bhojani, Marawan El Tayeb, Guido Kamphuis, David Leavitt, Ryan S. Hsi, and Kymora B. Scotland

Over-the-Counter Alkali Agents to Raise Urine pH and Citrate Excretion: A Prospective Crossover Study in Healthy Adults

Noah E. Canvasser, Marcelino Rivera, Seth K. Bechis, Johann Ingimarsson, John Knoedler, Karen Stern, Christa L. Stoughton, Daniel Wollin, Michael Borofsky, Naeem Bhojani, Marawan El Tayeb, Guido Kamphuis, David Leavitt, Ryan S. Hsi, and Kymora B. Scotland

OBJECTIVE To assess the effect of 2 over-the-counter alkalizing agents on 24 hour urinary parameters.

MATERIALS AND METHODS Ten healthy volunteers without a history of kidney stones were recruited to complete a baseline 24 hour urinalysis with a 4 day diet inventory. Participants then maintained the same diet on either LithoLyte (20 mEq 2 times per day) or KSPtabs (1 tablet 2 times per day) and submitted another 24 hour urinalysis. The process was repeated with the other supplement. Urinary alkali parameters were compared to baseline, and side effects were elicited with a questionnaire.

RESULTS LithoLyte intake resulted in a non-significant increase in citrate (597-758 mg/day, P =.058, an increase in urine pH (6.46-6.66, P =.028), and a decrease in urine ammonium (41-36 mmol/day, P =.005) compared to baseline. KSPtabs resulted in an increase in citrate (597-797 mg/day, P =.037) and urine pH (6.46-6.86, P =.037), with a non-significant decrease in ammonium (41-34 mmol/day, P =.059). No significant differences were seen comparing urinary analytes between LithoLyte and KSPtabs. With Litholyte, no side effects, mild, moderate, and severe side effects were seen in 50%, 40%, 10%, and 0%, respectively. With KSPtabs, rates were 60%, 20%, 10%, and 10%, respectively.

CONCLUSION In healthy participants without a history of kidney stones, LithoLyte and KSPtabs are effective over-the-counter alkali supplements, with a similar side effect profile to prescription potassium citrate. UROLOGY 00: 1−7, 2022. © 2022 Elsevier Inc.

Urinary citrate is a potent inhibitor of kidney stones[1]; hypocitraturia is a common abnormality in the recurrent stone former.[2] The American Urological Association (AUA) guidelines specifically recommend potassium citrate for urinary alkalization in hypocitraturic calcium stone formers, uric acid stone formers and cystine stone formers.[3] This is based on the significant improvement in urinary parameters, and the reduced risk of recurrent stone disease.[4]

However, there is poor adherence to prescribed potassium citrate therapy.[5] Some patients experience significant gastrointestinal side effects that preclude their ability to tolerate the medication.[6] In addition, the cost of prescription potassium citrate, as well as the size of the pills, can be prohibitive for some patients.

More recently, patients have had increased access to alternative over-the-counter alkali preparations.[7] These typically contain various combinations of both sodium and potassium alkali salts, although the efficacy of these supplements is unknown. Our goal was to assess the effect of two over-the-counter alkalizing agents on 24 hour urinary parameters in healthy adults without a history of kidney stones.

MATERIALS AND METHODS

We performed a prospective crossover study of 2 over-the counter alkali supplements used to raise urine pH and citrate

Declaration of competing interest: *None*

Source of funding: *This was an investigator-initiated project where the protocol, data collection, statistical analysis and drafting of the manuscript was performed by the authors. The study supplements, Litholyte and KSPtabs, and 24 hour urine testing were funded by the manufacturers.*

Institutional Review Board approval: *Yes*

From the Department of Urology, University of California Davis, Sacramento, CA; the Indiana University, Indianapolis, IN; the University of California San Diego, San Diego, CA; the Maine Medical Center, South Portland, ME; the Penn State University, Hershey, PA; the Mayo Clinic, Phoenix, AZ; the Brigham and Women's Hospital, Boston, MA; the University of Minnesota, Minneapolis, MN; the University of Montreal, Montreal, QC, Canada; the Baylor Scott and White Health, Temple, TX; the Amsterdam University Medical Center, Amsterdam, Netherlands; the Henry Ford Health System, Detroit, MI; the Vanderbilt University Medical Center, Nashville, TN; and the University of California Los Angeles, Los Angeles, CA

Address correspondence to: Kymora B. Scotland, M.D., Ph.D., Department of Urology, University of California Los Angeles, 200 UCLA Medical Plaza Suite 140, Los Angeles, CA 90095. E-mail: kscotland@mednet.ucla.edu

Submitted: December 31, 2021, accepted (with revisions): May 2, 2022

https://doi.org/10.1016/j.urology.2022.05.049
0090-4295

excretion. Institutional Review Board approval was obtained prior to study initiation (Vanderbilt IRB 191141). A total of 10 healthy adults without a history of kidney stone disease were recruited and informed consent was obtained.

Over-The-Counter Supplements

The following two supplements were chosen based on the most frequent over-the-counter alkalizing supplements taken by patients, as determined in our previous review.[7]

LithoLyte (Trent Woods, North Carolina) is a flavorless powder containing potassium citrate (200 mg = 4.5 mEq), magnesium citrate (30 mg = 2.5 mEq), and sodium bicarbonate (60 mg = 3.5 mEq), and is formulated as individual 10 mEq packets. Participants dissolved 2 packets in 16 oz of water and ingested 2 times per day per manufacturer recommendations.

KSPtabs (Austin, Texas) are effervescent tablets that contain vitamin B6 (7.5 mg), magnesium citrate/oxide (64 mg = 5 mEq), sodium bicarbonate and/or carbonate (170 mg = 5 mEq), and potassium citrate and/or bicarbonate (160 mg = 5 mEq), for a total of 15 mEq alkali per tablet. Each tablet is dissolved in 16 oz of water and ingested 2 or 3 times per day per manufacturer recommendations. For this study, participants consumed 1 tablet 2 times per day.

We maintained "2 times per day" to be consistent with supplement consumption despite different alkali doses, given potential inconsistency with a mid-day third dose.

24 Hour Urine Collections

Participants collected a total of three 24 hour urine collections and controlled their own diet throughout the study. While completing a diet inventory for 4 days, each participant collected a baseline 24 hour urinalysis (Urine 1) starting at day 4. Then, after a minimum 3 day washout period, participants were randomized 1:1 to start either LithoLyte or KSPtabs following the same diet inventory, and collected another 24 hour urinalysis starting at day 4 (Urine 2). After another washout of at least 3 days, the process was repeated with the other supplement (Urine 3). All 24 hour urine collections were performed at-home and analyzed through Litholink Corporation (LabCorp, Chicago, IL). Participants were blinded to the results of each collection until after study completion.

Adverse Events

Adverse events were assessed based on Common Terminology Criteria for Adverse Events v5.0,[8] with a focus on general and gastrointestinal disorders. Participants were provided an adverse event survey to complete after taking each supplement. Additionally, participants were asked whether or not they would be willing to tolerate long-term intake of the supplement.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22 (Armonk, New York). Each participant's urinary creatinine values were compared between the three collections to determine the coefficient of variation. Urinalysis median values of alkalization metrics (urinary citrate, pH, ammonium, sodium and potassium) were calculated among the 10 participants for each collection: baseline, LithoLyte, and KSPtabs. Values were compared between baseline and LithoLyte, baseline and KSPtabs, and LithoLyte and KSPtabs, using the Wilcoxon Signed Rank test. Statistical significance levels were set at $P < .05$.

RESULTS

There were 6 male and 4 female subjects with no prior kidney stone history, a mean age of 37 years, and mean body mass index of 23.1 kg/m^2. The mean coefficient of variation for urine creatinine was 9.2% (standard deviation 4.3%). No participant withdrew from the study.

Table 1 demonstrates median 24 hour urine values during baseline collections, and while participants ingested LithoLyte and KSPtabs. Compared to baseline, while participants consumed Litholyte there was an increase in urine pH (6.46-6.66, $P = .028$), and a decrease in urine ammonium (41-36 mmol/day, $P = .005$) (Fig. 1). A non-significant increase in citrate (597-758 mg/day, $P = .058$) and potassium (79-97 mmol/day, $P = .09$),

Table 1. Median 24 hour urinalyses values from baseline, LithoLyte, and KSPtabs collections.

	Baseline		LithoLyte			KSPtabs		
	Median	IQR	Median	IQR	*P* value	Median	IQR	*P* value
Volume (L)	2.42	1.68-2.88	2.73	2.06-3.58	0.059	2.27	1.75-3.05	0.4
SS CaOx	4.40	3.06-6.50	3.45	1.89-4.67	**0.005**	3.39	1.76-4.78	**0.037**
Calcium (mg)	193	78-240	171	43-210	0.2	120	55-237	**0.009**
Oxalate (mg)	37	30-46	38	28-52	0.2	40.0	30-56	0.5
Citrate (mg)	597	496-833	758	479-1116	0.058	797	606-959	**0.037**
SS CaPhos	1.05	0.26-1.52	0.90	0.29-1.39	0.1	0.99	0.41-1.80	0.8
pH	6.46	5.96-6.80	6.66	6.53-7.03	**0.028**	6.86	6.59-7.01	**0.037**
SS Uric Acid	0.28	0.11-0.86	0.11	0.08-0.18	**0.017**	0.09	0.06-0.19	**0.028**
Uric Acid (mg)	698	586-743	659	488-825	0.9	675	533-897	0.5
Sodium (mmol)	159	116-178	131	106-187	1.0	140	114-194	0.9
Potassium (mmol)	79	55-105	97	52-141	0.09	80	55-140	0.4
Magnesium (mg)	117	103-144	130	114-158	0.1	126	95-160	0.9
Phosphorus (mg)	817	712-1287	871	778-1077	0.9	886	605-1065	0.5
Ammonium (mmol)	41	37-48	36	27-41	**0.005**	34	24-41	0.059
Sulfate (mEq)	46	33-54	47	38-58	0.3	42	31-58	0.5
Urine Urea Nitrogen (g)	12	11-14	13	11-15	0.2	11	9-14	0.3
Urine Creatinine (mg)	1603	1334-1974	1620	1433-2245	0.6	1624	1297-2265	0.7

IQR, interquartile range; SS, supersaturation; CaOx, calcium oxalate; CaPhos, calcium phosphate.
P value represents comparison to baseline.
Boldface indicates level of significance ($P < 0.05$).

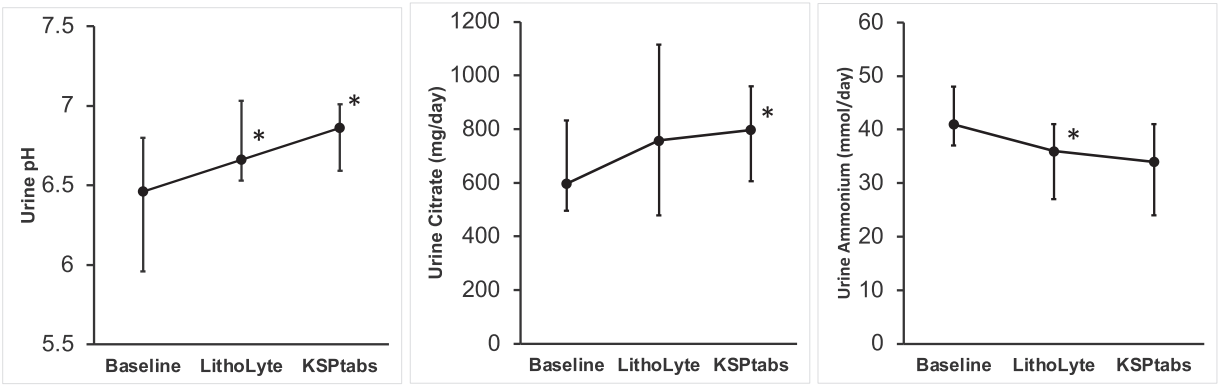

Figure 1. Changes in urine parameters based on alkali supplement. * denotes $P < .05$ compared to baseline. Error bars represent interquartile ranges.

and a non-significant decrease in calcium (193-171 mg/day, $P = .2$) were noted.

Compared to baseline, when participants consumed KSPtabs, an increase was seen in citrate (597-797 mg/day, $P = .037$), urine pH (6.46-6.86, $P = .037$) (Fig. 1), and a decrease in calcium (193-120 mg/day, $P = .009$). A non-significant decrease in ammonium (41-34 mmol/day, $P = .059$) and stable potassium levels (79-80 mmol/day, $P = .4$) were also noted. No significant differences were seen comparing urinary analytes between LithoLyte and KSPtabs supplements (all $P > .09$). Significant improvements in supersaturation of calcium oxalate (SS CaOx) and uric acid (SS Uric Acid) were seen with both supplements.

Side effects were reported with both supplements (Table 2). With LithoLyte, 5 (50%) participants had no general or gastrointestinal side effects. Mild side effects were reported in 4 (40%) participants, the most common being diarrhea, dyspepsia, and bloating. One participant (10%) had moderate side effects with cramping, bloating, and abdominal pain. No participants experienced severe side effects or stopped Litholyte supplementation early. Overall, 3 participants (30%) either disagreed or strongly disagreed with the scenario of having to take LithoLyte indefinitely, while the remaining 7 participants (70%) were neutral or agreeable. With KSPtabs, 6 participants (60%) noted no general or gastrointestinal side effects. Two (20%) participants had mild symptoms, most commonly abdominal distension, diarrhea, and dyspepsia. One participant (10%) had moderate bloating, and 1 (10%) had severe abdominal cramping. No participants stopped KSPtabs supplementation early. Overall, 3 participants (30%) disagreed or strongly disagreed with theoretically taking KSPtabs indefinitely, while the remaining 7 (70%) were neutral or agreeable.

DISCUSSION

In this prospective study of over-the-counter LithoLyte and KSPtabs supplementation, we demonstrated 24 hour urine parameter improvements attributable to an increased alkali load. Specifically, LithoLyte was associated with a significant increase in urinary pH and a decrease in urinary ammonia, while KSPtabs was associated with a significant increase in urinary citrate and urinary pH, and a decrease in urinary calcium. As a result, both supplements showed significant improvements in SS CaOx and SS Uric Acid.

Table 2. Side-effect profile of LithoLyte and KSPtabs.

	LithoLyte			KSPtabs		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Abdominal Distention	1	0	0	2	0	0
Abdominal Pain	0	1	0	0	1	0
Belching	1	0	0	1	0	0
Bloating	2	1	0	1	2	0
Constipation	0	0	0	0	0	0
Cramping	1	1	0	1	0	1
Diarrhea	3	0	0	2	0	0
Dysgeusia	0	0	0	0	0	0
Dyspepsia	3	0	0	2	0	0
Nausea	0	0	0	1	0	0
Vomiting	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0
Fever	0	0	0	0	0	0
Malaise	1	0	0	1	0	0
Allergic Reaction	0	0	0	0	0	0

Values represent the number of participants who experienced the various side effects at the listed severity. Shaded areas were not an option on the survey.

Urinary citrate is a potent inhibitor of calcium stone formation by directly complexing with calcium, and by binding to the calcium oxalate surface to prevent crystal agglomeration.[1] While citrate is freely circulating in serum, the quantity of urinary citrate is a direct reflection of one's acid-base status. With acidosis or acid loads, citrate is preferentially reabsorbed from the urine in its divalent form. With alkali loads, citrate is in a trivalent form and not able to be reabsorbed, hence higher excretion via the urine.[9]

Ingestible alkali is critically important for kidney stone prevention in hypocitraturic calcium stone formers. When given potassium citrate, they have a 75% risk reduction of stone recurrence.[4] While the AUA guidelines specifically recommend potassium citrate, only 8%-10% of ingested potassium citrate is believed to be directly excreted as non-metabolized in vivo citrate. Most is converted to bicarbonate via the citric acid cycle.[10] Therefore, other alkali salts could be considered in patients who do not want or cannot tolerate potassium citrate.

There are 4 prospective, randomized, placebo controlled trials of alkali citrate that are routinely cited in guidelines[3] and systematic reviews.[4] Although all of these studies were performed in patients with kidney stones, there is notable variation in urinary citate improvement likely due to different alkali salts, doses, and baseline urinary citrate levels.[6,11-13] Ettinger et al. gave potassium magnesium citrate 63 mEq to recurrent calcium oxalate stone formers for 3 years, and reported a 31% increase in urinary citrate from 587 to 769 mg/day (P <.05).[6] Their baseline urinary citrate levels were most consistent with our baseline of 597 mg/day. Similarly, 27% and 34% improvements were seen with LithoLyte (597-758 mg/day, P =.06) and KSPtabs (597-797 mg/day, P =.04), respectively. It is conceivable that these effects are dose-dependent, and that higher doses may result in greater improvement.

The remaining 3 studies all had lower baseline urinary citrate levels ranging from 235 to 365 mg/day, with more prominent increases in the treatment arms. Barcelo et al. gave hypocitraturic calcium stone formers a mean of potassium citrate 45 mEq, and reported a 74% increase from 365 to 634 mg/day.[11] In 39 patients given potassium sodium citrate 81 mEq, urinary citrate increased 56% from 259 to 405 mg/day(P =.007).[12] And in 46 patients given potassium citrate 60 mEq/day, hypocitraturic patients increased 123% from 235 to 525 mg/day, and normocitraturic patients increased 109% from 344 to 719 mg/day.[13]

Prior animal studies have demonstrated a hypocalciuric effect while taking potassium citrate.[14] This is hypothesized due to direct binding of intestinal and urinary calcium, and indirectly overtime through decreased bone resorption and increased renal calcium reabsorption. However, this effect in the previously mentioned alkali trials was not seen. Ettinger and colleagues showed no significant improvement in urinary calcium when given potassium magnesium citrate (237 mg-225 mg, P >.05),[6] while the remaining studies did not report calcium values.[11-13] In our study, both LithoLyte and KSPtabs supplementation decreased urinary calcium (193 mg-171 mg and 120 mg, respectively), but only KSPtabs showed significant improvement (P =.009). This could be due to the higher urinary citrate levels (797 mg), which is greater than any of the previously mentioned alkali trials.

Alkali loading is also beneficial for uric acid and cystine stone formers.[3] Uric acid crystal solubility is pH sensitive; urine pH less than the pKa of 5.35 increases crystallization, while urine pH above the pKa increases solubility.[15] Cystine has a pKa of 8.3,[16] and while increasing urine pH above that level is not pharmacologically possible, a higher urine pH of 7.0-7.5 is beneficial to reduce cystine crystallization.[17] Both LithoLyte and KSPtabs demonstrated a significant increase in urine pH from 6.46 to 6.66 (P =.03) and 6.86 (P =.04), respectively. This is consistent with the increase in urine pH from the previously noted studies from Ettinger et al. (6.01-6.29, P =.08)[6] and Barcelo et al. (5.4-6.4).[11] Additionally, effective supplemental alkali should reduce renal ammoniagenesis. Participants had a significant decrease in urine ammonium with LithoLyte (41.4-36.2 mmol/day, P =.005), and a non-significant decrease with KSPtabs (41.4-34.4 mmol/day, P =.06). This has also been previously reported to occur with potassium magnesium citrate by Ettinger and colleagues (38-28 mmol/day, P <.001).[6]

There are concerns regarding patient adherence to prescription alkali therapy. Reasons for stopping the medication can include side effects, cost, and/or pill size. In a retrospective study of 52 patients prescribed sodium potassium citrate over 5.6 years, only 62% consistently took their medication.[5] Similarly, Barcelo and colleagues noted only 58% of patients were compliant with the potassium citrate regimen.[11] In our short-term study in a small cohort, 70% of participants were neutral or agreed with continuing either LithoLyte or KSPtabs, indefinitely. It should be noted, however, that these were healthy volunteers and incentive to continue the supplementation may be higher in patients treating stone disease.

Patients are routinely counseled on the known risks of gastrointestinal side effects with prescription alkali citrate. Barcelo and colleagues reported mild nausea, epigastric pain, or abdominal distension in 17% (3/18) of patients who consistently took the medication.[11] Ettinger et al. reported that 42% of patients had new or worsening gastrointestinal symptoms, with 26% noting these were more than just slight changes.[6] Similarly, in our short-term study, up to 40% of participants noted bothersome side effects with either supplement. While long-term tolerability is unknown, this likely reflects that many forms of supplemental alkali, when given in sufficient quantities, can cause gastrointestinal discomfort in a notable percentage of patients.

Higher socioeconomic status has been associated with medication adherence,[18] perhaps due to the upfront cost of the medication. Prescription potassium citrate can be prohibitively expensive for some patients. LithoLyte costs approximately $2.00/day for a 40 mEq dose, while

KSPtabs is approximately $2.60-$3.90/day depending on the daily dose. Both of these can be upwards of a 50% savings compared to prescription potassium citrate based on a patient's prescription drug plan and copays.[7]

Although less common, the size of prescription potassium citrate pills can be problematic for some patients. Ettinger et al. reporting that 11% of patients stopped the study due to inability to swallow the large pills.[6] Both liquid and effervescent forms of prescription alkali can be challenging to find and potentially even more expensive. This could make either LithoLyte and KSPtabs more appealing.

Our study has multiple limitations that are worth noting. First, this was performed in healthy adults without known kidney stone history. While these findings may not be generalizable to those with kidney stone disease or those specifically with hypocitraturia, based on the supplements' mechanism of action there is likely similar benefit. Second, the efficacy of these supplements on stone recurrence is unknown. Third, participants maintained their own diets as controls. Although consistency was shown between collections, this is inherently less rigorous than a strict consistent metabolic research diet. Fourth, participants were not blinded to the type of supplement they were taking. This could introduce bias regarding side effects and/or dietary changes. Lastly, the sample size may have been insufficient to detect statistically significant differences in all of the urine parameters.

These limitations notwithstanding, we have shown that over-the-counter LithoLyte and KSPtabs are effective alkali supplements in a small cohort of healthy adults. Tolerability appears similar to prescription potassium citrate; patients given these supplements should still be closely monitored for side effects. Further study in a stone forming population is warranted to assess the impact on urinary parameters, as well as potential reduction in stone recurrence.

CONCLUSION

Over-the-counter LithoLyte and KSPtabs are effective alkali supplements, with a similar side effect profile to prescription potassium citrate. These supplements could be a better option for patients with recurrent kidney stone disease who cannot afford or tolerate prescription medications, or desire an over-the-counter alternative to pharmacologic preventative therapy.

ACKNOWLEDGMENT. We would like to thank Dr. John Asplin, MD, for his thoughtful contributions to the design of this project.

References

1. Ryall RL. Urinary inhibitors of calcium oxalate crystallization and their potential role in stone formation. *World J Urol*. 1997;15:155–164.
2. Zuckerman JM, Assimos DG. Hypocitraturia: pathophysiology and medical management. *Rev Urol*. 2009;11:134–144.
3. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol*. 2014;192:316–324.
4. Fink HA, Wilt TJ, Eidman KE, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. *Ann Intern Med*. 2013;158:535–543.
5. Jendle-Bengten C, Tiselius HG. Long-term follow-up of stone formers treated with a low dose of sodium potassium citrate. *Scand J Urol Nephrol*. 2000;34:36–41.
6. Ettinger B, Pak CY, Citron JT, et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol*. 1997;158:2069–2073.
7. Stern KL, Canvasser N, Borofsky M, et al. Alkalinizing agents: A review of prescription, over-the-counter, and medical food supplements. *J Endourol*. 2020;34:1–6.
8. National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE). 2018: 1−155. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm, accessed July 12, 2020.
9. Hamm LL, Hering-Smith KS. Pathophysiology of hypocitraturic nephrolithiasis. *Endocrinol Metab Clin North Am*. 2002;31:885−93−viii.
10. Sakhaee K, Alpern R, Poindexter J, et al. Citraturic response to oral citric acid load. *J Urol*. 1992;147:975–976.
11. Barcelo P, Wuhl O, Servitge E, et al. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol*. 1993;150:1761–1764.
12. Lojanapiwat B, Tanthanuch M, Pripathanont C, et al. Alkaline citrate reduces stone recurrence and regrowth after shockwave lithotripsy and percutaneous nephrolithotomy. *Int Braz J Urol*. 2011;37:611–616.
13. Soygür T, Akbay A, Küpeli S. Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: a randomized controlled trial. *J Endourol*. 2002;16:149–152.
14. Krieger NS, Asplin JR, Frick KK, et al. Effect of potassium citrate on calcium phosphate stones in a model of hypercalciuria. *J Am Soc Nephrol*. 2015;26:3001–3008.
15. Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis. *Curr Opin Nephrol Hypertens*. 2004;13:181–189.
16. Shekarriz B, Stoller ML. Cystinuria and other noncalcareous calculi. *Endocrinol Metab Clin North Am*. 2002;31:951–977.
17. Eisner BH, Goldfarb DS, Baum MA, et al. Evaluation and medical management of patients with cystine nephrolithiasis: a consensus statement. *J Endourol*. 2020;34:1103–1110.
18. Dauw CA, Yi Y, Bierlein MJ, et al. Factors associated with preventive pharmacological therapy adherence among patients with kidney stones. *Urology*. 2016;93:45–49.

EDITORIAL COMMENT

In 1985, potassium citrate was approved by the FDA for kidney stone prevention in distal renal tubular acidosis with calcium stones, hypocitraturic calcium oxalate nephrolithiasis of any etiology and uric acid lithiasis with or without calcium stones. Potassium citrate is now widely used either alone or in combination with thiazide or thiazide analogue diuretics for the treatment of calcium nephrolithiasis.

In this issue of Urology, Dr. Canvasser et al. [1] compare the effects of 2 over-the-counter alkali agents LithoLyte and KSPtabs effects on the urine alkalinity as well as urinary acid base profiles. The purpose of this study to show the less expensive over-the-counter alkali treatment would be as effective as the more expensive available potassium tablet, which is commonly used in clinical practice.

Over all, this study is well done; however, a strong conclusion will not be drawn given the lack of rigid dietary control and a small number of studied subjects. Due to the latter circumstances, the lack of significant increase in urinary citrate despite a significant rise in urinary pH, and a significant fall in urinary ammonium with LithoLyte, and conversely, the effect of KSPtabs in a significant rise in urinary citrate and urinary pH without a significant fall in urinary ammonium could not be fully explained.

The heterogeneous biochemical response with these 2 alkali preparations to a major extent is due to different amount of alkali delivered by 2 products. The alkali delivered by the 2 preparations differed by 9.5 mEq/day. Therefore, this difference in addition to lack of dietary control and a small sample size, have greatly affected the result and requires to be fully investigated in the future. Moreover, urinary potassium with both LithoLyte and KSPtabs, did not change significantly suggestive of either lack of compliance to the drug or due to diarrhea loss of potassium.

With regard to the side effects, both these preparations as well as previous studies in recurrent calcium oxalate stone formers by Ettinger et al. [2] and by Barcelo, et al in hypocitraturic calcium stone former, [3] showed similar minor gastrointestinal side effects including mild nausea, epigastric pain or abdominal distension. Although the dosage of alkali used in Ettinger and Barcelo studies was higher than this study [1] using 63 mEq/day of potassium magnesium citrate and 45 mEq/day potassium citrate, respectively. Thereby, no definitive conclusion can be made with the present study that LithoLyte and KSPtabs supplements would offer a more protective role with the gastrointestinal adverse effects.

It must be acknowledged that this is the first step toward the development of over-the-counter alkali therapy for the kidney stone formation concerning side effects, tolerability, and cost.

However, due to the deficiency in the design comprehensive studies under metabolic regimen using these alternative over-the-counter alkali supplements, must be performed in kidney stone forming population to overcome the limitation of this study. I feel until that time the AUA guidelines [4] recommended potassium citrate as the primary alkali therapy for kidney stone formers must be followed by urologists and nephrologists involved in management and care of this population.

Sakhaee Khashayar, Charles and Jane Pak Center of Mineral Metabolism and Clinical Research Department of Internal Medicine, University of Texas Southwestern Medical Center Dallas, Texas

References

1. Canvasser N. Editorial Comment. Over-the-counter alkali agents to raise urine pH and citrate excretion: a prospective crossover study in healthy adults. 2022.
2. Ettinger B, Pak CY, Citron JT, Thomas C, Adams-Huet B, Vangessel A. Potassium- magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol.* 1997;158:2069–2073. https://doi.org/10.1016/s0022-5347(01)68155-2.
3. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CY. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol.* 1993;150:1761–1764.
4. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol.* 2014;192:316–324. https://doi.org/10.1016/j.juro.2014.05.006.

https://doi.org/10.1016/j.urology.2022.05.050
UROLOGY 00: 5–6, 2022.

AUTHOR RESPONSE

Reply by authors:

We appreciate the thoughtful critique of this manuscript by the author of the editorial. The purpose of this study was not to show that these over-the-counter alternatives are as effective as potassium citrate; we did not have a control group on potassium citrate. Rather, we tested whether these commonly used alkali supplements actually change urine parameters in healthy subjects.

Online shopping has empowered patients to look for alternative therapies due to potassium citrate cost, side effects, pill size, and/or desire for a "natural" approach. While dozens of options exist, the endourology community needs to study these therapies so that patients are able to choose effective options based on science, not star ratings and online reviews.

Studying alkali alternatives in a small sample size is not novel. Twelve patients were given 2L of lemonade with significant improvements in urine citrate,[1] which continues to be 1 of the most common adjunctive therapies used. Thirteen subjects on a metabolic diet were studied to show that orange juice is a superior alkali compared to lemonade.[2] And 8 patients demonstrated the benefit of coconut water consumption due to the alkali effect of high malate intake.[3] Certainly, our 10-subject study with varied alkali loads between supplements on self-controlled diets is a limitation. While we were not directly comparing 1 supplement to the other, we chose to maintain a similar dosing frequency for consistency despite the alkali loads. In addition, given the lower potassium citrate content of these preparations compared to pure potassium citrate, we might not see a robust urinary potassium response. Any patient started on alkali therapy should be monitored with 24 hour urine studies to ensure efficacy. We will further study 24 hour urine parameters in an at-risk study population.

We are indebted to Dr. Sakhaee et al. at the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research at UT Southwestern, whose work on nephrolithiasis pathophysiology and prevention is the foundation for much of what we do. Products continue to be developed for kidney stone prevention, many within our own community. As stewards of preventative therapy, we need to study and be critical of these options in order to better guide our patients.

Noah E. Canvasser, Marcelino Rivera, Seth K. Bechis, Johann Ingimarsson, John Knoedler, Karen Stern, Christa L. Stoughton, Daniel Wollin, Michael Borofsky, Naeem Bhojani, Marawan El Tayeb, Guido Kamphuis, David Leavitt, Ryan S. Hsi, Kymora B. Scotland, for the Collaborative for Research in Endourology (CoRE).
Department of Urology, University of California Davis, Sacramento, CA; Indiana University, Indianapolis, IN; University of California San Diego, San Diego, CA; Maine Medical Center, South Portland, ME; Penn State University, Hershey, PA; Mayo Clinic, Phoenix, AZ; Brigham and Women's Hospital, Boston, MA; University of Minnesota, Minneapolis, MN; University of Montreal, Montreal, QC, Canada; Baylor Scott and White Health, Temple, TX; Amsterdam University Medical Center, Amsterdam, Netherlands; Henry Ford Health System, Detroit, MI;

Vanderbilt University Medical Center, Nashville, TN; University of California Los Angeles, Los Angeles, CA

References

1. Seltzer MA, Low RK, McDonald M, et al. Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. *J Urol.* 1996;156:907–909.
2. Odvina CV. Comparative value of orange juice versus lemonade in reducing stone-forming risk. *Clin J Amer Soc Nephrol.* 2006;1:1269–1274.
3. Patel RM, Jiang P, Asplin J, et al. Coconut water: an unexpected source of urinary citrate. *BioMed Res Intern.* 2018;2018:3061742.

https://doi.org/10.1016/j.urology.2022.05.051
UROLOGY 00: 6–7, 2022.