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ORIGINAL ARTICLE

Effect of diuretics on kidney stone-forming risk – an investigation using multiple timed urine collections

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ABSTRACT

Introduction: International guidelines recommend the use of 24-h urine collections to guide the management of patients at high risk of recurrent kidney stones. Thiazide diuretics are often prescribed to lower urinary calcium excretion, helping to prevent recurrent calcium stones. However, as dietary intake and urine chemistry varies throughout the day, a 24-h urine collection may not provide sufficient information to guide the optimal diuretic management of individual patients. Using multiple timed urine collections, we sought to identify times during the day when stone-forming risk is higher, allowing for therapy to be more accurately targeted.

Methods: In a pilot study, healthy adult volunteers took a 4-week course of either 25 mg/d hydrochlorothiazide (HCTZ) or 2.5 mg/d indapamide. They were assessed at baseline, and at days 7, 14 and 28. At each time point, blood samples were taken for analysis and multiple timed urine samples were collected throughout the day, together with one overnight sample.

Results: Diuretic treatment was well tolerated. Daily calcium excretion decreased, there was a trend towards decreased citrate excretion and phosphate excretion was unchanged. In the timed urine samples, calcium excretion declined, particularly on indapamide, in the morning. Indapamide, but not HCTZ, reduced urinary citrate excretion, most obviously in overnight and early morning urines. Decreased divalent phosphate excretion was observed at several time points in the indapamide group.

Conclusions: This study has demonstrated the diagnostic potential of multiple timed urine collections and, to the best of our knowledge, is the first study employing this approach to examine the effect of diuretics on the stone-forming risk of individual patients. Indapamide (2.5 mg/d) had a stronger protective effect against forming calcium kidney stones than HCTZ (25 mg/d). Most of the benefits were achieved during the daytime and it may therefore be beneficial to prescribe medication twice daily or in the evening to maximize the protective effects of these agents. The benefits of indapamide treatment were attenuated by a reduction in urinary citrate excretion, an effect which has not been previously described.

Keywords: hydrochlorothiazide; indapamide; kidney stones; citrate; urine collection.

INTRODUCTION

Calcium oxalate stones are the most common type of kidney stones and, together with calcium phosphate stones, account for approximately 80% of calculi seen in clinical practice [1]. Calcium phosphate precipitation (Randall's plaque) is the initiating event in most calcareous stone disease, including providing a nucleation site for calcium oxalate crystals [2]. Urine calcium, citrate and oxalate concentrations are the major determinants of calcium oxalate stone formation, whereas urinary pH is a major determinant of calcium phosphate and uric acid stone formation [3,4]. The urinary inhibitor substances which prevent crystal formation include citrate, magnesium, Tamm–Horsfall protein and nephrocalcin [3,5].

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Along the length of the nephron, the luminal concentrations of calcium and citrate are generally well matched. Citrate has a high affinity for calcium and, in the urine, forms a soluble complex with calcium with a one-to-one stoichiometry. Given the high association constant and solubility product, the implication is that with equimolar urinary concentrations of calcium and citrate, almost all the calcium is rendered as soluble complexes and little ionised calcium remains available for the formation of less soluble oxalate or phosphate complexes [6].

The characteristic of stone-forming patients that most clearly sets them apart from otherwise healthy individuals is a high urinary concentration of calcium for any given concentration of citrate. It appears to be this relative excess of calcium over citrate that mainly determines stone-forming risk [7,8].

Thiazide diuretics can lower urine calcium excretion, helping to prevent stones and promoting positive bone mineral balances [9-11]. Yendt et al. [11] demonstrated that stone progression ceases in at least 90% of patients treated with hydrochlorothiazide (50 mg HCTZ) twice daily, and that smaller doses were also effective in a significant proportion of patients. Martins et al. [12] found that lower doses of HCTZ (12.5–25 mg/d) produced a suboptimal effect and that 2.5 mg/d indapamide was as effective as 50 mg HCTZ in reducing urinary calcium excretion. They recommended that indapamide be viewed as the drug of choice in patients with hypercalciuria in view of its efficacy, safety profile and lack of any negative effect on urinary citrate excretion. HCTZ reduces urinary citrate excretion, which may limit the benefits of treatment [12].

One of the concerns with the use of diuretics is the risk of metabolic abnormalities, especially hypokalaemia. In the Martins study [12], potassium concentrations decreased during therapy with 50 mg/d HCTZ but never fell below the normal range, and no potassium supplementation was required. Indapamide also caused significant hypokalaemia (mean decrease in serum potassium from 4.2 to 3.6 mmol/L) but, again, no supplementation was required.

International guidelines recommend the use of 24-h urine collections to diagnose metabolic abnormalities and guide dietary and pharmacological therapy in patients at high risk of recurrent kidney stones [13,14]. However, it is unclear that this is consistently better than simply instituting empirical therapy [15]. It has been suggested that a single 24-h urine sample may be inadequate [16] and some authors recommend doing at least two 24-h collections. However, dietary intake and urine chemistry—and thus, the risk of stone formation—may vary considerably throughout the course of a day [17,18]. A 24-h collection combines many different urine specimens and averages out their data, and may therefore not provide sufficient information to guide the optimal management of kidney stones [18-20].

Our study involves the analysis of multiple timed urine collections within the 24-h period to examine the effect of HCTZ and indapamide on the urine chemistry and stone-forming risk at different times during the day. We hypothesized that the two drugs may have different effects on urine chemistry at different times of the day and that identifying periods of high risk would allow for more accurate targeting of therapy.

METHODS

A pilot study was conducted in which a small group of healthy volunteers were treated with a 4-week course of either HCTZ or indapamide. Four participants (3 females, 1 male) were assigned to 25 mg/d HCTZ and four (2 females, 2 males) to 2.5 mg/d indapamide. The participants had a median age of 32 years (range 25–44 yr) and a median mass of 65 kg (range 45–93 kg). There were no significant differences in age or mass between the groups. Participants were on no medication except for oral contraceptives, were not using any vitamin or nutritional supplements, and had normal baseline serum potassium and creatinine concentrations.

Participants were seen at baseline for a screening visit, then at days 7,14 and 28 (upon completion of the trial). At the screening visit, a medical history was taken, a physical examination performed, and baseline blood samples obtained. At all visits, blood and urine samples were collected for analysis. Mass, sitting and standing blood pressure, heart rates and fluid status were also assessed. Participants were asked about adverse events or concomitant medications taken. They were also asked about adherence with study medication and a pill count was done.

On the designated days, multiple timed urine samples were collected throughout the day, together with one overnight sample. Participants were required to measure and record the volume of urine produced in each period using a graduated measuring cylinder, and to decant an aliquot from each voiding for analysis. The times of voiding were also recorded.

Blood samples were analysed for sodium, potassium, chloride, urea, creatinine, bicarbonate, calcium, phosphate, magnesium, albumin, haemoglobin, haematocrit, uric acid

and glucose. Urine analysis included the measurement of sodium, potassium, chloride, urea, creatinine, osmolality, pH, calcium, phosphate, citrate, oxalate and uric acid on each sample. Laboratory tests were performed at an internationally accredited laboratory on a Roche/Hitachi cobas® c 501 system.

To facilitate comparisons at similar time points during the day, individual urine samples were combined to provide early morning (mean time 07:30), mid-morning (10:30), mid-day (13:30), afternoon (16:30), evening (19:30), night-time (22:30) and overnight (03:00) data. Where there was insufficient urine for a particular assay or a participant had not provided a urine sample at a particular time point, the mean of the preceding and subsequent samples was used for estimation. Data from all the samples in a 24-h period were also combined to yield 24-h urine values.

Divalent phosphate was calculated from total phosphate and urine pH [21]. Given that the pK of phosphate is 6.8, at that pH there are equal proportions of monovalent and divalent phosphate present in the urine. For every 0.3 pH units above or below 6.8, the proportion of divalent to monovalent phosphate in the urine sample increases or decreases by a factor of 2.

Data analysis

Repeated measures ANOVA, Bonferroni and Duncan tests were performed using Statistica® version 8, and Wilcoxon signed-rank tests were conducted using Stata/IC® version 10.1.

Ethical approval

Approval to conduct the study was granted by the Ethics Committee at Stellenbosch University (reference number N07/07/152). All participants provided written informed consent.

RESULTS

Adherence and adverse effects

Reported adherence to treatment and sampling regimens was excellent. This impression was supported by consistent 24-h creatinine excretion across the study for individual participants. One participant accidentally discarded a single urine sample and omitted two doses of indapamide during week 2. There was no significant use of concomitant medication.

Adverse events were reported by two members of the study population. One participant, on HCTZ, reported mild headaches during week 1 and an isolated episode of pre-syncope near study completion in week 4. It is unclear if these events were related to the use of HCTZ as they were self-limiting and required no specific treatment. The other participant, who was on indapamide, suffered a bout of acute gastroenteritis towards the end of week 1. This was reflected in the blood and urine results of that week, but recovery was complete by the next visit a week later.

Clinical and blood parameters (Table 1)

No significant changes were noted in mass or systolic blood pressure (SBP). On day 7, the participant who had developed acute gastroenteritis had a drop in SBP (from 95 to 86 mmHg).

For the combined group (n = 8), reductions in mean serum potassium concentrations from the baseline value of 4.3 mmol/L were seen on day 7 (to 3.8 mmol/L; P = 0.02) and day 28 (to 4.0; P = 0.04). When the two treatment groups were analysed separately (Figure 1), the pattern was similar but the reduction was only significant for the indapamide group at day 7 (P = 0.03). Only one participant, in the indapamide group, developed hypokalaemia (3.2 mmol/L on day 7) but recovered without potassium supplementation or stopping treatment. Serum potassium concentrations in this participant were 3.7 mmol/L and 4.2 mmol/L on days 14 and 28, respectively.

There was a small rise in mean magnesium concentrations from baseline values (0.91 mmol/L) to day 7 (0.96 mmol/L; P = 0.01) and day 14 (0.97; P = 0.03), followed by a decline towards baseline values thereafter. There was also a small rise in uric acid, from 0.32 mmol/L to 0.39 mmol/L, by days 7 and 14 (P = 0.01), followed by a decline towards baseline values.

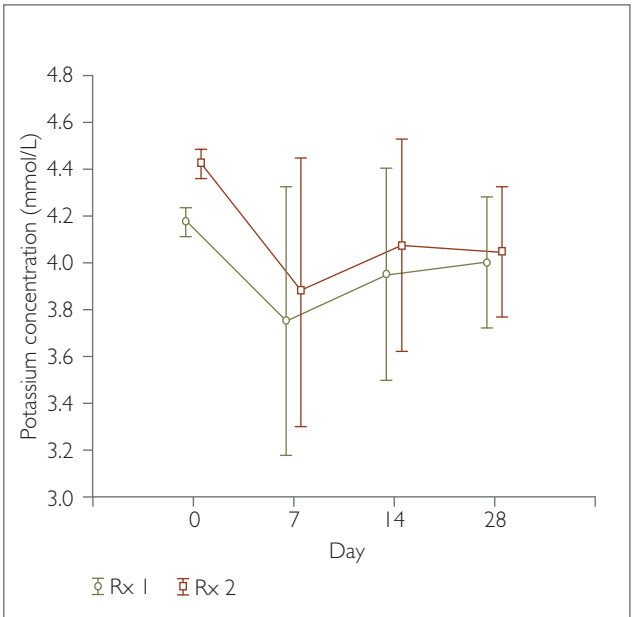

Figure 1. Serum potassium concentration in study subjects on hydrochlorothiazide (Rx1) and indapamide (Rx2). Means and 95% confidence intervals are shown.

Table 1. Mean values for clinical and blood parameters for the combined group (All, n = 8), participants receiving hydrochlorothiazide (HCTZ, n = 4) and those on indapamide (IND, n = 4). ND = no data available. See Appendix 1 for reference ranges. ** P < 0.05.

		Day 0	Day 7	Day 14	Day 28
Mass (kg)	All	70.0	69.5	69.5	69.8
	HCTZ	67.8	67.4	67.0	67.3
	IND	72.3	71.8	71.9	72.4
SBP (mmHg)	All	112	116	123	113
	HCTZ	116	124	122	122
	IND	108	109	124	105
Sodium (mmol/L)	All	140	139	140	140
	HCTZ	138	140	142	141
	IND	141	139	139	140
Potassium (mmol/L)	All	4.3	3.8**	4.0	4.0**
	HCTZ	4.2	3.8	4.0	4.0
	IND	4.4	3.9**	4.0	4.1
Urea (mmol/L)	All	5.5	6.5	5.7	5.6
	HCTZ	6.1	6.1	5.8	5.4
	IND	4.8	6.8	5.7	5.9
Creatinine (µmol/L)	All	93.9	92.2	94.1	94.6
	HCTZ	88.5	87.6	87.8	87.5
	IND	99.4	96.8	100.4	101.8
Calcium (mmol/L)	All	2.49	2.43	2.42	2.40
	HCTZ	2.42	2.45	2.41	2.42
	IND	2.56	2.41	2.43	2.38
Albumin (g/L)	All	47.0	48.9	48.1	48.3
	HCTZ	46.3	49.5	46.3	46.5
	IND	47.8	48.3	50.0	50.0
Magnesium (mmol/L)	All	0.91	0.96**	0.97**	0.94
	HCTZ	0.89	0.97	0.97	0.97
	IND	0.92	0.96	0.97	0.92
Phosphate (mmol/L)	All	1.27	1.20	1.27	1.20
	HCTZ	1.27	1.25	1.26	1.15
	IND	1.28	1.14	1.27	1.25
Bicarbonate (mmol/L)	All	ND	27.5	25.9	26.5
	HCTZ	ND	26.7	26.4	27.9
	IND	25.2	28.3	25.4	25.0
Uric acid (mmol/L)	All	0.32	0.39**	0.39**	0.35
	HCTZ	0.35	0.40	0.42	0.36
	IND	0.29	0.37	0.37	0.34
Haemoglobin (g/dL)	All	14.3	14.4	14.1	14.4
	HCTZ	14.3	14.7	14.1	14.4
	IND	14.4	14.1	14.2	14.4
Haematocrit (%)	All	42.9	42.9	42.1	42.9
	HCTZ	42.9	43.6	41.8	42.7
	IND	42.9	42.3	42.4	43.1
Random glucose (mmol/L)	All	5.3	5.4	5.8	5.1
	HCTZ	5.1	5.9	5.7	5.4
	IND	4.5	4.9	5.9	4.9

While there were no significant changes in bicarbonate concentrations, the highest mean values were seen on day 7 (27.5 mmol/L). Only one participant, in the HCTZ group, had a concentration exceeding 30 mmol/L – this was 31.4 mmol/L on day 28.

There were no changes in random blood glucose. The highest recorded value at baseline was 7.7 mmol/L, while during the treatment phase the highest recorded value was 6.6 mmol/L. No changes were observed in concentrations of sodium, creatinine, albumin, calcium and phosphate. Haemoglobin concentrations and haematocrit were also unchanged.

24-h urine data (Table 2)

No significant changes occurred in 24-h urine volume or sodium excretion across the period of the study. Baseline 24-h sodium excretion was higher in the HCTZ group than in the indapamide group (mean of 147 mmol versus 105 mmol) but this difference was not statistically significant and was not maintained throughout the study period.

Mean 24-h potassium excretion declined from 80 mmol at baseline to 66 mmol at day 28 but this change was not significant. No differences were noted across the period of the study in urine osmolality, nor in the excretion of urea, creatinine, phosphate or uric acid.

For the indapamide group there was a non-significant drop in mean urine pH from 6.03 to 5.64, while in the HCTZ group it remained unchanged.

Mean daily calcium excretion declined from 4.25 mmol at baseline to 2.95 mmol at day 7 (P = 0.05), and 3.24 mmol on days 14 and 28; the changes at these last two time points were not significant. Citrate excretion declined from 3.43 mmol/24-h at baseline to 2.34 mmol at day 14, and

Table 2. Mean values for 24-h urine parameters for the combined group (All, n = 8), participants receiving hydrochlorothiazide (HCTZ, n = 4) and those on indapamide (IND, n = 4). ** P < 0.05.

		Day 0	Day 7	Day 14	Day 28
Volume (mL/d)	All	1895	1938	1620	1878
	HCTZ	2104	1753	1533	1708
	IND	1687	2123	1708	2048
Sodium (mmol/d)	All	126	109	109	134
	HCTZ	147	112	112	128
	IND	105	107	107	139
Potassium (mmol/d)	All	80	73	66	66
	HCTZ	84	74	58	67
	IND	76	73	74	65
Urea (mmol/d)	All	398	378	381	356
	HCTZ	440	375	372	338
	IND	355	381	389	374
Creatinine (mmol/d)	All	15.6	14.8	15.3	14.7
	HCTZ	14.6	14.4	16.5	13.6
	IND	16.7	15.1	14.1	15.8
Osmolality (mOsmol/kg)	All	597	548	487	549
	HCTZ	558	552	582	568
	IND	637	543	392	530
pH	All	6.00	5.88	5.93	5.77
	HCTZ	5.96	5.88	5.89	5.89
	IND	6.03	5.89	5.97	5.64
Urate (mmol/d)	All	3.19	3.04	3.30	3.16
	HCTZ	3.20	3.08	3.63	3.48
	IND	3.18	3.00	2.98	2.85
Calcium (mmol/d)	All	4.25	2.95**	3.24	3.24
	HCTZ	4.35	3.40	3.80	3.63
	IND	4.15	2.50	2.68	2.85
Citrate (mmol/d)	All	3.43	2.31	2.34	2.58
	HCTZ	2.83	1.73	2.08	2.45
	IND	4.03	2.90	2.60	2.70
Phosphate (mmol/d)	All	29.7	31.5	31.1	30.2
	HCTZ	34.1	30.7	27.7	28.4
	IND	25.3	32.3	34.4	32.0
Divalent phosphate (mmol/d)	All	7.2	6.4	6.4	4.7
	HCTZ	6.9	6.1	6.0	5.0
	IND	7.6	6.7	6.8	4.5
Oxalate (mmol/d)	All	0.36	0.30	0.30	0.28
	HCTZ	0.35	0.30	0.25	0.30
	IND	0.38	0.30	0.35	0.25

2.58 mmol at day 28 but this trend did not reach statistical significance.

Whereas 24-h total phosphate excretion remained stable around 30 mmol, divalent phosphate excretion declined from 7.2 mmol at baseline to 4.7 mmol at day 28 [P = not significant (NS)]. Mean oxalate excretion declined from 0.36 mmol at baseline to 0.28 mmol at day 28 (P = NS).

Timed urine collections

A median of 8 urine samples was obtained per participant during each of the 24-h collection periods (range 6–10 samples; no difference between the groups). As expected, urine flow rates tended to be lowest in the overnight samples, with a mean of 0.8 mL/min. Mean flow rates at the other time points ranged from 1.2–1.9 mL/min. There were no significant changes in flow rates over the course of the study.

A decrease in mean calcium concentrations was observed in the early morning urines (at mean time 07:30) in the indapamide group, from 4.91 mmol/L at baseline to 1.75 mmol/L on day 7 (P = 0.02) and 2.01 mmol/L at day 28 (P = 0.02) (Figure 2). The HCTZ group had a similar trend but this was not statistically significant. Mid-morning urines (mean time 10:30) also revealed declines in mean calcium concentrations for the indapamide group, from 5.92 mmol/L at baseline to 1.60 mmol/L on day 7 (P < 0.01) and 2.68 mmol/L at day 28 (P < 0.01). Calcium concentrations for the HCTZ group were unchanged. Non-significant decreases were also demonstrated throughout the day in the indapamide group. No significant changes were seen in the HCTZ group.

Citrate concentrations declined in the indapamide group in overnight and morning urines (Figure 3), with non-significant decreases also noted through the rest of the day. Mean values for the early morning samples decreased from 4.92 mmol/L at baseline to 1.65 mmol/L at day 28 (P = 0.04), and for the overnight samples, from 3.91 mmol/L to 1.65 mmol/L (P = 0.01). In the HCTZ group, there were no significant changes.

There was a tendency towards decreases in urine pH in the indapamide group, reaching significance in the evening samples. For the 19:30 samples, mean pH values were 6.93 and 5.95 at baseline and on day 28, respectively (P < 0.01). For the 22:30 samples, pH was 6.76 at baseline and 5.94 at day 28 (P = 0.01). The HCTZ group demonstrated no significant changes (Figure 4).

While total phosphate concentrations at each of the time points remained unchanged, declines in divalent phosphate concentrations were noted in the indapamide group at 07:30 (from 4.97 to 0.81 mmol/L on day 28; P = 0.03), 19:30 (from 7.42 to 1.60 mmol/L on day 14; P = 0.04) and 22:30 (from 9.06 to 2.26 mmol/L on day 28; P = 0.01). In the HCTZ group, no significant changes were seen.

No significant changes from baseline were recorded in urine oxalate concentrations, although levels in the indapamide group tended to decrease over the course of the study.

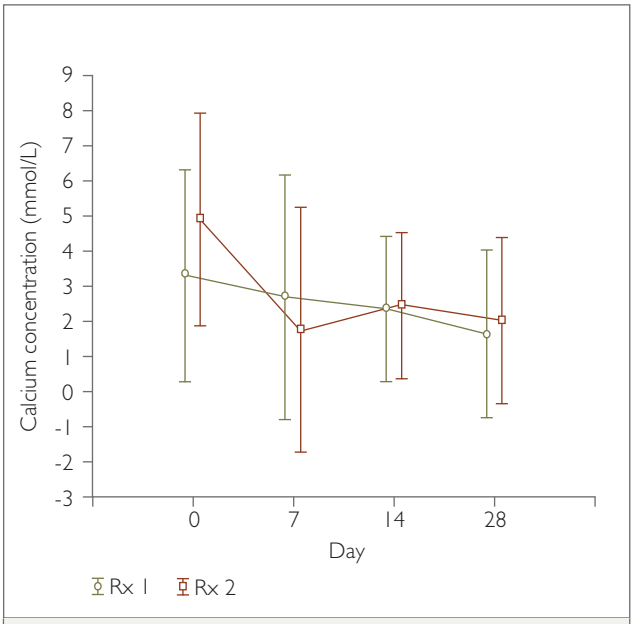

Figure 2. Early morning (07:30) urinary calcium concentrations in participants on hydrochlorothiazide (Rx1) and indapamide (Rx2).

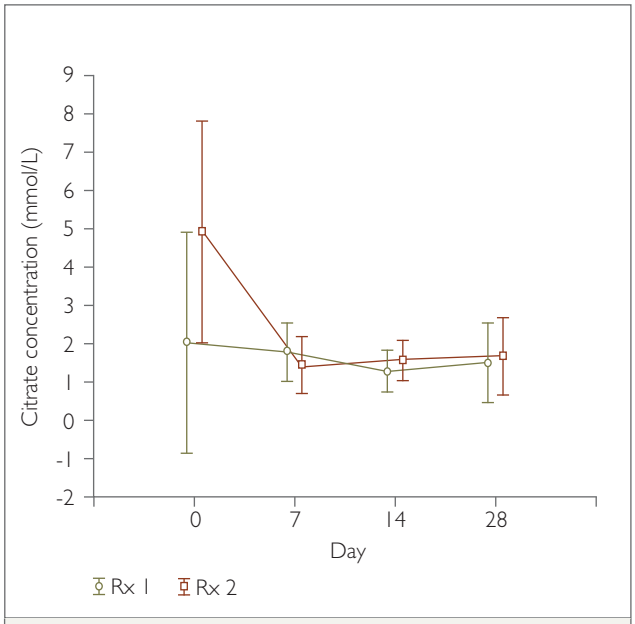

Figure 3. Early morning (07:30) urinary citrate concentrations in participants on hydrochlorothiazide (Rx1) and indapamide (Rx2).

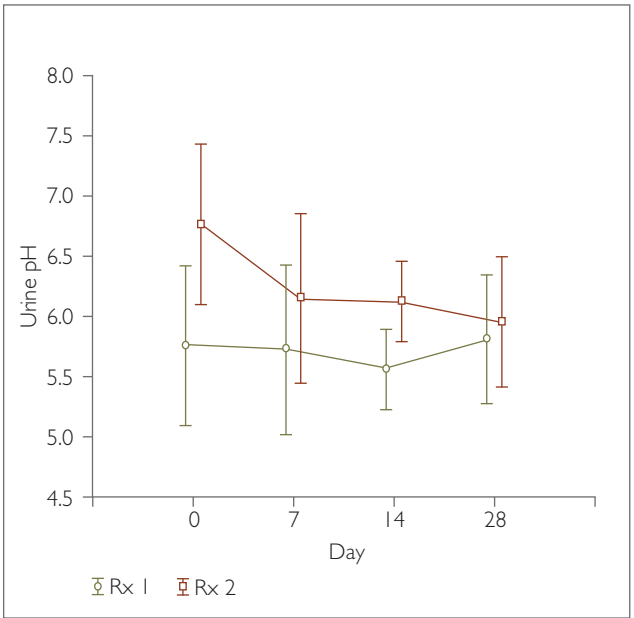

Figure 4. Urine pH in participants on hydrochlorothiazide (Rx1) and indapamide (Rx2) at 22:30.

DISCUSSION

This study has demonstrated the potential of analysing multiple timed urine samples within a 24-h period to provide additional insights into the stone-forming risk profile of individual patients. To the best of our knowledge, this is the first study to employ this approach to examine the effects of thiazide diuretics on urine chemistry and stone-forming risk. We found that urinary calcium excretion was decreased by diuretic therapy, with indapamide the more effective agent, having its most potent effect in the morning.

The decrease in calcium excretion due to diuretic therapy is mainly due to avid proximal tubular reabsorption as the extracellular fluid (ECF) volume declines. Dietary salt intake modulates this effect. We found no indication of treatment-induced decreases in ECF volume in any individual participant or in the group as a whole, as reflected in the measurements of mass, systolic blood pressure, albumin concentration and haematocrit. We also did not observe any correlation between baseline sodium and baseline calcium excretion.

Contrary to previous reports [12], urinary citrate concentration was decreased by indapamide in our study, offsetting some of the benefits achieved with indapamide treatment in reducing urinary calcium excretion. This effect was observed throughout the day and was most prominent overnight and in the early morning. There were no changes in urinary citrate concentrations in participants taking HCTZ.

The desirable trend towards decreased oxalate excretion was more prominent with indapamide than HCTZ. Reductions in urinary divalent phosphate, the form that combines with calcium and contributes to stone-forming risk, occurred in participants on indapamide in the early morning and evenings.

Concerns about the safety of thiazide diuretic use relate mainly to the development of electrolyte disturbances such as hypokalaemia, metabolic alkalosis, hyponatraemia and hypomagnesaemia. In addition, they may cause volume depletion and hypotension, hypercalcaemia, hyperuricaemia and glucose intolerance.

Diuretic treatment in our study did not significantly alter the serum concentrations of sodium, bicarbonate, calcium, random glucose or uric acid. As might be expected, serum potassium levels decreased during treatment in both groups. The biggest change was recorded at day 7 (a mean fall of 0.5 mmol/L), with recovery towards baseline from day 14 onwards. Even at its lowest level, mean potassium remained within the normal range and only one participant, on indapamide, dropped into the mildly hypokalaemic range (3.2 mmol/L), recovering without any intervention. The small transient change in magnesium level was not considered be of any clinical significance.

Our study group demonstrated no decreases in blood pressure. There are two possible reasons for this. First, it may take up to three months for the maximum antihypertensive effects of diuretics to occur [22] and, second, the effects of the diuretics may be attenuated in the absence of dietary salt restriction. Our participants continued their usual diet during the course of the study and all had sodium intakes well in excess of the "adequate intake" level of 65 mmol/L for young adults [23].

Our study has some limitations. Although the participants were studied in detail, the small numbers might explain why some trends did not achieve statistical significance. The findings need to be confirmed in larger studies, and in populations of stone-forming patients. Participants were not required to alter their diet in any way, and intake may have varied during the study period. In this study, 25 mg/d of HCTZ and 2.5 mg/d of indapamide were used. In future studies, it would be useful to include participants on 50 mg/d HCTZ, ideally using a cross-over trial design, and also to study the effects of administering the diuretics twice daily or in the evening.

CONCLUSIONS

This study has demonstrated that the analysis of multiple timed urine collections within a 24-h period provides insights into the stone-forming risk profile of individual

patients, which may not be detected by analysing only 24-h collections. This approach may allow therapy to be targeted more effectively.

We found that diuretics lowered the risk of forming stones during the day, but not overnight, with 2.5 mg/d indapamide having a stronger protective effect than 25 mg/d HCTZ. It might therefore be beneficial to give these medications in the evening or twice daily, although nocturia may limit adherence to such regimens. The benefits of indapamide treatment were attenuated by a reduction in urinary citrate excretion, an effect which has not been described previously.

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Conflicts of interest

No conflicts of interest to declare.

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APPENDIX 1

Normal values for blood tests.	
Creatinine (male) (µmol/L)	53–115
Creatinine (female) (µmol/L)	35–97
Urea (male) (mmol/L)	3.2–7.2
Urea (female) (mmol/L)	2.5–7.2
Sodium (mmol/L)	135–145
Potassium (mmol/L)	3.6–5.0
Chloride (mmol/L)	98–107
Calcium (mmol/L)	2.10–2.55
Albumin (g/L)	38–54
Phosphate (mmol/L)	0.87–1.45
Uric acid (male) (mmol/L)	0.21–0.51
Uric acid (female) (mmol/L)	0.15–0.37
Magnesium (mmol/L)	0.66–1.00
Bicarbonate (mmol/L)	22.0–29.0
Random glucose (mmol/L)	3.0–7.8
Haemoglobin (male) (g/dL)	13.0–18.0
Haemoglobin (female) (g/dL)	11.6–15.6
Haematocrit (male) (%)	40.0–54.0
Haematocrit (female) (%)	35.0–49.0