The effects of oral sodium bicarbonate on extracellular water in patients with chronic kidney disease

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Abstract

Background: Metabolic acidosis in chronic kidney disease (CKD) is often treated with oral sodium bicarbonate. There is limited evidence around the effects of sodium bicarbonate on extracellular fluid and blood pressure in CKD.

Methods: In a double blind randomised comparison patients with stage 3-5 CKD were randomised to either oral sodium bicarbonate 1.5 g three times a day (n=18) or placebo (n=21) for 4 weeks. Assessments performed at 0 and 4 weeks included: body weight, office blood pressure and assessment for peripheral/pulmonary oedema; serum creatinine, electrolytes and venous bicarbonate; 24-hour urine for sodium excretion; extracellular fluid volume and total body water determined by sodium bromide and deuterium oxide dilution respectively; extracellular fluid volume and total body water by bioimpedance. Differences between the active and placebo groups at week 4 were analysed by ANCOVA.

Results: At week 4, serum bicarbonate was higher (25.6±2.4 vs 23.3±3.1 mmol/l) and blood urea lower (14.2±5.6 vs 17.0±5.8 mmol/l) in the active treatment group. Urine sodium concentration was also higher (82.7±25.3 vs 59.0±21.9 mmol/l). Extracellular fluid volume (20.0±4.3 vs 18.0±2.9) and total body water (42.3±9.6 vs 39.0±6.8) measured by bioimpedance and total body water by deuterium dilution (41.7±8.3 vs 39.4±6.2) were significantly greater in the treatment arm at week 4. Differences in systolic and diastolic blood pressure did not reach statistical significance.

Conclusions: Oral sodium bicarbonate has a biological effect and increases body water content, without evidence of a clinical consequence. This may reflect the fact that some of the ingested sodium is excreted in the urine.

Keywords: Acidosis; Chronic kidney disease; Extracellular water; Hypertension; Sodium bicarbonate; Total body water
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**Introduction**

Chronic metabolic acidosis is a common finding in patients with chronic kidney disease (CKD) and has been associated with a range of potential adverse consequences [1], including more rapid progression of CKD [2], an increased risk of death [3], impaired protein [4] and bone metabolism [5] and worsening hyperkalaemia [6]. Correction of the acidosis may ameliorate some of these metabolic effects [1]. In addition, oral bicarbonate supplementation in patients with CKD may delay progression of kidney disease [7]. For these reasons oral sodium bicarbonate is frequently prescribed to CKD patients and correction of serum bicarbonate to a level of $\geq 22$ mmol/L is recommended in international guidelines [8].

However, worsening kidney function is also characterised by sodium and fluid retention. As well as causing peripheral or pulmonary oedema, sodium and water retention may exacerbate the hypertension that is a frequent complication of CKD. Hypertension in turn is associated with left ventricular hypertrophy and an increased risk of heart failure and sudden death, as well as being a risk factor for macrovascular diseases including coronary artery disease, cerebrovascular disease and peripheral vascular disease. There are therefore legitimate safety concerns around the administration of oral sodium bicarbonate to this patient group. A systematic review of six trials concluded that oral sodium bicarbonate “was not associated with a higher likelihood of initiating or escalating anti-hypertensive medications”, with no significant effect on systolic or diastolic blood pressure [9].

However in this study, the relative risk of initiating or escalating anti-hypertensive medications was 1.58, with confidence intervals of 0.53-4.74, reflecting the poor quality of the included trials. In a more recent study that randomised 188 subjects with stage 3/4 CKD to a mean oral sodium bicarbonate dose of 2.3 g/day or placebo 28.7% of actively treated subjects had worsening oedema as compared to 15% of controls and 35.1% vs 22.3% had worsening hypertension, differences that did not reach statistical significance [10]. There was a significant increase in the prescription of diuretics in the active treatment arm, implying clinical significance to these effects, and systolic and diastolic blood pressures were 4 and 2 mmHg higher respectively [10].

At present there is insufficient evidence on the effect of sodium bicarbonate on extracellular fluid and blood pressure control in CKD. We therefore conducted a prospective study to investigate the consequences of oral sodium bicarbonate loading on extracellular water, the body compartment that would be expected to expand if sodium retention occurred, and blood pressure.

**Method**

This was a 4-week double blind randomised comparison of oral sodium bicarbonate versus placebo for patients with chronic kidney disease. The null hypotheses being tested were that sodium bicarbonate increases neither extracellular fluid nor blood pressure in patients with CKD. Patients were randomised to either oral sodium bicarbonate 1.5 g (3 x 500 mg tablets) three times a day (54 mmol sodium/day) or oral placebo (3 tablets 3 times
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per day). This is within the licensed therapeutic dose range for sodium bicarbonate in patients with CKD. Subjects were included if they had stage 3-5 CKD (MDRD eGFR<60 ml/min). Exclusion criteria included patients on dialysis; current treatment with oral sodium bicarbonate; poorly controlled hypertension (systolic BP >160 mmHg; diastolic BP >90 mmHg); peripheral oedema on clinical assessment; active nephrotic syndrome; history of congestive cardiac failure and/or pulmonary oedema). Compliance with the treatment was measured by returned pill count.

Height, weight, office blood pressure, medication history and a clinical assessment for peripheral oedema were recorded at baseline and on day 28 of the study. Blood pressure was measured in the non-dominant arm after sitting for at least 5 minutes using a calibrated automated blood pressure machine. The average of three readings was recorded. Subjects were asked to complete a 3-day dietary diary for estimation of oral sodium intake. Blood was analysed for serum creatinine, electrolytes and venous bicarbonate. A 24-hour urine was collected for volume and sodium concentration. A tetrapolar bioelectric impedance measurement was taken for estimation of extracellular fluid volume (Vecf) and total body water (TBW). Blood and saliva samples were collected immediately before and 4 hours (blood) and 4, 5 and 6 hours (saliva) after ingestion of pre-prepared solutions of sodium bromide and deuterium oxide administered according to patient weight.

Extracellular fluid volume and total body water were determined by sodium bromide and deuterium oxide (\( ^2 \text{H}_2\text{O} \)) dilution respectively. Plasma bromide was measured by ion chromatography with suppressed conductivity detection in samples taken pre- and 4 hours post- a 50 mg/kg body weight oral dose of 3.22% sodium bromide. Plasma bromide levels are stable at 4 hours following an oral bromide dose, as gastrointestinal absorption is complete, bromide has a long biological half-life, and urine excretion is not significant at this time.

The bromide space (equivalent to Vecf) was calculated as:

\[
\text{Bromide ECF (l)} = \frac{\text{Br}_0}{(\text{Br}_{\text{post}} - \text{Br}_{\text{pre}})}
\]

where \( \text{Br}_0 \) is the oral bromide dose (g) and \( \text{Br}_{\text{post}} \) and \( \text{Br}_{\text{pre}} \) the post and pre dose plasma bromide concentrations (g/l) respectively. The bromide space was corrected by a factor of 0.855 [11].

Total body water (TBW) was estimated by \( ^2 \text{H}_2\text{O} \) dilution. The enrichment of \(^2\text{H}\) in body water (saliva samples) was measured by isotope ratio mass spectrometry pre- and at 4, 5 and 6 hours post- a 0.07 g/kg body weight oral dose of \( ^2 \text{H}_2\text{O} \). TBW is then derived:

\[
\text{TBW} = \frac{T \times A \times (E_a - E_t)}{a \times E_s - E_p}
\]

where \( A \) is the oral dose (g) of isotope administered, and \( a \) is the amount (g) of the dose diluted for mass-spectrometric analysis in \( T \) (g) of tap water and \( E_a \) is the enrichment of the portion, \( E_t \) is the enrichment of tap water, \( E_s \) is the mean enrichment of the 4-6 hour post dose samples and \( E_p \) is enrichment of the pre-dose saliva sample [12]. Isotopic composition was determined by mass spectrometry, using platinum catalysed equilibration with hydrogen gas [13]. The study was approved by the Research Ethics Committee and all subjects gave signed informed consent. Statistical Methods and Sample Size. In the absence of meaningful data on which to base a power calculation, we estimated that 30 subjects per group would detect a significant difference in Vecf between normovolaemic and fluid overloaded patients with \( \alpha \) of 0.1 and power 0.9, based on our previous observations of ECF/TBW ratios of <0.48 in normovolaemic subjects and of >0.50 in CKD and end-stage renal failure patients with hypervolaemia. The significance of differences between the active
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(bicarbonate) and placebo groups at week 4 was analysed by ANCOVA with week 0 (baseline) data as the covariate [14]. A value of <0.05 was taken as statistically significance. Randomisation was performed by an independent computerised process and identical active/placebo tablets were provided via the pharmacy department in pre-packed containers.

Results

Thirty-nine patients completed the study. The study was ended before reaching the recruitment target because it was clear that this would not be achieved (Figure 1). Eighteen were randomised to active treatment (sodium bicarbonate) and 21 to placebo. One available deuterium result was not included in the analysis, because the result was clearly biologically impossible (TBW > actual weight). Table 1 shows the baseline characteristics of the study groups (mean and standard error of the mean (SEM). Patients randomised to the active treatment were significantly younger (64.1±2.6 yrs versus 73.4±2.2 yrs, p=0.009; non-paired t test), but there were no other significant differences between the 2 groups. The comparison of active and placebo groups at week 4 was therefore reanalysed adjusting for age as a second covariate. There was no difference in the mean number of blood pressure medications prescribed, class of blood pressure medications prescribed nor the use of diuretics between the 2 groups (table 2).

By ANCOVA adjusted for baseline value (table 3), serum bicarbonate was significantly higher (25.6±2.4 vs 23.3±3.1 mmol/l, p=0.03) and blood urea significantly lower (14.2±5.6 vs 17.0±5.8 mmol/l, p=0.02) at week 4 in the active treatment group. Urine sodium concentration was significantly higher in the active treatment group (82.7±25.3 vs 59.0±21.9 mmol/l, p=0.001).

Adjusting for baseline value, extracellular fluid volume (20.0±4.3 vs 18.0±2.9, p=0.005) and total body water (42.3±9.6 vs 39.0±6.8, p=0.02) measured by bioimpedance were significantly greater in the treatment arm as compared to the placebo arm at week 4. Intracellular fluid volume was not different. By deuterium dilution, total body water (41.7±8.3 vs 39.4±6.2, p=0.01) was significantly greater in the treatment arm as compared to the placebo arm at week 4, adjusting for baseline values. There was no difference in extracellular fluid volume by bromide space. There were no other significant differences between the groups (Table 3). Adjusting the analyses with age as a 2nd covariate did not weaken these findings, but the Vecf/TBW ratio by bioimpedance adjusted for age was greater in the treatment arm than placebo arm, although this did not reach significance (p=0.06). The mean difference for the change in blood pressure between week 0 to week 4 compared between the treatment and placebo groups was +8.08 for the systolic blood pressure (95% confidence intervals -2.35 to 18.51) and +2.53 for diastolic blood pressure (95% confidence intervals -4.38 to 9.44).

Adverse events. During the course of the study 2 adverse events were recorded that may have been causally linked with the study. Both occurred in the active (bicarbonate) arm. One patient developed peripheral oedema that resolved spontaneously after 2 weeks (no intervention); another required admission with acute renal colic secondary to a ureteric stone on day 27.
Figure 1: Participant Flow diagram.

Assessed for eligibility  n=157
- Excluded n=111
  - Not meeting inclusion criteria n=0
  - Declined to participate n=111
  - Other reasons n=0

Randomised n=46
- Allocated to sodium bicarbonate n=22
  - Received sodium bicarbonate n=19
  - Did not receive sodium bicarbonate n=3
  - Prescribed sodium bicarbonate for clinical reasons prior to 1st visit n=1
  - Withdrew prior to 1st visit n=2

- Allocated to placebo n=24
  - Received placebo n=22
  - Did not receive placebo n=2
  - Withdrew prior to 1st visit n=1
  - Withdrawn prior to 1st visit (hypertension) n=1

Lost to follow up n=0
- Discontinued intervention n=1
- Withdrawn prior to 2nd visit (hospital admission) n=1

Analysed n=18
- Excluded from analysis n=0

Analysed n=21
- Excluded from analysis n=0
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Table 1: Comparison of baseline characteristics.

|                    | Sodium bicarbonate (n=18) | Placebo (n=21) |
|--------------------|---------------------------|----------------|
| n                  | mean±SEM                  | n              | mean±SEM               |
| Male/Female        | 14/4                      | 16/5           |
| Age (years)        | 18                        | 21             | 64.1±2.6               | 73.4±2.2               |
| Weight (kg)        | 18                        | 21             | 86.6±4.2               | 81.5±2.8               |
| Systolic BP (mmHg) | 18                        | 21             | 137.8±4.2              | 141.4±3.9             |
| Diastolic BP (mmHg)| 18                        | 21             | 73.8±2.7               | 70.7±2.6               |
| 24 hr urine sodium (mmol) | 17                      | 17             | 133.8±15.2             | 133±17                |
| Urine sodium (mmol/l) | 18                        | 19             | 62.5±4.5               | 61.9±5.0               |
| Serum potassium (mmol/l) | 17                        | 21             | 4.8±0.9                | 4.8±0.1               |
| Serum creatinine (μmol/l) | 18                        | 21             | 227±16.5               | 241±24.3              |
| Creatinine clearance (C-G) (ml/min/1.73m²) | 18                        | 21             | 29.9±2.5               | 24.7±2.1               |
| Serum bicarbonate (mmol/l) | 18                        | 21             | 24.2±0.6               | 23.2±0.7               |
| Albumin (g/l)      | 18                        | 21             | 42.8±0.7               | 41.1±0.5               |
| Sodium intake (mmol/day) | 18                        | 20             | 125.6±7.2              | 117.8±9.0             |
| Water intake (ml/day) | 18                        | 20             | 2288±163               | 2032±163              |
| ECF BIA (litres)   | 18                        | 21             | 19.5±1.0               | 18.2±0.6               |
| ICF BIA (litres)   | 18                        | 21             | 22.5±1.4               | 21.3±1.0               |
| TBW BIA (litres)   | 18                        | 21             | 42.0±2.3               | 39.5±1.5               |
| ECF Bromide (litres) | 18                        | 21             | 24.6±1.2               | 24.4±1.0               |
| TBW Deuterium (litres) | 18                        | 19             | 43.2±3.1               | 40.0±1.4               |
| ECF/TBW ratio      | 18                        | 19             | 0.58±0.02              | 0.61±0.02              |
| Mean no. of BP drugs | 18                        | 21             | 2.3±0.3                | 1.81±0.4               |

ECF=extracellular fluid volume; ICF = intracellular fluid volume; TBW=total body water; BIA = bioelectric impedance; C-G = Cockcroft-Gault.

Table 2: Comparison of blood pressure medication and diuretic prescription between the treatment and placebo arms at baseline. There were no changes in these medications during the study.

|                              | Sodium bicarbonate group (n=18) | Placebo group (n=21) | p (Chi²) |
|------------------------------|---------------------------------|----------------------|----------|
| Not taking blood pressure drugs | 3                              | 6                    |          |
| Total number of blood pressure drugs | 2.3±0.3                       | 1.8±0.4              | 0.4      |
| ACE-i/A2RB                   | 14                              | 10                   | 0.1      |
| Beta blocker                 | 7                               | 3                    | 0.1      |
| Vasodilators                 | 10                              | 9                    | 0.5      |
| Diuretic                     | 6                               | 8                    | 1.0      |

Vasodilator=calcium antagonist or alpha blocker.
Table 3: Outcome values at week 4 for active and placebo groups. Between group comparison by ANCOVA with the baseline value as the primary covariate and age as the second covariate (final column).

|                                | Mean | Std. Deviation | Std. Error Mean | Significance (ANCOVA) | Significance (Age adj.) |
|--------------------------------|------|----------------|-----------------|-----------------------|------------------------|
| **Weight**                     |      |                |                 |                       |                        |
| Active (n=18)                  | 87   | 18             | 4.2             | p=0.7                 | p=0.8                  |
| Placebo (n=21)                 | 81.7 | 13.1           | 2.9             |                       |                        |
| **Systolic BP**                |      |                |                 |                       |                        |
| Active (n=18)                  | 139.4| 16.6           | 3.9             | p=0.2                 | p=0.2                  |
| Placebo (n=21)                 | 134.9| 14.7           | 3.2             |                       |                        |
| **Diastolic BP**               |      |                |                 |                       |                        |
| Active (n=18)                  | 72.2 | 13.3           | 3.1             | p=0.4                 | p=0.2                  |
| Placebo (n=21)                 | 66.6 | 9.2            | 2               |                       |                        |
| **24 hour Urine Volume**       |      |                |                 |                       |                        |
| Active (n=16)                  | 1.89 | 0.52           | 0.13            | p=0.1                 | p=0.4                  |
| Placebo (n=17)                 | 2.14 | 0.81           | 0.2             |                       |                        |
| **24 hour Urinary Sodium**     |      |                |                 |                       |                        |
| Active (n=16)                  | 149.1| 41.3           | 10.3            | p=0.6                 | p=0.3                  |
| Placebo (n=17)                 | 135.2| 86.4           | 21              |                       |                        |
| **Urinary sodium mmol/litre**  |      |                |                 |                       |                        |
| Active (n=17)                  | 82.9 | 25.3           | 6.1             | p=0.001               | p=0.003                |
| Placebo (n=18)                 | 59   | 21.9           | 5.2             |                       |                        |
| **Serum sodium**               |      |                |                 |                       |                        |
| Active (n=16)                  | 139.4| 2.3            | 0.6             | p=0.1                 | p=0.1                  |
| Placebo (n=21)                 | 138.6| 3              | 0.7             |                       |                        |
| **Serum Potassium**            |      |                |                 |                       |                        |
| Active (n=16)                  | 4.7  | 0.5            | 0.1             | p=0.5                 | p=0.5                  |
| Placebo (n=21)                 | 4.8  | 0.5            | 0.1             |                       |                        |
| **Serum Urea**                 |      |                |                 |                       |                        |
| Active (n=18)                  | 14.2 | 5.6            | 1.3             | p=0.02                | p=0.007                |
| Placebo (n=21)                 | 17   | 5.8            | 1.3             |                       |                        |
| **Serum Creatinine**           |      |                |                 |                       |                        |
| Active (n=18)                  | 233.8| 78.1           | 18.4            |                       |                        |
| Placebo (n=21)                 | 251.3| 121.9          | 27              | p=0.8                 | p=0.6                  |
| **Serum Bicarbonate**          |      |                |                 |                       |                        |
| Active (n=17)                  | 25.6 | 2.4            | 0.6             | p=0.03                | p=0.005                |
| Placebo (n=21)                 | 23.3 | 3.1            | 0.7             |                       |                        |
| **Serum Albumin**              |      |                |                 |                       |                        |
| Active (n=18)                  | 42.5 | 2.7            | 0.6             | p=0.8                 | p=0.9                  |
| Placebo (n=21)                 | 41.1 | 2.6            | 0.6             |                       |                        |
| **Sodium intake**              |      |                |                 |                       |                        |
| Active (n=17)                  | 120.1| 42             | 10.2            | p=0.4                 | p=0.4                  |
| Placebo (n=19)                 | 109.3| 39.4           | 9               |                       |                        |
| **Fluid intake**               |      |                |                 |                       |                        |
| Active (n=17)                  | 2295.5| 980.5         | 237.8           | p=0.6                 | p=0.1                  |
| Placebo (n=19)                 | 2011.3| 614           | 140.9           |                       |                        |
| **ECF BIA**                    |      |                |                 |                       |                        |
| Active (n=18)                  | 20   | 4.3            | 1               | p=0.005               | p=0.008                |
| Placebo (n=21)                 | 18   | 2.9            | 0.6             |                       |                        |
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Table 4: Mean difference between the change in in systolic and diastolic blood pressure in the treatment and placebo groups (with 95% confidence interval for the treatment effect).

| Mean difference between change in variable from 0 to 4 weeks (active vs placebo groups) | t-test for Equality of Means |
|--------------------------------|----------------------|
|                               | Mean Difference | 95% Confidence Interval of the Difference |
|                               | Lower | Upper |
| Systolic blood pressure       | 8.08  | -2.35 | 18.51 |
| Diastolic blood pressure      | 2.53  | -4.38 | 9.44  |

Discussion

The findings in the active (sodium bicarbonate) treatment arm are limited by the small sample size. However venous bicarbonate increased, demonstrating that the active treatment was being taking and had a biological effect. Serum urea decreased, which is biologically plausible given that previous studies have suggested a decrease in protein catabolism with correction of acidosis. The urine sodium concentration increased significantly, although the observed increase in 24 hour urine sodium did not reach statistical significance. This suggests that the ingested sodium load is at least partly excreted in the urine, with no change in fluid intake (as estimated by 3-day food diary) or urine volume. This is consistent with animal data that show that intravenous sodium is retained when administered as a chloride salt, but excreted when administered as a bicarbonate salt [15]. Changes in extracellular water were inconsistent between the 2 measurement methods. However, the Vecf by bioimpedance and the TBW by both methods were significantly greater in the treatment than placebo arm at week 4, adjusting for the week 0 values. The Vecf as a ratio of TBW estimated...
by bioimpedance was greater in the treatment arm at week 4 when corrected for age, although this did not reach statistical significance. This correction for age is biologically relevant as it is known that the Vecf to TBW ratio changes with age. Despite these measured changes in TBW, there was no change in actual body weight. Blood pressure did not change significantly, but the mean difference in the change in systolic blood pressure between the treatment and placebo arms was +8.08 mmHg (95% confidence intervals -2.4 to +18.5). While the confidence interval crosses 0, this does raise the possibility of an effect on systolic blood pressure that would be biologically important in terms of cardiovascular risk. This difference in blood pressure is comparable to the findings in larger clinical trials [7,10]. One of these reported no change in blood pressure, but found that 61% of the treatment group had worsening hypertension compared to 48% of controls and 39% had worsening oedema leading to an increased diuretic dose, compared to 30% of controls [7]. While these differences did not reach statistical significance, a study of 134 subjects may not have been sufficiently powered to detect statistical significance.

Conclusions

Our results suggest that 4 weeks treatment of sodium bicarbonate in patients with CKD is associated with an increase in body water content. There was no statistically significant clinical consequence (increase in body weight or blood pressure), though the study may not have been sufficiently powered to detect such differences. This may at least in part reflect the fact that some of the ingested sodium load is excreted in the urine as suggested by an increased urine sodium concentration, although the change in 24 hour urine sodium excretion did not reach statistical significance. There were no changes in blood pressure medication (including diuretics) during the study period to account for the increased urinary sodium concentration or maintenance of actual weight or blood pressure.

Our findings provide further evidence that the beneficial effects of oral sodium bicarbonate in CKD may be obtained at a biological ‘price’. Clinicians prescribing sodium bicarbonate need to pay careful attention to blood pressure and look for evidence of fluid retention.

Short summary

Oral sodium bicarbonate is frequently prescribed to correct the metabolic acidosis of chronic kidney disease. The effect of oral sodium bicarbonate on total body water (TBW) and distribution of water between body compartments in humans with CKD is unknown. This study suggests that oral sodium bicarbonate does increase TBW in CKD patients, but this does not have observable clinical consequences after four weeks of treatment.

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