Urol Res (2005) 33: 116–124
DOI 10.1007/s00240-005-0466-6

ORIGINAL PAPER

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Prophylactic and therapeutic properties of a sodium citrate preparation in the management of calcium oxalate urolithiasis: randomized, placebo-controlled trial

Received: 2 April 2004 / Accepted: 4 May 2004 / Published online: 4 May 2005

Abstract The purpose of this study was to investigate the prophylactic and therapeutic effects of a hitherto untested preparation containing sodium citrate in the management of calcium oxalate urolithiasis. In this study, a host of calcium oxalate kidney stone risk factors was investigated using a randomised, placebo controlled, ''within-patient'' clinical trial. The trial involved four groups of subjects: healthy male controls, healthy female controls , calcium oxalate stone-forming males and calcium oxalate stone-forming females. There were 30 subjects in each group. Twenty subjects in each group ingested the preparation containing sodium citrate and ten subjects in each group ingested a placebo for 7 days. Collection of 24 h urines were carried out at baseline, at day 7 and day 10 (i.e. 3 days after suspension of drug/placebo ingestion). These were analysed for biochemical and physicochemical risk factors. They were also tested for their inhibitory properties in crystallization experiments. Data were statistically analyzed using analysis of variance (ANOVA). Key risk factors were significantly and beneficially altered across all groups after ingestion of the preparation. The pH and urinary citrate excretion increased while urinary oxalate and calcium excretions decreased, as did relative supersaturations of calcium oxalate and uric acid. In addition, inhibition of calcium oxalate crystallization increased. Beneficial carryover effects were observed for some risk factors. The results of this study have demonstrated, for the first time, that a sodium citrate-containing preparation favourably alters the risk factors for calcium oxalate urolithiasis.

Keywords Calcium oxalate urolithiasis · Prophylactics · Therapy · Randomized, placebo-controlled trial · Sodium-citrate-bicarbonate-tartrate

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Introduction

The role of citrate and citrate-containing preparations in urolithiasis has been extensively described by Pak in three excellent reviews [1, 2, 3]. Compelling evidence in support of the use of such compounds in the management of calcium oxalate (CaOx) urolithiasis is based on comprehensive data derived from three sources: in vitro crystallization experiments, measurement of citraturia in normal and CaOx stone-forming subjects and, finally, empirical determinations of CaOx urinary stone risk factors and stone recurrence rates in patients following administration of various citrate-containing preparations.

In vitro experiments during the past 20 years have demonstrated that citrate is an effective inhibitor of CaOx crystal nucleation [4, 5, 6], growth [7, 8] and aggregation [7, 9–11]. Similarly, numerous studies over the past 20 years have demonstrated the prevalence of hypocitraturia in CaOx kidney stone sufferers, thereby providing convincing evidence in support of it being a critical risk factor in this disease [12–16]. Thus, there is a sound rationale and strong motivation for the preparation and testing of citrate-containing compounds which might induce beneficial changes in the risk factors associated with CaOx urolithiasis.

Several different kinds of citrate-containing compounds have been used in clinical trials to investigate their efficacy in the treatment and management of urolithiasis. Among these are potassium citrate [17–21], sodium potassium citrate [22–27], calcium citrate [28, 29], calcium-sodium citrate [30] and potassium-magnesium citrate [31–32]. A combination of calcium lactate and sodium potassium citrate has also been administered [33]. Historically, sodium citrate has been used in the management of uric acid urolithiasis [34, 35] but has not been considered as an efficacious drug for the treatment of calcium urolithiasis because of reports that it may increase the risk of urinary crystallization of calcium oxalate and calcium phosphate in uric acid stone patients [34–37]. We are not aware of any rigorous

study investigating its efficacy in the management of calcium oxalate stone formation risk factors.

In a recent study, we administered a sodium-citrate-bicarbonate-tartrate preparation (CitroSoda, Adcock Ingram, South Africa) to eight healthy male volunteers to examine its synergistic effects with two other health supplements [38]. Several beneficial changes in the urinary risk factors for CaOx urolithiasis were recorded and attributed to this preparation. These results, as well as the fact that there has not been any previous extensive investigation involving Na-Cit in the treatment of CaOx stones, prompted us to expand the size and scope of our earlier study and to focus specifically on the effects of CitroSoda in the management of this particular type of urolithiasis.

Materials and methods

In this study, four groups of subjects were investigated viz. 30 healthy males (MC) with no history of kidney stone disease, 30 healthy females (FC) with no history of kidney stone disease, 30 male calcium oxalate stone-formers (MSF) and 30 female calcium oxalate stone-formers (FSF). Subjects were matched for age but not for body weight. Female subjects (FC and FSF) were pre-menopausal. This study was approved by the Medical Ethics and Research Committee of the University of Cape Town (Rec. Ref. 282/2000); all of the subjects gave their informed consent prior to participation. All of the patients were first-time stone-formers who had passed a CaOx stone (or had one surgically removed) during the preceding 6 months and were recruited from private urologists. The healthy subjects were recruited from the student cohort of the University of Cape Town. The experimental design used in this study was a randomized, placebo controlled, ''within-patient'' design. All of the subjects were required to provide two 24 h urine collections prior to the commencement of the trial. These were used as baseline samples. Subjects remained on their free unrestricted diets throughout the trial. Twenty subjects in each group took four sachets Citro-Soda (Adcock Ingram) per day (equivalent to 2,452 mg sodium citrate, 6,864 mg sodium bicarbonate, 2,808 mg citric acid and 3,432 mg tartaric acid). This preparation will henceforth be referred to as Na-Cit. Ten subjects in each group were given a blinded placebo (Glucose Powder: Pinnacle Pharmaceuticals, South Africa). The placebo did not contain bicarbonate and was a white powder like Na-Cit. Subjects were required to ingest the supplement at mealtimes (two sachets at breakfast and two at lunch). Supplementation lasted for 7 days. Compliance and tolerability were monitored by questionnaire. In addition to the baseline 24 h urine samples, subjects provided 24 h collections on day 7 (final day of supplementation) and on day 10 (3 days after supplementation was suspended). The latter collections were examined for carry-over effects. All urines throughout the trial, as well as at baseline, were collected without an acid preservative since the presence of acid would have rendered our pH measurements following Na-Cit administration meaningless.

Urines were tested for the presence of blood and infection (Combur 10 test strip, Boehringer Mannheim, Mannheim, Germany) and were discarded if the test was positive. After recording volume and pH, aliquots were filtered through a 0.74 μm filter to remove cellular debris and proteinaceous material. The samples were then analyzed for Na, K, Ca and Mg using flame atomic absorption spectrometry [39–41]. Oxalate was determined using oxalate decarboxylase [42]. Citrate was determined by conversion to oxaloacetate using citrate lyase [43]. Inorganic phosphorus was determined using ammonium molybdate [44–45], creatinine using picric acid [46], uric acid using uricase [47] and chloride using an ion selective chloride electrode. Relative supersaturation (RS) values of calcium oxalate, brushite and uric acid were computed using urinalysis data and the EQUIL program [48]. The Tiselius risk index for each sample was also calculated [49].

Crystallization experiments were conducted in each urine using a Coulter Counter (Multisizer 1, Coulter Electronic, England). These involved the determination of each sample's calcium oxalate metastable limit [50]. followed by measurement of the particle size distribution of the samples 120 minutes after crystallization of CaOx had been initiated [51]. Crystal deposition experiments involving radioactive ^{14}C-oxalate [51] were also conducted on the baseline and day 7 samples. Data were statistically analyzed using analysis of variance (ANOVA) and t-tests.

Results

Urine chemistries after Na-Cit administration are given in Tables 1, 2, 3 and 4. In addition, tables 2 and 4 show the statistically significant changes which occurred after placebo administration.

Male controls

Statistically significant favourable changes occurred in five key risk factors after 7 days of Na-Cit ingestion (Table 1): pH and citrate excretion increased while Ca excretion and the RS values of CaOx and uric acid decreased. Increased urinary citrate excretion was still apparent at day 10 i.e. 3 days after suspension of Na-Cit, thereby indicating a carryover effect. There were no unfavourable changes. No significant changes in urine chemistry occurred after taking placebo.

There was no significant change in the calcium oxalate metastable limit after ingestion of Na-Cit and placebo, respectively. A favourable decrease in the CaOx crystal deposition rate occurred after ingestion of Na-Cit (Fig. 1), but not after placebo. There were no statistically significant changes in crystal volume or size following Na-Cit and placebo ingestion.

Table 1 Male controls: urine chemistry after Na-Cit administration. * Indicates a significant change. RS: relative supersaturation, MSL: metastable limit

Variable	Baseline	Day 7	*P* Control vs 7 days	Day 10	P Control vs 10 days
pH	6.40 ± 0.07	7.35 ± 0.09	< 0.0001*	6.60 ± 0.09	0.0682
Volume (ml)	1476.8 ± 78.4	1497 ± 105.4	0.8783	1475.2 ± 105.5	0.9904
Citrate (mmol/24h)	2.95 ± 0.21	3.68 ± 0.28	0.0363*	3.71 ± 0.28	0.0307*
Oxalate (mmol/24h)	0.16 ± 0.01	0.14 ± 0.01	0.1949	0.15 ± 0.01	0.7354
Calcium (mmol/24h)	3.33 ± 0.23	2.40 ± 0.31	0.0166*	2.94 ± 0.31	0.3066
Magnesium (mmol/24h)	4.96 ± 0.27	4.42 ± 0.36	0.2281	2.64 ± 0.36	0.3251
Sodium (mmol/24h)	222.7 ± 18.6	253.9 ± 25.0	0.3171	236.6 ± 25.0	0.6557
Potassium (mmol/24h)	47.24 ± 5.47	49.06 ± 7.36	0.8422	72.74 ± 7.36	0.7673
Urate (mmol/24h)	3.49 ± 0.16	3.48 ± 0.22	0.9566	3.58 ± 0.22	0.7397
Creatinine (mmol/24h)	16.60 ± 0.67	15.82 ± 0.90	0.4901	16.26 ± 0.90	0.7659
Phosphate (mmol/24h)	29.39 ± 1.51	27.98 ± 2.03	0.5798	29.40 ± 2.03	0.9960
Chloride (mmol/24h)	155.0 ± 10.3	134.0 ± 13.8	0.3853	161.8 ± 13.8	0.6927
Risk index	112.3 ± 25.7	93.0 ± 36.3	0.6661	119.2 ± 37.58	0.8799
RS brushite	1.36 ± 0.11	1.33 ± 0.16	0.8651	1.44 ± 0.17	0.7022
RS uric acid	0.97 ± 0.16	0.18 ± 0.23	0.0058*	0.51 ± 0.24	0.1113
RS CaOx	2.04 ± 0.18	1.34 ± 0.26	0.0286*	1.71 ± 0.27	0.3114
CaOx MSL (mol/dm^3)	0.07 ± 0.01	0.08 ± 0.01	0.4929	0.08 ± 0.01	0.3319

Male CaOx stone formers

Statistically significant favourable changes occurred in six key risk factors after 7 days of Na-Cit ingestion (Table 2). The same risk factors were favourably changed in this group as were changed in the control group. In addition, oxalate excretion was significantly decreased in the stone formers (Table 2). However, after placebo ingestion, urinary oxalate was also significantly decreased at day 7 (Table 2). After 10 days (i.e. 3 days after suspension of Na-Cit ingestion), urinary calcium and oxalate were still significantly lower than at baseline, thereby resulting in the RS CaOx being significantly lower as well (Table 2) There were no changes in urinary calcium and oxalate at day 10 in the placebo group, but creatinine excretion, RS uric acid and RS CaOx were significantly lower (Table 2).

The calcium oxalate metastable limit increased significantly after ingestion of Na-Cit (Table 2), but not after ingestion of placebo. There were no statistically significant changes in the CaOx deposition rate, crystal

Table 2 Male stone formers. * Indicates a significant change. RS: relative supersaturation, MSL: metastable limit

Variable	Baseline	Day 7	*P* (control vs 7 days)	Day 10	*P* (control vs 10 days)
Urine chemistry after Na-Cit administration					
pH	6.07 ± 0.06	7.04 ± 0.09	< 0.0001*	6.14 ± 0.09	0.5332
Volume (ml)	1363.9 ± 75.8	1370.8 ± 105.5	0.9582	1266.0 ± 105.5	0.4526
Citrate (mmol/24h)	2.40 ± 0.20	3.10 ± 0.28	0.0453*	2.65 ± 0.28	0.4600
Oxalate (mmol/24h)	0.18 ± 0.01	0.12 ± 0.01	< 0.0001*	0.13 ± 0.01	< 0.0001*
Calcium (mmol/24h)	3.26 ± 0.22	2.16 ± 0.31	0.0046*	2.27 ± 0.31	0.0099*
Magnesium (mmol/24h)	2.60 ± 0.26	2.38 ± 0.36	0.6312	2.64 ± 0.36	0.9203
Sodium (mmol/24h)	188.8 ± 17.9	241.5 ± 25.0	0.0895	154.6 ± 25.0	0.2681
Potassium (mmol/24h)	61.19 ± 5.29	64.72 ± 7.36	0.6972	72.74 ± 7.36	0.2052
Urate (mmol/24h)	3.43 ± 0.16	3.86 ± 0.22	0.1091	3.40 ± 0.22	0.9185
Creatinine (mmol/24h)	15.51 ± 0.64	15.02 ± 0.90	0.6641	14.30 ± 0.90	0.2753
Phosphate (mmol/24h)	30.96 ± 1.46	28.72 ± 2.03	0.3731	28.25 ± 2.03	0.2825
Chloride (mmol/24h)	168.8 ± 9.9	156.4 ± 13.8	0.4655	146.5 ± 13.83	0.1927
Risk index	162.4 ± 25.7	114.0 ± 36.3	0.2791	107.7 ± 37.6	0.2327
RS brushite	1.10 ± 0.11	1.04 ± 0.16	0.7697	0.90 ± 0.17	0.3240
RS uric acid	± 1.91 ± 0.16	0.32 ± 0.23	< 0.0001*	1.80 ± 0.24	0.6792
RS CaOx	3.16 ± 0.18	1.15 ± 0.26	< 0.0001*	1.61 ± 0.27	< 0.0001*
CaOx MSL (mol/dm^3)	0.05 ± 0.01	0.08 ± 0.01	0.0013*	0.06 ± 0.01	0.2845
Urine chemistry after placebo administration					
Oxalate (mmol/24h)	0.19 ± 0.01	0.13 ± 0.01	0.0004*	0.16 ± 0.01	0.1011
Creatinine (mmol/24h)	17.33 ± 0.93	16.30 ± 1.27	0.5127	14.07 ± 1.27	0.0402*
Tiselius risk index	275 ± 36	119 ± 51	0.0151*	305 ± 51	0.6314
RS brushite	0.89 ± 0.16	1.52 ± 0.23	0.0239*	1.14 ± 0.23	0.3588
RS uric acid	2.46 ± 0.23	1.88 ± 0.33	0.1492	1.63 ± 0.33	0.0403*
RS CaOx	3.71 ± 0.26	2.35 ± 0.37	0.0032*	2.61 ± 0.37	0.0163*

Table 3 Female controls: urine chemistry after Na-Cit administration. * Indicates a significant change. RS: relative supersaturation, MSL: metastable limit

Variable	Baseline	Day 7	*P* Control vs 7 days	Day 10	*P* Control vs 10 days
pH	6.42 ± 0.07	7.5 ± 0.09	< 0.0001*	6.55 ± 0.10	0.2971
Volume (ml)	1674.2 ± 70.4	1896.0 ± 96.3	0.0659	1463.4 ± 99.6	0.0872
Citrate (mmol/24h)	2.91 ± 0.17	3.90 ± 0.23	0.0007*	3.06 ± 0.24	0.6144
Oxalate (mmol/24h)	0.20 ± 0.01	0.15 ± 0.01	< 0.0001*	0.16 ± 0.01	0.0013*
Calcium (mmol/24h)	1.98 ± 0.17	1.62 ± 0.23	0.2068	1.99 ± 0.24	0.9704
Magnesium (mmol/24h)	2.37 ± 0.15	2.55 ± 0.21	0.4696	2.50 ± 0.22	0.6252
Sodium (mmol/24h)	101.2 ± 13.9	252.3 ± 19.0	< 0.0001*	164.7 ± 19.7	0.0098*
Potassium (mmol/24h)	42.92 ± 3.40	32.90 ± 4.65	0.0848	38.18 ± 4.81	0.4234
Urate (mmol/24h)	2.75 ± 0.13	2.98 ± 0.18	0.2848	2.64 ± 0.18	0.6149
Creatinine (mmol/24h)	10.32 ± 0.31	10.31 ± 0.44	0.9905	10.46 ± 0.44	0.7899
Phosphate (mmol/24h)	19.36 ± 1.08	19.13 ± 1.53	0.9003	21.63 ± 1.53	0.2293
Chloride (mmol/24h)	111.1 ± 7.2	125.1 ± 10.2	0.2613	119.4 ± 10.2	0.5055
Risk index	220.8 ± 17.8	148.3 ± 26.0	0.0234*	161.6 ± 26	0.0632
RS brushite	0.79 ± 0.12	0.52 ± 0.17	0.1924	0.73 ± 0.17	0.7463
RS uric acid	0.78 ± 0.14	0.06 ± 0.21	0.0055*	0.58 ± 0.21	0.4264
RS CaOx	2.22 ± 0.22	0.61 ± 0.32	< 0.0001*	1.38 ± 0.32	0.0305*
CaOx MSL (mol/dm^3)	0.13 ± 0.01	0.17 ± 0.01	< 0.0001*	0.14 ± 0.01	0.3011

volume or crystal size after ingestion of Na-Cit and placebo, respectively.

Female controls

Statistically significant favourable changes occurred in 6 key risk factors after 7 days of Na-Cit ingestion (Table 3): pH and citrate excretion increased while oxalate excretion, Tiselius risk index and RS values for CaOx and uric acid decreased. Although urinary sodium increased significantly, there was not a concomitant increase in urinary calcium. Indeed, urinary calcium decreased, albeit not significantly. After 10 days, urinary oxalate and RS CaOx were still significantly lower than at baseline, indicating a carry over effect. There were no significant changes after placebo ingestion.

The calcium oxalate metastable limit increased significantly after ingestion of Na-Cit (Table 3) but not after ingestion of placebo. A statistically significant decrease in the CaOx deposition rate occurred after Na-Cit (Fig. 2) but not after placebo. The total crystal volume which was deposited after Na-Cit ingestion for 7 days decreased significantly (Fig. 3). This effect did not occur after placebo ingestion nor was it apparent after suspension of Na-Cit ingestion, i.e. at day 10. Mean crystal

Table 4 Female stone formers. * Indicates a significant change. RS: relative supersaturation, MSL: metastable limit

Variable	Baseline	Day 7	*P* (control vs 7 days)	Day 10	*P* (control vs 10 days)
Urine chemistry after Na-Cit administration					
pH	6.33 ± 0.07	7.16 ± 0.09	< 0.0001*	6.16 ± 0.11	0.1919
Volume (ml)	1303.5 ± 71.7	1322.5 ± 96.31	0.8747	1314.5 ± 111.6	0.9341
Citrate (mmol/24h)	2.47 ± 0.17	3.17 ± 0.23	0.0149*	3.25 ± 0.26	0.0131*
Oxalate (mmol/24h)	0.17 ± 0.01	0.14 ± 0.01	0.0387*	0.11 ± 0.01	0.0002*
Calcium (mmol/24h)	3.08 ± 0.17	2.60 ± 0.23	0.0952	3.69 ± 0.26	0.0553
Magnesium (mmol/24h)	2.18 ± 0.16	1.86 ± 0.21	0.2313	2.27 ± 0.24	0.7550
Sodium (mmol/24h)	131.7 ± 14.2	140.8 ± 19.0	0.7005	149.5 ± 22.1	0.4971
Potassium (mmol/24h)	40.32 ± 3.46	36.54 ± 4.66	0.5162	53.44 ± 5.39	0.0422*
Urate (mmol/24h)	2.90 ± 0.13	2.66 ± 0.17	0.2780	2.98 ± 0.20	0.7391
Creatinine (mmol/24h)	10.57 ± 0.32	9.85 ± 0.43	0.1765	9.89 ± 0.49	0.2487
Phosphate (mmol/24h)	20.55 ± 1.10	20.70 ± 1.48	0.9317	24.32 ± 1.71	0.0650
Chloride (mmol/24h)	122.1 ± 7.3	97.9 ± 9.8	0.0505	127.6 ± 11.4	0.6821
Risk index	282.7 ± 17.8	204.4 ± 26.0	0.0145*	180.3 ± 28.0	0.8310
RS brushite	0.93 ± 0.12	1.40 ± 0.17	0.0266*	1.02 ± 0.19	0.6942
RS uric acid	1.70 ± 0.14	0.48 ± 0.21	< 0.0001*	1.56 ± 0.24	0.6142
RS CaOx	3.29 ± 0.22	2.13 ± 0.31	0.0027*	1.94 ± 0.35	0.0016*
CaOx MSL (mol/dm^3)	0.08 ± 0.01	0.11 ± 0.01	0.0037*	0.07 ± 0.01	0.4603
Urine chemistry after placebo administration					
Calcium (mmol/24hr)	3.72 ± 0.24	3.13 ± 0.34	0.1582	2.48 ± 0.34	0.0037*
Creatinine (mmol/24hr)	10.30 ± 0.45	9.40 ± 0.63	0.2487	8.41 ± 0.63	0.0166*
Chloride (mmol/24hr)	134.8 ± 10.3	108.2 ± 14.6	0.0352*	103.4 ± 14.6	0.0476*
RS CaOx	4.91 ± 0.31	5.11 ± 0.47	0.7239	3.53 ± 0.50	0.0215*

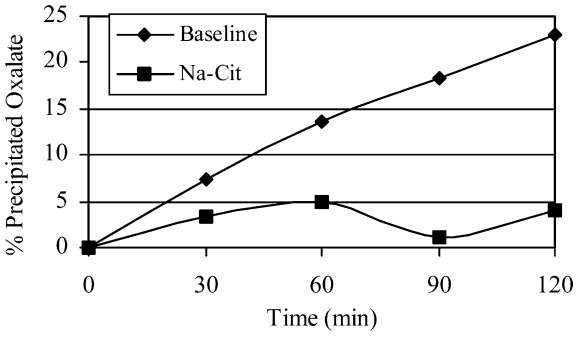

Fig. 1 Percentage precipitated [^{14}C]-oxalate after in vitro addition of a sodium oxalate load for male controls. Decrease in precipitated oxalate = 85.46%, $P = 0.0542$

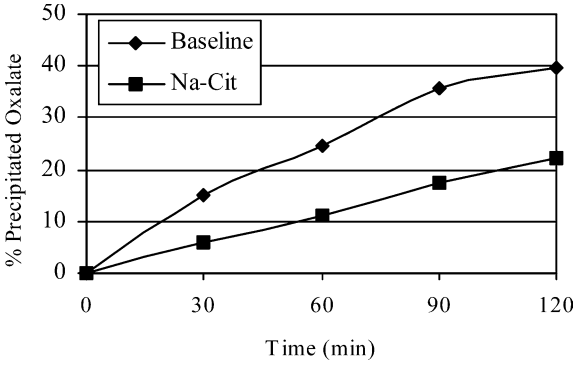

Fig. 2 Percentage precipitated [^{14}C]-oxalate after in vitro addition of a sodium oxalate load for female controls. Decrease in precipitated oxalate = 43.98%, $P = 0.0239$

sizes did not change significantly after ingestion of Na-Cit and placebo, respectively.

Female CaOx stone formers

Statistically significant favourable changes occurred in six key risk factors after 7 days of Na-Cit ingestion (Table 4). These corresponded with the risk factors which were favourably altered in the female controls. However, an additional risk factor—RS brushite—was unfavourably increased (Table 4). After 10 days, urinary citrate was still significantly higher than at baseline, while urinary oxalate and RS CaOx were still significantly lower than at baseline (Table 4). None of these changes occurred after placebo ingestion at 7 days. However, after 10 days (placebo protocol), there were statistically significant decreases in urinary calcium, creatinine, RS CaOx and chloride (Table 4).

The calcium oxalate metastable limit increased significantly after ingestion of Na-Cit (Table 4), but not after ingestion of placebo. There were no statistically significant changes in deposition rate, crystal volume or crystal size after ingestion of Na-Cit and placebo respectively.

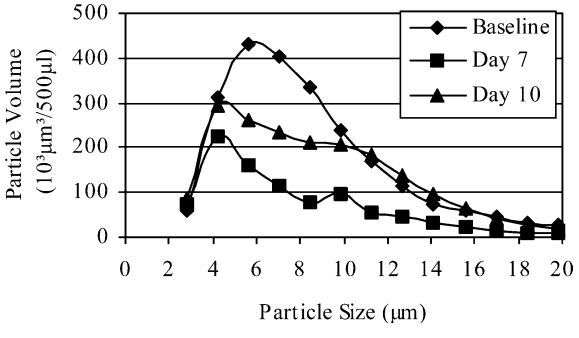

Fig. 3 Particle volume-particle size distribution after in vitro addition of a sodium oxalate load for female controls. *Day 7*: after 7 days ingestion of Na-Cit. *Day 10*:3 days after suspension of Na-cit ingestion. Baseline vs day 7: decrease in total volume = 61.57%, $P = 0.0035$. Decrease in mean particle size = 26.7%, $P > 0.05$. Baseline vs day 10: decrease in total volume = 17.03%, $P > 0.05$. Decrease in mean particle size = 30.0%, $P > 0.05$

Tolerability and compliance

There were no reported side-effects across all four groups. All subjects claimed 100% compliance.

Discussion

The results of the present study have provided physiological and physicochemical evidence to warrant the use of CitroSoda as a prophylactic and therapeutic agent in the conservative treatment and management of CaOx urolithiasis. We have shown that this preparation unequivocally altered three biochemical risk factors in all of the groups, viz. pH, citrate excretion and the RS of uric acid. In addition, we have shown that oxalate excretion decreased significantly in female controls and female stone formers following sodium citrate administration, and that the same effect was not achieved after placebo. On the other hand, no effect on oxalate excretion in male controls was observed, but it decreased in male stone formers after sodium citrate *and* placebo. This latter observation is puzzling. Perhaps this apparent effect after placebo may simply reflect the relatively small number of subjects in this group. Indeed, given the day-to-day variation in oxalate excretion, ten subjects may not have been enough to establish a reliable placebo-based value for oxalate excretion. Alternatively, we suggest that the observed placebo results might be an example of the stone clinic effect [52] in which the patients might have become more vigilant of their dietary oxalate intake once they had commenced the (placebo) protocol. As such, their urinary oxalate excretion decreased. As a consequence of the decrease in oxalate excretion, the Tiselius risk index and RS calcium oxalate also show significant decreases at day 7 (Table 2). It can be speculated that the decrease in the pool of oxalate ions available for binding to calcium ions would be accompanied by an increase in the concentration of free unbound calcium. These ions would then be available

for binding to phosphate, giving rise to the observed increase in RS brushite (Table 2).

Of course, it could be argued that the decrease in oxalate excretion observed in female controls and female stone formers might have occurred for the same reason. However, this argument is easily dismissed since the placebo protocol did not lower urinary oxalate in these two groups. Thus, the decrease in oxalate excretion in female controls and female stone formers cannot be attributed to the stone clinic affect and must be correctly credited to sodium citrate. Decreases in oxalate excretion have not been reported for any of the citrate-containing preparations which are currently in wide use. Indeed, an increase in this parameter has been observed following K-Mg-Cit therapy [32]. Moreover, in the present study, the protocol did not allow urine to be collected in acid, which would have prevented the spontaneous conversion of any endogenous ascorbate to oxalate. Thus, since oxalate excretion is a crucial risk factor in CaOx stone formation, the *lowering* of this urinary parameter following sodium citrate administration represents an important clinical result.

It is also of interest to note that we observed an increase in citrate excretion and a concomitant decrease in calcium excretion following sodium citrate administration even though it is well known that sodium intake *increases* calcium excretion [53–54]. The increase in citrate excretion after citrate administration could be due to the excretion of absorbed sodium citrate which escaped metabolic degradation in vivo and directly appeared in the urine [55]. On the other hand, it is well known that oestrogen status is linked to citrate excretion [56]. However, since none of our female subjects were receiving oestrogen replacement therapy, the observed increase in the excretion of this parameter in FC and FSF can indeed be attributed to the administration of sodium citrate.

The increase in pH observed in all of our groups is a result of the in vivo oxidation of citrate to bicarbonate, which results in a change in the acid-base balance of the urine [55]. We recognize that it would have been useful to have measured serum biochemistry to assess the effect on plasma bicarbonate, but such analyses were not performed.

The implication of the increase in urinary pH itself is worthy of comment. Previous studies have revealed that there appears to be a dual role of pH in calcium oxalate urolithiasis. On the one hand, the solubility of CaOx decreases with increasing pH [57], while on the other hand, inhibitory activity towards calcium oxalate crystallization increases with increasing pH [3]. At a higher pH, more phosphate and citrate ions become dissociated; this augments the complexation of calcium, thereby lowering the urinary saturation of stone forming salts [3]. Indeed, the increase in pH following administration of citrate preparations is widely regarded as a key factor in accounting for its success in the management of calcium oxalate urolithiasis [17, 18 24, 25, 27]. The increase in pH observed in the present study is therefore in agreement with these latter results.

As mentioned earlier, the present study has also provided physicochemical data which demonstrate the beneficial effect of sodium citrate administration on CaOx urolithiasis. Our RS values for CaOx and uric acid illustrate the point. The RS of CaOx was uniquely and favourably decreased in all of the groups studied except in male stone formers for whom the placebo also achieved this result (mainly due to the decrease in oxalate excretion following placebo administration discussed above). Despite this apparent anomaly, the decrease in RS of CaOx in all of the groups represents another important finding in favour of sodium citrate administration. The same is true for our observation of decreased RS values for uric acid. A previously reported concern about sodium citrate therapy has been the observed increase in the RS of sodium urate [34–36]. Although this parameter was not directly measured in the present study, it is unlikely to have been affected since sodium excretion did not increase in three of the four groups. The only group in which sodium excretion increased was FC. Another reported concern has been an increase in the RS of brushite (in uric acid stone formers) [34]. In the present study (involving healthy controls and CaOx SF), this physicochemical risk factor increased, but only in FSF. As such, this is an unfavourable result. On the other hand, the decrease in the Tiselius risk index in female controls and female stone formers is yet another favourable finding, even though the same effect did not occur in males.

Crystallization experiments in the present study demonstrated a favourable increase in the calcium oxalate metastable limits in three of the groups following sodium citrate ingestion. This effect supports our contention that this preparation has potential as a prophylactic agent in the management of calcium oxalate urolithiasis. However, our other crystallization measurements revealed only a few statistically significant changes (decreases in the crystal deposition rates in MC and FC, and a decrease in the total crystal volume in FC), and, as such, did not consistently reflect the observed alterations in relative supersaturation values. This suggests that our crystallization measurements, in some cases, might not have been sufficiently sensitive to detect small changes under the conditions in which the experiments were performed.

The results of the present study also provide evidence for carryover effects: citrate excretion (MC, FC), oxalate excretion (MSF, FC, FSF) and RS CaOx (MSF, FC, FSF).

The absence of any side effects (stomach pain, mild diarrhoea and nausea) is in contrast to those which have been reported for potassium salts [17, 18, 20] and potassium-sodium salts [26]. Because of the high tolerability, the absence of a multi-tablet dosage and the short-term nature of the present study, there is no reason to doubt the 100% compliance rate claimed by the subjects. This too is in contrast with other studies which

have reported disappointing compliance rates as a result of these factors [20, 26]. Nevertheless, the statistically significant decreases in creatinine excretion observed in the stone formers at day10 of the placebo protocols (Tables2 and 4), i.e. 3 days after suspension of placebo ingestion, are indicative of a relaxation in urine collection compliance by these subjects. This may account for the other changes observed in these collections (Tables 2 and 4).

Since the results of our study provide evidence for the use of sodium citrate in the management of calcium oxalate urolithiasis, it would be appropriate for us to review the reasons for the apparent abandonment of sodium citrate preparations as a potential therapeutic agent in the treatment of this disease. Firstly, we note that in their studies comparing the effects of potassium citrate and sodium citrate, Sakhaee et al. [34] and Preminger et al. [35], refer to papers which reported an increase in the risk of calcium stone formation following sodium alkali therapy. We respectfully draw attention to the fact that the alkalinizing agent in these studies was sodium bicarbonate and not sodium citrate per se [58, 59]. Secondly, we note that there have been very few studies on stone risk factors following sodium citrate administration [34–36] and that, more importantly, these studies have involved very small patient groups (four, five and six subjects, respectively). This raises serious doubts about the validity of the so-called statistical analyses.

Thirdly, it appears to us that the main concern about sodium citrate therapy is that it increases the urinary saturations of sodium urate [34–36] and calcium phosphate (brushite) [34]. We agree that these parameters constitute urinary physicochemical risk factors. Indeed, in vitro studies have demonstrated that the former effect could promote urate-induced crystallization of calcium oxalate [60, 61] while the latter would increase the risk of brushite precipitation. However, it is intriguing to us that potassium citrate therapy has caused the same two effects [34], yet it has not been discredited in any way. Admittedly, the inhibitor activity against calcium oxalate precipitation (given by the formation product ratio) significantly increased with potassium citrate while sodium citrate had no effect [34], but we regard this as being indicative of relative risk rather than absolute risk.

Fourthly and as stated earlier, we note that the concerns which have been reported about sodium citrate administration have arisen following the treatment of uric acid urolithiasis as opposed to calcium oxalate urolithiasis.

Thus the apparent concerns about the administration of sodium citrate in calcium oxalate urolithiasis seems to be based on tenuous scientific data and are somewhat unfounded.

In conclusion, this study offers several new aspects regarding research on citrate-containing preparations in the field of CaOx urolithiasis. It is the first in-depth calcium oxalate stone risk investigation involving a sodium-citrate-bicarbonate-tartrate preparation. Indeed, the presence of tartrate is probably significant, as previous studies have demonstrated that it is an effective inhibitor of CaOx crystallization, by virtue of its ability to complex free calcium ions [62]. Secondly, unlike many of the studies involving other citrate-containing preparations, the present study investigated four groups of subjects. The participation of males and females allowed us to identify certain gender-based similarities and differences while the participation of healthy subjects allowed us to examine potential prophylactic effects of sodium citrate. Thirdly, our group sizes (30 subjects) were substantially larger than in many other studies, thereby lending credibility to our statistical analyses. Fourthly, our results have dispelled the concerns that sodium citrate (in general) may increase the risk of stone formation in calcium oxalate stone formers. While such a concern may be true for uric acid stone formers (we cannot comment thereon), our results have demonstrated that sodium citrate, in the form of CitroSoda, may prove to be an effective preparation for the prophylactic and therapeutic management of calcium oxalate urolithiasis. It is important to note that the present study was only a short-term one which focused on the effects of this preparation on urine biochemistry. Its long-term effect on stone recurrence rates remains to be investigated.

Acknowledgements Funding for this study was received from the South African Medical Research Council, the South African National Research Foundation, the University of Cape Town and Adcock Ingram Limited, South Africa. There was no involvement by any of these bodies in the design of the study or in the collection, analysis and interpretation of data or in the decision to approve publication of the finished manuscript.

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