The Impact of Alternative Alkalinizing Agents on 24-Hour Urine Parameters

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OBJECTIVES To determine if alternative alkalinizing agents lead to similar changes in 24-hour urine pH and citrate compared to potassium citrate (KCIT). Many stone formers cannot tolerate KCIT due to side effects or cost. In these patients, we have prescribed potassium bicarbonate or sodium bicarbonate as alternative alkali (AA), though their efficacy is unclear.

METHODS We performed a retrospective cohort study of adult stone formers seen from 2000 to 2018 with 24-hour urine analyses. Two analyses were performed. The first evaluated the alkalinizing and citraturic effects in patients with baseline low urine pH or hypocitraturia off of any alkalinizing medications, who were subsequently treated with either KCIT or AA. The second analysis compared the pH and citrate in patients changing from KCIT to an AA. Reasons for switching were abstracted by chart review and cost savings percentages were calculated using GoodRx medication prices.

RESULTS When starting alkali therapy, the median increase in pH from baseline was 0.64 for KCIT and 0.51 for AA ($P = .077$), and the median increase in citrate from baseline was 231 mg for KCIT and 171 mg for AA ($P = .109$). When switching alkali therapy, median pH and citrate did not significantly change. Hyperkalemia (24%), GI upset (19%), and cost (17%) were the most common reasons cited for switching to an AA. AA represented a savings of 86%-92% compared to KCIT.

CONCLUSION Alternative alkali appear to offer comparable improvements in 24-hour urine parameters and significant cost-savings compared to KCIT. UROLOGY 142: 55–59, 2020. © 2020 Elsevier Inc.

Nephrolithiasis is an increasingly common condition with a significant economic burden, exceeding $5 billion in direct and indirect costs in the United States annually.[1-3] Accordingly, the American Urological Association has emphasized the medical management of urolithiasis in recent guidelines,[4,5] as prevention costs less than intervention.[6] Potassium citrate (KCIT) is a urinary alkalinizing agent that has been shown in randomized trials to significantly increase urinary citrate, pH, and potassium as well as decrease stone formation rate compared to placebo in patients with hypocitraturia and calcium or uric acid stones.[7-13] KCIT may also lower urinary calcium, although the evidence for this is mixed.[14,15] It follows that the guidelines recommend KCIT for patients with recurrent calcium stones and low or relatively low urinary citrate, recurrent stone formers with absent or corrected metabolic abnormalities, and for patients with uric acid and cystine stones in order to raise urinary pH.

Despite its efficacy in raising urinary citrate and pH and reducing stone events for both calcium and uric acid stone formers, many patients are intolerant to KCIT due to its gastrointestinal side effects. Moreover, rising generic drug prices in the United States and variable medical insurance have made KCIT cost-prohibitive for some individuals. Indeed, these barriers have contributed to the nearly 50% dropout rate in prior studies evaluating the use of KCIT.[16] Alternative urinary alkalinizing agents, such as sodium bicarbonate (NAB) and potassium bicarbonate (KB), may be reasonable options for patients who are unable to adhere to or afford KCIT therapy. However, evidence for the use of these alternative alkali (AA) medications in recurrent stone formers is lacking. In this retrospective cohort study, we sought to evaluate the impact of AA on 24-hour urine parameters relative to those patients who continued on KCIT.

MATERIALS AND METHODS

Defining the Cohort and Initial Urine Parameters

After obtaining an exemption for review from the Institutional Review Board, we collected clinical and demographic information via electronic medical record from all adult stone formers seen at the Duke Comprehensive Kidney Stone Center between 1/2000 and 6/2018. This dataset was then linked programmatically to a database of 24-hour urine collection data (Litholink, Chicago, IL) to produce our cohort. We refined our cohort by excluding subjects who (1) had urine volume of <0.5 L/day, (2) did not have a repeat 24-hour urine collection after starting

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medication, or (3) did not have either a low urine pH (<6.0) or hypocitraturia (<450 mg in men, <550 mg in women) on initial metabolic evaluation. The standard practice at our center is to obtain an initial comprehensive metabolic evaluation, when indicated, consisting of two 24-hour urine collections on a random diet performed on consecutive days. If a metabolic abnormality is identified and medical therapy initiated, we routinely repeat the 24-hour urine collection 3 months later. For the purposes of this study, when 2 tests were available from the initial metabolic evaluation and both met criteria for inclusion, the results were averaged. In cases where only 1 baseline test was obtained, the result from the single study was used.

Statistical Analysis

To evaluate the impact of starting AA compared to KCIT, we first compared the baseline 24-hour urine parameters of patients with low urine pH and/or hypocitraturia (untreated) to the same urine parameters after at least 3 months of medical therapy with either KCIT or AA.

Primary outcomes of interest included 24-hour urinary citrate, pH, calcium, sodium, ammonium, sulfate, supersaturation (SS) of calcium oxalate (CaOx), and SS calcium phosphate (CaP) values as well as changes in these values over time from baseline (pre-therapy) to follow-up (on therapy). Secondary outcomes included reasons for starting AA instead of KCIT, cost-savings of AA relative to KCIT, and medication adherence rate including reasons for nonadherence. Cost-savings were calculated using GoodRx.com prices (April 2019) for a 1-month supply purchased at CVS of the most commonly prescribed doses of AA or KCIT at our institution. Medication adherence rate was determined from patient-reported adherence after careful review of follow-up clinic visit notes. Differences between patient characteristics by medication type (KCIT or AA) were tested using Chi-Square for categorical variables (Fisher's exact test is used for categorical variables with small expected counts) and 2-group Kruskal-Wallis test for continuous variables.

On Shapiro-Wilk testing, deviance from normality was detected, so nonparametric testing was used to test whether there were differences in 24-hour urinary parameters between baseline and follow-up. Adherence rates were compared using 2-sample test for equality of proportions with continuity correction.

We additionally performed a second analysis to evaluate the impact of switching from KCIT to an AA. We identified a subset of patients within our cohort who had both 24-hour urine data while taking KCIT and then subsequently after being switched to AA, and these sets of urinary parameters were compared. The primary outcome of interest in the second analysis was the change in 24-hour urinary parameters (same parameters as Analysis 1) following the switch from KCIT to AA. Wilcoxon Signed Rank tests for matched pairs were used to compare additional 24-hour urinary parameters values within single patients at different points in time. This cohort was also used to determine the most commonly prescribed doses of medications at our institution via retrospective chart review.

A P value of .05 was considered statistically significant. All analyses were implemented using the R statistical software, version 3.5.2 (The R Foundation, Vienna, Austria).

RESULTS

We identified 70 patients who started AA (65 on NAB and 5 on KB) and 482 patients who started KCIT following diagnosis of either low urinary pH or hypocitraturia on initial comprehensive metabolic evaluation. Baseline patient characteristics and urinary parameters (Table 1), show that patients on AA had an older median age (62.86 years vs 58.82 years, $P = .028$), higher prevalence of diabetes mellitus (51.4% vs 31.3%, $P = .001$), lower median GFR (56.75 ml/min/1.73 m^2 vs 69.72 ml/min/1.73 m^2, $P < .001$), lower median urinary citrate (265.52 mg vs 418.21 mg, $P < .001$), lower median urinary pH (5.43 vs 5.61, $P < .001$), lower median urinary calcium (106.58 mg vs 161.74 mg, $P < .001$), and lower SS values for CaOx and CaP relative to the patients on KCIT (4.54 vs 7.04, $P < .001$ and 0.16 vs 0.48, $P < .001$, respectively).

Table 2 illustrates changes in urinary parameters after starting therapy in the AA and KCIT groups. Urinary citrate, pH, sodium, and SS CaP significantly increased after therapy in both the AA and KCIT groups (all $P < .025$) while ammonium decreased in both AA ($P = .01$) and KCIT groups ($P < .001$). Urinary calcium did not significantly change in either group. SS CaOx trended toward a significant reduction in the AA group ($P = .087$) and was significantly reduced in the KCIT group ($P < .001$). The median changes in urinary parameters after initiating therapy were not significantly different between the AA and KCIT groups for any of the urine parameters.

The most common reasons cited for starting AA included history of hyperkalemia (24%), history of gastrointestinal upset (19%), anticipated cost (17%), and renal insufficiency (17%). NAB 1300 mg BID ($4) and KB 25 mEq BID ($14.60) represented a cost-savings percentage compared to KCIT 20 mEq BID ($51.05) of 86% and 92%, respectively. The reported doses are the ones most commonly prescribed for these alkali in our practice based on our dosage frequency determination within the Analysis 2 cohort. When compared to age, sex, and BMI category-matched KCIT controls, the patient-reported adherence rate at the 3-month follow-up visit for AA and KCIT was 69% and 58%, respectively ($P = .287$).

In Analysis 2, where we evaluated the impact of switching from KCIT to an AA, 71 patients were identified (65 switched to NAB, 6 switched to KB) with a 24-hour urine collection while on KCIT who also had a subsequent collection after switching to an AA. The baseline demographics of these patients are presented in Table 3. Before switching, 56% (40/71) of patients were on a KCIT dose of 20 mEq twice daily. The most commonly used AA doses after switching were NAB 1300 mg twice daily (35/65) and KB 25 mEq twice daily (4/6). There were no statistically significant differences in 24-hour urinary parameters after switching to an alternate alkali from KCIT (all $P > .11$) (Table 4).

COMMENT

We report here the first evaluation of the efficacy of alternative alkali medications using the commonly utilized endpoint of 24-hour urine collection. It is accepted that recurrent stone formers with low urine pH and/or hypocitraturia may benefit from medical therapy with urinary alkalization. Unfortunately, the most widely recommended agent, KCIT, is costly and intolerable to many patients. Our results demonstrate that patients taking AA experience comparable improvements in urinary parameters relative to patients taking KCIT. Furthermore, switching from KCIT to AA does not significantly affect urinary parameter values. We have also demonstrated the significant cost-savings which AA agents represent

Table 1. Baseline demographics (Analysis 1)

	Alternate Alkali	Potassium Citrate	*P* Value
N	70	482	
Age (median [IQR])	62.86 [53.42, 69.63]	58.82 [47.93, 67.12]	**.028**
Race (*n* [%])			.153
Black or African American	13 [18.6]	53 [11]	
White	53 [75.7]	403 [83.6]	
Other	4 [5.7]	26 [5.4]	
Male gender (*n* [%])	39 [55.7]	263 [54.6]	.958
BMI (median [IQR])	28.81 [24.72, 33.46]	29.85 [26.39, 35.15]	.056
Insurance (*n* [%])			.175
Managed care	23 [32.9]	185 [38.4]	
Medicare	24 [34.3]	117 [24.3]	
NC medicaid	0	7 [1.5]	
Self pay/other	2 [2.9]	5 [0.9]	
Unknown/uninsured	21 [30.0]	168 [34.9]	
Chronic disease presence (*n* [%])			
Diabetes	36 [51.4]	151 [31.3]	**.001**
Hypertension	36 [51.4]	238 [49.4]	.847
Inflammatory bowel disease	4 [5.7]	13 [2.7]	.320
GFR (median [IQR])	56.75 ml/min/1.73 m^2 [40.89, 72.21]	69.72 ml/min/1.73 m^2 [57.15, 84.43]	**<.001**
Baseline 24-h urine parameters (median [IQR])			
Volume (L)	1.54 [1.15, 2.10]	1.53 [1.15, 2.13]	.691
Citrate (mg)	265.52 [106.41, 488.08]	418.21 [246.91, 640.54]	**<.001**
pH	5.43 [5.31, 5.64]	5.61 [5.45, 5.78]	**<.001**
Calcium (mg)	106.58 [52.13, 173.76]	161.74 [97.68, 248.81]	**<.001**
Sodium (mmol)	142.95 [111.62, 192.54]	150.16 [105.77, 212.06]	.484
Ammonium (mmol)	33.72 [22.45, 38.96]	33.99 [24.98, 45.23]	.090
Sulfate (meq)	33.72 [22.75, 44.09]	35.54 [25.75, 47.85]	.138
SS calcium oxalate	4.54 [3.08, 7.88]	7.04 [4.27, 9.35]	**<.001**
SS calcium phosphate	0.16 [0.08, 0.52]	0.48 [0.21, 0.91]	**<.001**

IQR, interquartile range; SS, supersaturation.
Values in bold signify statistical significance in the difference between the listed outcomes.

relative to KCIT and that patient adherence to these medications is similar between groups.

Although our findings indicate similar 24-hour urine collection outcomes with AA compared to KCIT, the body of evidence supporting their use in the literature is sparse. Pinheiro et al have provided the best evidence for the use of NAB in hypocitraturic calcium stone formers.[17] In a prospective, double-blinded crossover study, patients received 3 days of therapy with equivalent doses of either NAB or KCIT (60 mEq/day divided into 3 doses) following a period of diet control and acted as their own controls. Both of these medications exhibited significant alkalinizing and citraturic effects, but the study was limited by a small sample size and short duration of medication therapy. NAB was also evaluated in a cohort of homozygous cystinurics by Fjellstedt et al using a similar, prospective crossover study evaluating 2 weeks of NAB therapy followed by 2 weeks of KCIT.[18] Most of the patients were also taking tiopronin. The authors observed that KCIT and NAB had comparable alkalinizing effects.

A common criticism of the use of NAB for urinary alkalinization is the potential to exacerbate hypercalciuria due to the excess sodium load. In the Pinheiro et al study, a significant increase in urinary sodium excretion from baseline was seen while taking NAB, but the hypothesized concomitant increase in urinary calcium was not observed. Fjellstedt et al also found a significant increase in urinary sodium from baseline with NAB, but urinary calcium was not reported. In the present study, urinary sodium increased significantly from baseline in both AA and KCIT groups in Analysis 1, but no significant increase in urinary calcium was seen. Nevertheless, caution is advised with the use of NAB in patients with hypertension or congestive heart failure, and coordination with these patients' primary care physician or cardiologist may be fruitful in order to avoid complications which could arise from increase sodium load.

Evidence for the use of potassium bicarbonate is also limited. A metabolic study comparing NAB and KB in regard to calcium balance found that NAB did not affect urine calcium excretion or total body calcium balance vs control, while KB reduced urinary calcium excretion and increased total body calcium balance vs control.[19] Neither agent was found to affect net intestinal calcium absorption. In a separate study, no new uric acid stone formation was reported in the case of a single recurrent uric acid stone former treated with KB[12] after a follow-up period of 18 months. Unfortunately, the proportion of AA patients taking KB in the present study is prohibitively small to allow for any meaningful subgroup analysis of its individual efficacy compared to NAB or KCIT.

We found that history of hyperkalemia was the primary reason for initiating AA instead of KCIT in our practice,

Table 2. Changes in 24-hour urinary parameters after starting alkali therapy (Analysis 1)

	Alternate Alkali ($n = 70$)			Potassium Citrate ($n = 482$)		
24-hour Urine Parameter	Baseline (Median [IQR])	After Therapy (Median [IQR])	*P* Value	Baseline (Median [IQR])	After Therapy (Median [IQR])	*P* Value
Citrate (mg)	265.52 [106.41, 488.08]	496.16 [233.51, 757.00]	**<.001**	418.21 [246.91, 640.54]	656.29 [410.69, 990.47]	**.003**
Median change in citrate (mg)	171.62 [5.80, 324.91]			231.03 [32.70, 439.29]		.109
pH	5.43[5.31, 5.64]	5.98 [5.67, 6.39]	**<.001**	5.61 [5.45, 5.78]	6.24 [5.78, 6.68]	**<.001**
Median change in pH	0.51 [0.13, 0.84]			0.64 [0.23, 1.04]		.077
Calcium (mg)	106.58 (52.13, 173.76)	104.06 (52.96, 178.63)	.915	161.74 (97.68, 248.81)	168.13 (105.20, 237.82)	.894
Median change in calcium (mg)	−4.53 [−24.91, 37.85]			2.55 [−56.76, 53.49]		.727
Sodium (mmol)	142.95 (111.62, 192.54)	176.83 (130.88, 228.08)	**.025**	150.16 (105.77, 212.06)	178.11 (129.41, 241.83)	**<.001**
Median change in sodium (mmol)	26.14 [−26.02, 77.03]			26.59 [−20.72, 77.62]		.926
Ammonium (mmol)	33.72 [22.45, 38.96]	22.66 [15.12, 36.67]	**.01**	33.99 [24.98, 45.23]	26.34 [17.39, 38.21]	**<.001**
Median change in ammonium (mmol)	−6.63 [−12.77, 4.03]			−7.83 [−16.19, 1.16]		.214
Sulfate (meq)	33.72 [22.75, 44.09]	34.91 [21.81, 42.17]	.794	35.54 [25.75, 47.85]	37.07 [26.44, 50.00]	.195
Median change in sulfate (meq)	0.73 [−7.84, 5.13]			1.55 [−6.35, 9.54]		.263
SS calcium oxalate	4.54 [3.08, 7.88]	3.89 [1.88, 6.73]	.087	7.04 [4.27, 9.35]	5.10 [3.04, 7.43]	**<.001**
Median change in SS calcium oxalate	−0.81 [−3.15, 1.03]			−1.43 [−3.74, 0.55]		.205
SS calcium phosphate	0.16 [0.08, 0.52]	0.4 [0.11, 0.87]	**.006**	0.48 [0.21, 0.91]	0.76 [0.31, 1.47]	**<.001**
Median change in SS calcium phosphate	0.08 [−0.02, 0.40]			0.21 [−0.07, 0.72]		0.188

IQR, interquartile range; SS, supersaturation.

Table 3. Baseline demographics (Analysis 2)

Characteristic	Value
N	71
Age (median [IQR])	60.70 [49.80, 68.98]
Race (*n* [%])	
Black or African American	9 [12.7]
White	56 [78.9]
OTHER	6 [8.5]
Male gender (*n* [%])	33 [46.5]
BMI (median [IQR])	28.90 [25.77, 33.28]
Insurance (*n* [%])	
Managed care	22 [31.0]
Medicare	25 [35.2]
Unknown/uninsured	24 [33.8]
Chronic disease presence (*n* [%])	
Diabetes	30 [42.3]
Hypertension	28 [39.4]
Inflammatory bowel disease	1 [1.4]

IQR, interquartile range.

accounting for 24% of such patients. An increase in serum potassium is a known potential risk of medical therapy with potassium-containing medications,[18] although the degree of serum potassium increase in these cases is generally mild and adverse sequelae are uncommon. Close monitoring of serum levels and potential interactions with other medications, such as potassium-sparing diuretics, is advisable. Since knowledge of patients' baseline renal function is routinely available prior to initial prescription of alkali medication, and chronic kidney disease can be a risk for hyperkalemia, it is not surprising that the patients in our AA group had significantly lower median baseline GFR relative to the KCIT group as they were likely selected to receive AA based in part on that fact.

Our study is inherently limited in several ways by its retrospective nature. It should be noted that our AA and KCIT groups in Analysis 1 have several key differences in their baseline characteristics, indicating nonhomogeneity between the groups. Additionally, medication dosing was not standardized prospectively within groups, and although most patients in our practice are started on the same initial dose, these doses may be titrated over time based on 24-hour urine parameters and clinical stone activity, and this dose change information is not captured in the present study. Moreover, a relatively high degree of nonadherence was observed with all alkali therapy, which is consistent with prior studies and generally reflective of clinical practice. Importantly, our most commonly prescribed dose of NAB, 1300 mg twice daily, offers only ~30 mEq of total 24-hour base equivalent compared with the most commonly prescribed KCIT dose of 40 mEq and KB dose of 50 mEq of total 24-hour base. Despite this apparently lower effective dose of medication, however, our cohorts experienced comparable increases in 24-hour urine pH and citrate. A future prospective study could be designed to better address the concerns of inter-group heterogeneity and dose standardization.

The rise in urinary sodium observed within the KCIT group is thought to be secondary to dietary factors and

Table 4. Changes in 24-hour urinary parameters after switching alkali therapy (Analysis 2)

24-h Urine Parameter	Value on Potassium Citrate (Median [IQR])	Value on Alternative Alkali (Median [IQR])	*P* Value
N	71	71	
Volume (L)	1.74 [1.40, 2.39]	1.84 [1.31, 2.70]	.707
Citrate (mg)	454.38 [257.56, 695.72]	362.28 [245.20, 646.70]	.534
pH	6.28 [5.69, 6.77]	6.24 [5.81, 6.88]	.640
Calcium (mg)	109.68 (12.22, 162.91)	123.23 (55.49, 179.96)	.752
Sodium (mmol)	145.92 (118.15, 192.60)	175.95 (127.21, 220.77)	.110
Ammonium (mmol)	20.70 [12.35, 29.72]	20.61 [13.38, 30.85]	.911
Sulfate (meq)	27.33 [21.52, 37.60]	27.72 [20.90, 38.09]	.969
SS calcium oxalate	3.86 [0.92, 6.64]	4.29 [2.56, 7.11]	.733
SS calcium phosphate	0.47 [0.24, 1.19]	0.68 [0.24, 1.32]	.825

IQR, interquartile range; SS, supersaturation.

again represents a limitation of this study's retrospective nature. While there exists legitimate concern that iatrogenic hypernatriuria could cause a secondary hypercalciuria, in fact this was not observed in either group herein or in several prior studies which have similarly documented trends toward increased urinary sodium with stable urinary calcium following initiation of KCIT.[9,13,15]

Strengths of our work include the high number of recurrent nephrolithiasis patients on either primary or secondary alkali therapy with longitudinal 24-hour urine collection data—to our knowledge, this is the largest reported series of such a group.

CONCLUSION

Both AA and KCIT significantly increase urinary citrate and pH. In patients who are taking KCIT but do not tolerate it, urinary citrate and pH do not significantly change when switching from KCIT to AA. AA do represent a significant >85% cost savings relative to KCIT, and the medications seem to have similar patient adherence. AA may be a safe and effective option for urinary alkalization in patients who are unable to take the gold-standard KCIT.

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