NaHCO₃ and KHCO₃ ingestion rapidly increases renal electrolyte excretion in humans

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NaHCO₃ and KHCO₃ ingestion rapidly increases renal electrolyte excretion in humans. J. Appl. Physiol. 88: 540–550, 2000.—This paper describes and quantifies acute responses of the kidneys in correcting plasma volume, acid-base, and ion disturbances resulting from NaHCO₃ and KHCO₃ ingestion. Renal excretion of ions and water was studied in five men after ingestion of 3.57 mmol/kg body mass of sodium bicarbonate (NaHCO₃) and, in a separate trial, potassium bicarbonate (KHCO₃). Subjects had a Foley catheter inserted into the bladder and indwelling catheters placed into an antecubital vein and a brachial artery. Blood and urine were sampled in the 30-min period before, the 60-min period during, and the 210-min period after ingestion of the solutions. NaHCO₃ ingestion resulted in a rapid, transient diuresis and natriuresis. Cumulative urine output was 44 ± 11% of ingested volume, resulting in a 555 ± 119 ml increase in total body water at the end of the experiment. The cumulative increase (above basal levels) in renal Na⁺ excretion accounted for 24 ± 2% of ingested Na⁺. In the KHCO₃ trial, arterial plasma K⁺ concentration rapidly increased from 4.25 ± 0.10 to a peak of 7.17 ± 0.13 meq/l 140 min after the beginning of ingestion. This increase resulted in a pronounced, transient diuresis, with cumulative urine output at 270 min similar to the volume ingested, natriuresis, and a pronounced kaliuresis that was maintained until the end of the experiment. Cumulative (above basal) renal K⁺ excretion at 270 min accounted for 26 ± 5% of ingested K⁺. The kidneys were important in mediating rapid corrections of substantial portions of the fluid and electrolyte disturbances resulting from ingestion of KHCO₃ and NaHCO₃ solutions.

IN ATTEMPTS TO IMPROVE short-term, high-intensity exercise performance, NaHCO₃ loading has long been used (19). There is, however, little information regarding the time course and magnitude of acute renal responses in humans who have ingested an amount of NaHCO₃ that may be considered to be of ergogenic benefit (minimum of 0.3 g/kg body mass). The chronic responses to ingested or infused bicarbonate solutions in clinical situations have been extensively documented (2, 9, 14, 23, 30, 37). Few studies, however, have examined the effects of ingested KHCO₃ (37, 38), and there do not appear to be studies that have compared the early renal responses to large, equimolar doses of NaHCO₃ (sufficient to be of ergonomic benefit in humans, see Ref. 27) and KHCO₃ in humans. The physicochemical origins of plasma fluid and ion disturbances to ingested Na⁺ and K⁺ are expected to be different due to differences in their distribution and cellular transport in the intestine, kidneys, muscles, and other tissues (27). The bulk of Na⁺ absorbed from the intestinal tract remains in the extracellular fluids (ECFs) and, if not fully excreted, will result in an increased ECF volume (ECFV); on the other hand, K⁺ rapidly enters intracellular fluid compartments (27).

Although acute effects of KHCO₃ ingestion have not been extensively studied in humans (27, 37, 38), a generalized comparison of the responses to NaHCO₃ and KHCO₃ may be obtained from various studies. Renal responses to ingested or infused NaHCO₃ or NaCl and KHCO₃ or KCl include increased excretion of the cation and water and a decreased reabsorption of HCO₃ (2, 30, 37). There are, however, some notable differences among responses, depending on the cation (Na⁺ vs. K⁺) and the accompanying anion (Cl⁻ or HCO₃⁻). NaHCO₃ loading, compared with NaCl loading, results in increased renal excretion of K⁺ (U₁K⁺) and Cl⁻ excretion (37). KCl loading, compared with NaCl loading, results in an increased glomerular filtration rate (GFR) (29), increased plasma aldosterone (30), and increased renal U₁K⁺ and U₁Cl⁻ excretion (24, 30, 37, 38). KCl loading is also associated with increases in plasma volume (PV) and ECFV (3, 37). KHCO₃ loading, compared with KCl loading, results in a prolonged period of urine alkalinization associated with increased HCO₃⁻ and Cl⁻ excretion and decreased excretion of NH₄⁺ (U₁NH₄⁺) and titratable acid (TA) (37).

The main purposes of this paper are to describe and interpret the acute renal contribution to the correction of the volume, acid-base, and ion disturbances resulting from NaHCO₃ and KHCO₃ loading in humans. An aim of this paper is to integrate the renal responses

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with the vascular and skeletal muscle responses described previously in these subjects (27). The hypothesis was tested that the kidneys play an important role in the acute correction of fluid and ion disturbances resulting from NaHCO₃ and KHCO₃ ingestion. It was also hypothesized that in the NaHCO₃ trial, compared with the KHCO₃ trial, the kidneys would excrete excess water, solute, and base equivalents at a greater rate, resulting in a more rapid correction of the fluid and ion disturbance. This study also analyzed urine composition with respect to the independent variables of acid-base control in biological fluids, namely the strong ion difference (SID) concentration ([SID]), the total concentration of weak acids and bases ([Atot]), and the concentration difference (SID) concentration ([SID]), the total concentration of CO₂ (28, 35). These three variables determine the measured concentrations of H⁺ and HCO₃⁻ ([H⁺] and [HCO₃⁻], respectively), and analysis of changes in these variables provides insight as to the mechanisms of acid-base control.

METHODS

Five healthy men (age 29 ± 2 yr, mass 80 ± 5 kg) participated in this study. Written informed consent was obtained after the procedures and potential risks were fully described to the subjects. The study was approved by the University's human ethics committee. A sixth subject was treated for hyperkalemia (see Ref. 27); this individual's data were excluded from the experiment.

Experimental protocol. In the 24-h period before each trial, subjects abstained from caffeine and alcohol. About 2 h before their arrival at the laboratory, the subjects ate a light meal (toasted bread and juice). All experiments began at ~8:00 AM and consisted of ~1 h of preparation time and 5 h of data collection.

A brachial artery and antecubital vein (opposite arms) were catheterized percutaneously with a 20-gauge 1.25-in. long Teflon catheter (Angiocath, Becton Dickinson, Baxter, Mississauga, ON) after the skin was infiltrated with 0.5 ml of 2% Xylocaine without epinephrine (Astra Pharma, Mississauga, ON). The patency of the catheter was maintained using a slow saline drip (~200 µl/min). The urinary tract was infiltrated aseptically with Xylo-Gel (Astra Pharma) and a Foley urinary catheter (Baxter) inserted into the bladder. The urinary analgesic Pyridium (Parke-Davis, Scarborough, ON) was prescribed for 1–3 days following each experiment.

After insertion of the catheters, each subject was seated in a comfortable chair for the remainder of the experiment. During a 30-min baseline period, urine and blood samples were obtained at 15-min intervals. At the end of this period (time 0), subjects ingested 3.57 mmol/kg body mass of either KHCO₃ or NaHCO₃ during the next 60 min. The ~920 ml of solution ingested, which had an osmolarity of ~600 mosm/l, was flavored with Kool-Aid and sweetened with Nutrasweet. The order of presenting the experimental treatments was randomized for each trial, and trials were separated by at least 2 wk to allow for normalization of hemoglobin concentration. The subjects were observed for a further 210 min in the postingestion period. Urine drained continuously into a sealed collection bag and was completely collected at 20-min intervals until 120 min and then at 30-min intervals until 270 min.

Measurements and analysis. Arterial and venous blood sampling and analysis have been described (27). Arterial plasma aldosterone concentration was determined by RIA (Coat-A-Count TKAL1, Diagnostics Products, Los Angeles, CA).

Urine volume was measured with graduated cylinders at timed intervals for calculation of urine flow rate (UFR). Urine pH was immediately measured (Brinkman Metrohm 632 pH meter). Urine lactate and ammonium ([NH₄⁺]) concentrations were measured by using enzymatic fluorometric techniques (5) on 400-µl samples deproteinized in 800 µl of 6% perchloric acid. Urine P₅₀ concentration ([P₅₀]) was assayed by spectrophotometric analysis (Sigma kit 670, Sigma Chemical, St. Louis, MO). Urine sodium ([Na⁺]), potassium ([K⁺]), and calcium ([Ca²⁺]) concentrations were measured, after appropriate dilution in deionized water, using ion-selective electrodes (Nova Statprofile 5, Nova Biomedical, Waltham, MA). Urine Cl⁻ concentration ([Cl⁻]) was measured by coulometric titration (Buchler-Coliove chlorideometer, Buchler Instruments, Fort Lee, NJ). Plasma and urine creatinine concentrations were determined with the use of an enzymatic fluorometric technique (5) after urine was first diluted 49:1 (20 µl in 980 µl H₂O) in deionized water. Differences between duplicate measurements for the assays were 0.3 ± 0.1 meq/l for [Na⁺], 0.6 ± 0.2 meq/l for [Cl⁻], 0.02 ± 0.02 meq/l for [K⁺], 0.2 ± 0.2 meq/l for [Ca²⁺] and 0.3 ± 0.2 mmol/l for creatinine and phosphate concentrations.

Urine TA minus bicarbonate concentration ([TA – HCO₃⁻]) was determined by using a double titration procedure (20) as described previously (28). Briefly, immediately after collection, a 15-ml sample of urine was acidified to below pH 5 with 20 µl of concentrated (60%) nitric acid. The titration was performed on 1.0-ml urine samples by using pH and reference electrodes (MI-406, MI-403, Microelectrodes, Londonderry, NH) with a digital pH meter (PHM 73, Radiometer, Copenhagen, Denmark). Humidified room air (23.6 ± 0.1°C) was bubbled through the urine samples for 15 min to complete the removal of HCO₃⁻ from solution. A digital micrometric syringe (model S4200A, Roger Gilmore Instruments, Great Neck, NY) was used to dispense 0.1 N NaOH to titrate the sample back to the corresponding arterial plasma pH.

Calculations. Urine [TA – HCO₃⁻] was calculated after Hills (20)

$$[TA \ - \ HCO_3^{-}] = \frac{(EPBT \times N_a) - (V_a \times N_a)}{V_a}$$

where EPBT is the end-point base titration volume (liters), and the volume of base added to reach the desired pH end point; $N_a$ and $N_b$ are the normality of NaOH and HNO₃; $V_u$ is the volume of urine titrated (liters); and $V_a$ is the volume of HNO₃ added (liters) to remove the HCO₃⁻. Net acid excretion was calculated as $U_{Na} \cdot V + TA - HCO_3^{-}$ excretion ($U_{TA - HCO_3^{-}} \cdot V$).

Creatinine clearance was used as an estimate of GFR and was calculated as previously described (36). In normal subjects, during the time of day when the study was conducted (8 AM to 1 PM), creatinine clearance reportedly exceeded GFR by a nearly constant 12 ± 2 ml/min (mean ± SE, $n = 14$; Ref. 36). Therefore, the small tubular secretion of creatinine is not expected to affect the time course of the observed responses in the present study. Ion excretion rates and ion fractional excretions were calculated with standard equations (36).

Cumulative electrolyte excretion was determined by integration of ion excretion rates over time. Basal electrolyte excretion was calculated on the basis of the preingestion excretion rates. The difference between total cumulative and cumulative basal excretion was referred to as “extra” and represents the amount of ion excreted in excess of basal levels.
and after ingestion of NaHCO₃ and KHCO₃

Table 1. Renal Responses to KHCO₃ and NaHCO₃ Loading

Results

Plasma acid-base state, ions, and aldosterone. In the NaHCO₃ trial, plasma [H⁺] decreased by 7.8 ± 3 neq/l by 60 min, compared with a 5.9 ± 1.6 neq/l decrease in the KHCO₃ trial (Table 1). In both trials, plasma [H⁺] remained significantly lower than initial levels until the end of the experiment. With 30 min of the beginning of NaHCO₃ ingestion, arterial plasma [HCO₃] increased and remained elevated until the end of the experiment. In the KHCO₃ trial, arterial plasma [HCO₃] increased above initial levels by 80 min and returned toward initial values by 120 min. Detailed responses and interpretation for both arterial and venous plasma have been published (27).

In the NaHCO₃ trial, arterial plasma [Na⁺] and [Cl⁻] did not change (Table 1); in contrast, in the KHCO₃ trial both [Na⁺] and [Cl⁻] significantly decreased between 100 and 150 min, with [Na⁺] remaining depressed until the end of the experiment. Plasma [K⁺] and aldosterone did not change in the NaHCO₃ trial (Fig. 1). In the KHCO₃ trial, plasma [K⁺] peaked at 7.17 ± 0.13 meq/l at 110 min and then slowly decreased to 5.1 ± 0.8 by 270 min. The increase in plasma aldosterone concentration paralleled that of plasma [K⁺], with aldosterone concentration exceeding 1 µmol/l between 90 and 150 min.

Water balance, GFR, and UFR. In the NaHCO₃ trial, there was no change in plasma volume during the ingestion period, and then plasma volume progressively increased, peaking at 7.5 ± 2.0% above initial levels at 210 min (Table 1). In contrast, in the KHCO₃ trial, ingestion of the solution resulted in an immediate and pronounced decrease in plasma volume that reached a

Table 1. Plasma ions and percent change in plasma volume before (time 0), during (20, 40, and 60 min), and after ingestion of NaHCO₃ and KHCO₃
accompanying the NaHCO₃ or KHCO₃ dose; saline infused, measured compartment (27). In contrast, in the KHCO₃ trial, ECFV consistent with the retention of Na⁺ was estimated to be in negative balance by about 800 ml, consistent with a net movement of water into cells (27).

In the NaHCO₃ trial, initial GFR was 90 ± 18 ml/min and did not change throughout the experiment (Fig. 2A). In contrast, in the KHCO₃ trial, GFR increased rapidly from 71 ± 16 ml/min (time 0) to 306 ± 45 ml/min by 60 min and remained elevated until 120 min. In the NaHCO₃ trial, UFR increased two- to threefold from 0.6 ± 0.2 ml/min (time 0) to 2.6 ± 0.4 ml/min between 80 and 120 min (Fig. 2B). After KHCO₃ ingestion, UFR increased up to eightfold greater than initial within 80 min and remained significantly greater than in the NaHCO₃ trial until 150 min.

Sodium. In the NaHCO₃ trial, 270 min after ingestion of 280 meq of Na⁺ was begun, 10% of ingested Na⁺ remained in the plasma compartment, 46% remained in the interstitial fluid compartment, and renal UNa⁺ accounted for 30% of ingested Na⁺ (Table 3).

In the NaHCO₃ trial, urine [Na⁺] increased twofold between the end of ingestion (123 ± 27 meq/l at 60 min) and 270 min (255 ± 14 meq/l). UNa⁺ was three- to fourfold greater than initial values between 80 and 180 min, and it remained elevated (298 ± 14 µeq/min) at 270 min compared with initial levels.

Table 2. Water balance with NaHCO₃ and KHCO₃ ingestion at 120 and 270 min

<table>
<thead>
<tr>
<th></th>
<th>NaHCO₃</th>
<th>KHCO₃</th>
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<tbody>
<tr>
<td></td>
<td>120 min</td>
<td>270 min</td>
</tr>
<tr>
<td>Fluid ingested, ml</td>
<td>936 ± 70</td>
<td>936 ± 70</td>
</tr>
<tr>
<td>Saline infused, ml</td>
<td>251 ± 36</td>
<td>434 ± 79</td>
</tr>
<tr>
<td>Blood sampling, ml</td>
<td>240</td>
<td>400</td>
</tr>
<tr>
<td>Urine volume, ml</td>
<td>207 ± 20</td>
<td>415 ± 36</td>
</tr>
<tr>
<td>ΔPV, ml</td>
<td>69 ± 57</td>
<td>173 ± 67</td>
</tr>
<tr>
<td>ΔISFV, ml</td>
<td>311 ± 255</td>
<td>780 ± 303</td>
</tr>
<tr>
<td>ΔECFV, ml</td>
<td>380 ± 311</td>
<td>954 ± 370</td>
</tr>
<tr>
<td>ΔTBW, ml</td>
<td>740 ± 93</td>
<td>555 ± 119</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5. Fluid ingested, fluid volume accompanying the NaHCO₃ or KHCO₃ dose; saline infused, measured from iv drip at 270 min; blood sampling, estimated blood volume loss due to blood sampling; urine volume, cumulative urine volume produced. ΔPV, change in arterial plasma volume; ΔISFV, change in interstitial fluid volume; ΔECFV, change in extracellular fluid volume; ΔTBW, change in total body water. The change in ECFV was partitioned between the changes in PV and ISFV. Minus sign indicates decrease in volume. *KHCO₃ mean significantly different from NaHCO₃ mean, P < 0.05.

Fig. 1. Plasma K⁺ concentration ([K⁺], solid symbols) and aldosterone concentration ([aldosterone], open symbols) before (up to 0 min), during (1–60 min), and after (61–270 min) ingestion of NaHCO₃ (squares) or KHCO₃ (circles) at a dose of 3.57 mmol/kg body mass. Hatched bar indicates 60-min period of HCO₃ ingestion. Values are means ± SE; n = 5. *K⁺ and aldosterone concentration significantly greater in KHCO₃ trial compared with NaHCO₃ trial.

Fig. 2. Glomerular filtration rate (GFR, A) and urine flow rate (B) before (up to 0 min), during (1–60 min), and after (61–270 min) ingestion of NaHCO₃ (■) or KHCO₃ (●) at a dose of 3.57 mmol/kg body mass. Urine flow rate in the KHCO₃ trial was significantly (P ≤ 0.05) greater than in the NaHCO₃ trial between 60 and 180 min. GFR in the KHCO₃ trial was significantly (P ≤ 0.05) greater than in the NaHCO₃ trial between 60 and 120 min. Hatched bars indicate the 60-min period of HCO₃ ingestion. Values are means ± SE; n = 5. *Significantly different (P ≤ 0.05) from preingestion (–20 and 0 min). ‡Significant difference between treatments.

nadir of −14.9 ± 1.7% below initial levels at 120 min; this was followed by a slow, significant partial recovery. Water balance summaries (Table 2) are based on estimates of complete intestinal absorption of the solutions by 270 min (see Ref. 27). The net increase in total body water in the NaHCO₃ trial was 555 ± 119 ml, compared with complete restoration of fluid balance (25 ± 83 ml) in the KHCO₃ trial. In the NaHCO₃ trial, the ECF compartment was in positive fluid balance, consistent with the retention of Na⁺ in the ECF compartment (27). In contrast, in the KHCO₃ trial, ECFV was estimated to be in negative balance by about 800 ml.
Table 3. Na\textsuperscript{+} balance with NaHCO\textsubscript{3} ingestion and K\textsuperscript{+} balance with KHCO\textsubscript{3} ingestion at 270 min

<table>
<thead>
<tr>
<th></th>
<th>Na\textsuperscript{+} Balance With NaHCO\textsubscript{3} Ingestion</th>
<th>K\textsuperscript{+} Balance With KHCO\textsubscript{3} Ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount ingested</td>
<td>Na\textsuperscript{+} meq</td>
<td>K\textsuperscript{+} meq</td>
</tr>
<tr>
<td></td>
<td>% Ingested</td>
<td>% Ingested</td>
</tr>
<tr>
<td></td>
<td>280 ± 21</td>
<td>281 ± 23</td>
</tr>
<tr>
<td>ΔPlasma content</td>
<td>28 ± 9</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>ΔISF content</td>
<td>128 ± 42</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>ΔECF content</td>
<td>157 ± 51</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>Tissue flux</td>
<td>30 ± 158</td>
<td>1 ± 49</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>84 ± 7</td>
<td>93 ± 16</td>
</tr>
<tr>
<td>Other effectors</td>
<td>−8 ± 157</td>
<td>34 ± 6</td>
</tr>
<tr>
<td>Total</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5. Not shown is −65 meq of Na\textsuperscript{+} infused with the saline drip. ΔPlasma content, change in arterial plasma content; ΔISF content, change in interstitial fluid content; ΔECF content, change in extracellular fluid content. For changes in Plasma, ISF, and ECF contents, minus sign indicates decrease. Tissue flux, total whole body skeletal muscle influx (+) or efflux (−) of Na\textsuperscript{+} or K\textsuperscript{+} (27); renal excretion, cumulative Na\textsuperscript{+} or K\textsuperscript{+} excretion; other effectors (gastrointestinal tract, erythrocytes), changes in ECF content not accounted for. % Ingested, percent ingested Na\textsuperscript{+} or K\textsuperscript{+} accounted for by tissue flux, renal excretion, and other effectors.

(78 ± 21 meq/min; Fig. 3A). The fractional excretion of Na\textsuperscript{+} increased fourfold by 120 min, and the mean cumulative fractional excretion was approximately two-fold greater than baseline after NaHCO\textsubscript{3} ingestion (Fig. 3B).

In the KHCO\textsubscript{3} trial, urine [Na\textsuperscript{+}] did not change and was lower than in the NaHCO\textsubscript{3} trial between 60 and 270 min (not shown). With KHCO\textsubscript{3} ingestion, U\textsubscript{Na}\textsubscript{-}V increased rapidly and was greater than initial values between 60 and 120 min and then declined toward initial values by 180 min (Fig. 3A). Between 60 and 120 min, U\textsubscript{Na}\textsubscript{-}V was greater in the KHCO\textsubscript{3} than in the NaHCO\textsubscript{3} trial. There was no significant change in the fractional excretion of Na\textsuperscript{+} (Fig. 3B).

Potassium. In the NaHCO\textsubscript{3} trial, urine [K\textsuperscript{+}] remained unchanged at ~104 ± 16 meq/l (not shown); excretion and the fractional excretion of K\textsuperscript{+} also did not change (Fig. 3, C and D). In contrast, in the KHCO\textsubscript{3} trial, urine [K\textsuperscript{+}] increased rapidly from 77 ± 19 meq/l at 120 min to 241 ± 37 meq/l at 270 min. This increase was accompanied by a sixfold increase in U\textsubscript{K}\textsubscript{-}V between 120 and 180 min (Fig. 3C) and an elevated K\textsuperscript{+} fractional excretion to 71 ± 12% of the filtered load in the last 30 min of the experiment (Fig. 3D). In the KHCO\textsubscript{3} trial, of the 281 meq of K\textsuperscript{+} ingested, the increase in ECF K\textsuperscript{+} content only accounted for 3%, whereas net K\textsuperscript{+} flux into tissues accounted for 37% (Table 3). Over the 270 min of the experiment, increased (above basal) U\textsubscript{K}\textsubscript{-}V accounted for 26 ± 5% of the ingested K\textsuperscript{+} or 76% of the total cumulative U\textsubscript{K}\textsubscript{-}V of 93 ± 16 meq (Table 3).

Chloride. In the NaHCO\textsubscript{3} trial, urine [Cl\textsuperscript{−}] decreased from 186 ± 16 meq/l at 0 min to 40 ± 7 meq/l at 120 min, with no change in Cl\textsuperscript{−} excretion or fractional excretion (Fig. 3, E and F). In contrast, in the KHCO\textsubscript{3} trial, urine [Cl\textsuperscript{−}] decreased by only ~80 meq/l, from 197 ± 29 meq/l at 0 min to 119 ± 12 meq/l at 80 min, returning to 173 ± 15 meq/l at 270 min. Despite the decrease in urine [Cl\textsuperscript{−}], the marked increases in UFR and GFR resulted in a significantly increased renal Cl\textsuperscript{−}.

![Fig. 3. Renal ion excretions (U\textsubscript{Na}, V, A; U\textsubscript{K}, V, C; and U\textsubscript{Cl}, V, E) and fractional excretions of Na\textsuperscript{+} (B), K\textsuperscript{+} (D), and Cl\textsuperscript{−} (F) before (0 min), during (1–60 min), and after (61–270 min) ingestion of NaHCO\textsubscript{3} (●) or KHCO\textsubscript{3} (▲) at a dose of 3.57 mmol/kg body mass. Hatched bars indicate the 60-min period of HCO\textsubscript{3} ingestion. Values are means ± SE; n = 5. *Significantly different (P ≤ 0.05) from preingestion (−20 and 0 min). †Significant difference between treatments.](http://jap.physiology.org/DownloadedFrom/10220.336.on_May_30,2017)
excretion between 60 and 120 min (Fig. 3E). Cl\(^{-}\) fractional excretion did not change significantly in either trial, although Cl\(^{-}\) fractional excretion was greater in the KHCO\(_3\) trial than in the NaHCO\(_3\) trial between 80 and 270 min (Fig. 3F).

Calcium, Pi, and lactate. In both trials, urine [Ca\(^{2+}\)] decreased two- to threefold from 3.6 ± 0.6 meq/l at 0 min to between 1 and 2 meq/l from 80 and 270 min, with no difference between trials. Renal Ca\(^{2+}\) excretion and Ca\(^{2+}\) fractional excretion did not change from initial values (3 ± 1 µeq/min and 1.7 ± 0.7%, respectively) in either trial, with no difference between treatments.

In the NaHCO\(_3\) trial, urine [P\(_i\)] remained unchanged at about 24 ± 4 mmol/l. In the KHCO\(_3\) trial, urine [P\(_i\)] decreased threefold (from 26 ± 13 mmol/l) at time 0 to 4.3 ± 1.6 mmol/l within 80 min and remained low thereafter. P\(_i\) excretion did not change (20 ± 9 µmol/min) in either treatment, with no difference between trials.

Urine lactate concentration was initially 0.02 ± 0.01 meq/l in both trials, and in both trials it approached zero by 270 min (not shown).

[SID], pH, and [H\(^+\)]. In the NaHCO\(_3\) trial, urine [SID] increased rapidly until 80 min and then increased slowly until the end of the experiment (Fig. 4A). In the KHCO\(_3\) trial, urine [SID] increased gradually and was greater than initially between 180 and 270 min, but it remained 125–175 meq/l lower than in the NaHCO\(_3\) trial.

In both trials, the magnitude and time course of increase in urine pH were similar, with nadirs reached at 80 min; there were no differences between trials (Fig. 4B). In the NaHCO\(_3\) trial, urine [H\(^+\)] decreased significantly from 354 ± 283 neq/l (time 0) to 6.8 ± 0.4 neq/l at 270 min, compared with 1,414 ± 1,319 neq/l (time 0) and 13.7 ± 3.9 neq/l at 270 min in the KHCO\(_3\) trial.

Urine [SID] (meq/l) was a good predictor of urine [H\(^+\)] (neq/l), as shown by the monoexponential curve fit to the data (Fig. 4C). The lower dotted line in Fig. 4C represents the relationship between [H\(^+\)] and [SID] in the absence of CO\(_2\) and weak acids in the solution (35). The difference between the dotted line and the experimental data represents the acidification contributed by urine PCO\(_2\). The dashed line represents the relationship between [H\(^+\)] and [SID] when solution PCO\(_2\) is 40 Torr with no weak acids present ([A\(_{ac}\)] = 0): [H\(^+\)] = K\(_C\) × PCO\(_2\)/[SID], with units for [SID] in meq/l (35). The dashed line fits the data well, supporting the assumption that urine PCO\(_2\) was similar to arterial PCO\(_2\). The relationship also shows that acidification by CO\(_2\) was pronounced at low and negative urine [SID] (before bicarbonate ingestion) and minor when [SID] was >100 meq/l (after the start of bicarbonate ingestion). The small amount of weak acids present in urine did not contribute substantially to the relationship (35).

TA, NH\(_4\), and net acid excretion. In both trials, there were large and rapid decreases in urine [TA–HCO\(_3\)], U\(_{TA–HCO_3}\), and net acid excretion (Fig. 5). Urine [TA–HCO\(_3\)] was significantly decreased from initial values by 80 min in both trials, with similar magnitudes and time course of change (Fig. 5A). The associated large and rapid decrease in U\(_{TA–HCO_3}\) (Fig. 5B) represented a pronounced net excretion of titratable base between 80 and 180 min; there was no difference between trials.

In both trials, urine [NH\(_4\)] decreased sevenfold by 100 min, with no difference between trials (Fig. 5D). U\(_{NH_4}\) did not change in either trial (Fig. 5D). Urine net acid concentration (Fig. 5E) and net acid excretion (Fig. 5F) were quantitatively similar to that for TA–HCO\(_3\), because U\(_{NH_4}\) formed only a small (1–3%) proportion of total acid excretion. In the NaHCO\(_3\) trial, an amount equivalent to 23 ± 3% of the ingested base was excreted, whereas in the KHCO\(_3\) trial

- **Figure 3A**: Graph showing the relationship between urine [SID] and urine [H\(^+\)] in both trials, with data points and a fitted line.
- **Figure 3B**: Graph showing the relationship between urine pH and [SID] in both trials, with data points and a fitted line.
- **Figure 3C**: Graph showing the relationship between urine [TA–HCO\(_3\)] and urine [SID] in both trials, with data points and a fitted line.
- **Figure 4A**: Graph showing the time course of urine [SID] in both trials, with data points and a fitted line.
- **Figure 4B**: Graph showing the time course of urine pH in both trials, with data points and a fitted line.
- **Figure 4C**: Graph showing the relationship between urine [H\(^+\)] and [SID] in both trials, with data points and a fitted line.
- **Figure 5A**: Graph showing the time course of urine [TA–HCO\(_3\)] in both trials, with data points and a fitted line.
- **Figure 5B**: Graph showing the time course of urine [NH\(_4\)] in both trials, with data points and a fitted line.
- **Figure 5C**: Graph showing the relationship between urine [TA–HCO\(_3\)] and urine [SID] in both trials, with data points and a fitted line.
- **Figure 5D**: Graph showing the time course of urine [NH\(_4\)] in both trials, with data points and a fitted line.
- **Figure 5E**: Graph showing the relationship between urine net acid concentration and urine [SID] in both trials, with data points and a fitted line.
- **Figure 5F**: Graph showing the relationship between urine net acid excretion and urine [SID] in both trials, with data points and a fitted line.
DISCUSSION

This appears to be the first study to compare the acute renal responses to large, equimolar doses (3.57 mmol/kg body mass) of ingested NaHCO₃ and KHCO₃ in humans and in mammals in general. The dose of NaHCO₃ used is sufficient to be of ergogenic benefit (19), but this dose of KHCO₃ was three to four times greater than that used in previous studies. Earlier studies focused on longer term responses and therefore missed the rapidity with which the kidneys respond to large fluid and electrolyte loads. Furthermore, the ingested Na⁺ and K⁺ resulted in marked differences in renal fluid and ion excretion, consistent with differences in intestinal Na⁺ and K⁺ absorption and differences in the distribution of these cations within body fluid compartments. It is noteworthy that, despite such differences, there was little difference in the renal excretion of base between the two treatments.

Urine acid-base status. Stewart (35) has mathematically described the physicochemical relationships among independent variables contributing to [H⁺] and [HCO₃⁻] in physiological solutions. The independent determinants of [H⁺] and [HCO₃⁻] in urine are the concentrations of strong (fully dissociated) ions represented by the [SID], the total concentration of weak acids and base represented by [A_tot], and P_CO₂ (28, 35). In healthy, resting humans, the main determinants of [SID] are [Na⁺], [K⁺], [Cl⁻], and [Ca²⁺]. The ions NH₄⁺ (pK 9.26), Mg²⁺, lactate⁻ (pK = 3.8), and SO₄²⁻ play minor roles and largely cancel each other with respect to charge. In urine, the sum of the charges of strong ions, the [SID], thus provides an index of total acid excretion (8). The main determinants of [A_tot] are weak organic anions [the most abundant of which are citrate and some amino acids (8)] and Pi. [A_tot] is equivalent to the TA minus bicarbonate term of classical renal physiology. TA refers to the amount of secreted acid titrated by nonvolatile buffers, i.e., weak acids, in the tubular lumen and subsequently excreted as fixed acid. Pi with an apparent pK’ = 6.8 accounts for most of the TA content of the urine (20, 35). In classical renal physiology, acid is excreted in the urine as NH₄⁺ and TA, so that net acid excretion equals NH₄⁺ + TA - HCO₃⁻ excretion.

An unexpected result was the marked similarity in renal base excretion in both trials despite the marked differences in rate and magnitude of plasma fluid and ion disturbances and differences in renal water and ion handling (see below). The rate of renal base excretion, however, paralleled that of arterial alkalization, of which changes in plasma [SID] were the primary determinant (27). The primary determinant of changes in urine [H⁺] in both trials was the change in urine [SID]. In general, KHCO₃ ingestion resulted in lower urine [Na⁺], [K⁺], and [Ca²⁺] than in the NaHCO₃ trial.

Fig. 5. Urine titratable acid minus HCO₃⁻ concentration ([TA - HCO₃⁻]; A), renal TA - HCO₃⁻ excretion ([TA - HCO₃⁻]; B), [NH₄⁺] (C), NH₄⁺ excretion ([NH₄⁺]; D), net acid concentration ([net acid]; E), and net acid excretion ([net acid]; F) before (0 min), during (1–60 min), and after (61–270 min) ingestion of NaHCO₃ (●) or KHCO₃ (●) at a dose of 3.57 mmol/kg body mass. Negative values represent net base excretion. Hatched bars indicate 60-min period of HCO₃⁻ ingestion. Values are means ± SE; n = 5. *Significantly different (P < 0.05) from preingestion (−20 and 0 min). †Significant difference between treatments.
In addition, urine [Cl\(^{-}\)] was greater throughout the KHCO\(_3\) trial. Urine [SID] increased by \(\sim 175\) meq/l greater in the NaHCO\(_3\) trial than in the KHCO\(_3\) trial, and this balanced the decrease in urine [TA – HCO\(_3\)] and net acid concentration. In general, KHCO\(_3\) ingestion resulted in lower urine [Na\(^{+}\)], [K\(^{+}\)], and [Ca\(^{2+}\)], and higher [Cl\(^{-}\)] than in the NaHCO\(_3\) trial. Changes in CO\(_2\) did not contribute substantially to urine [H\(^{+}\)] (see Fig. 4C), consistent with the fact that arterial, and hence renal, P\(_{CO_2}\) (not shown) changed little in both trials.

An increase in urine [A\(_{tot}\)] also contributed to the measured urine [H\(^{+}\)]. In both trials large decreases in [TA – HCO\(_3\)] were largely independent of changes in urine [P\(_i\)], with urine [P\(_i\)] only accounting for a small fraction of [TA – HCO\(_3\)]. As previously described (8), this suggests that there was an increased excretion of weak acids and bases, but their identity and contributions are not known in the present study. The contribution of NH\(_4\)\(^{+}\) to net acid excretion was small (1–3%), consistent with a previous report of decreased U\(_{NH_4}\)\(^{-}\) after KHCO\(_3\) and KCl ingestion (37).

In the present study, and in that by Van Buren et al. (37), much of the decrease in net acid excretion would be classically described as due to increased excretion of HCO\(_3\). This characterization is consistent with an apparent 40% reduction in tubular HCO\(_3\) reabsorption in rats with acute metabolic alkalosis (33) and with studies showing that loading with KHCO\(_3\), NaHCO\(_3\), KCl, and NaCl results in decreased renal HCO\(_3\) reabsorption and decreased urine [H\(^{+}\)] in dogs (29) and humans (2, 37). In addition, there is also evidence that electronegic proton secretion is reduced in rat nephrons as soon as 3 h after the onset of NaHCO\(_3\) loading (24). This is consistent with the large, transient decreases in TA (37) and TA – HCO\(_3\) (present study) excretion observed 1–3 h after K\(^{+}\) loading in humans.

Water balance. Ingestion of NaHCO\(_3\) resulted in a prolonged retention of fluid with total cumulative urine volume accounting for only 44% of ingested volume. An estimated 56% of ingested Na\(^{+}\) remained in the ECF compartment at the end of the experiment (Table 3) consistent with the nearly 1-liter expansion of ECFV (27). Increases in the delivery of Na\(^{+}\), K\(^{+}\), and base, i.e., increased osmolar clearance, to the distal tubules, without concomitant change in GFR, suggest that decreased tubular fluid reabsorption occurred in association with increased distal tubule Na\(^{+}\) delivery. The increase in UFR, however, was largely normalized 2 h after ingestion of the solution, indicating that there was a decreased sensitivity of the volume regulatory system or some feed-forward mechanism to prevent overadjustment in terms of water excretion and U\(_{Na}\)\(^{-}\).

In contrast, ingestion of KHCO\(_3\) resulted in a rapid and pronounced decrease in plasma volume that was attributed to an initial rapid net movement of fluid into the proximal small intestine to bring intestinal contents toward plasma osmolarity, with subsequent absorption of water and K\(^{+}\) in more distal portions of the small intestine (27). Despite the \(-0.5\)-liter reduction in plasma volume, UFR increased two- to threefold more than in the NaHCO\(_3\) trial, and there were rapid, fourfold increases in GFR and excretion of Na\(^{+}\), Cl\(^{-}\), and K\(^{+}\).

The magnitude of increase in GFR in response to KHCO\(_3\) ingestion appears to be without precedence in the literature. One study on humans reported no change in GFR in the second hour after oral ingestion of a small amount (1 mmol/kg body mass) of KCl (37). Modest increases (+19 ml/min) in GFR in sheep given KCl have been reported (4), whereas in rats a decrease in GFR occurring one or more hours after K\(^{+}\) loading has been reported (6, 7, 40). Also, earlier studies did not report GFR until at least 1 h after K\(^{+}\) loading. From Fig. 2, it is evident that the increase in GFR was rapid and transient and had returned to preingestion values within 210 min after KHCO\(_3\) ingestion was completed. It is difficult to provide a mechanistic explanation for the fourfold increase in GFR in the absence of measures of blood pressure, peripheral vascular resistance, and heart rate. It is not likely that KHCO\(_3\) ingestion was associated with marked increases in blood pressure, given that PV decreased markedly, nor with increases in vascular resistance, given that elevated plasma [K\(^{+}\)] has vasodilatory effects. The rapidity and magnitude at which the hyperkalemia ensued, compared with earlier studies (9, 30, 37), may have induced indirect effects by increasing renal blood flow and thereby contributing to an increase in net filtration pressure and perfusion pressure at the level of the juxtaglomerular apparatus. However, it is unknown if the changes in tubular water and ion handling were due to the increase in GFR or to the increase in filtered K\(^{+}\) (7), and further study is required to understand the mechanistic relationships responsible for these observations.

Na\(^{+}\) excretion. In the NaHCO\(_3\) trial, the rapid and large increases in urine [Na\(^{+}\)], U\(_{Na}\)\(^{-}\), and fractional excretion accounted for 24% of ingested Na\(^{+}\), with the bulk of the Na\(^{+}\) remaining in the ECF compartment (27). The increase in U\(_{Na}\)\(^{-}\) can be attributed to the modest increases in GFR and increased Na\(^{+}\) delivery with decreased proximal tubule Na\(^{+}\) reabsorption. The primary mechanism for reduced proximal tubule Na\(^{+}\) reabsorption is through inhibition of proximal tubular Na\(^{+}\)-K\(^{+}\)-ATPase (2, 22), resulting in increased Na\(^{+}\) (and water) delivery to the distal tubules. There is also evidence that acute, transient elevations in dietary Na\(^{+}\) induce a natriuresis by a dopamine-mediated decrease in proximal tubule Na\(^{+}\)-K\(^{+}\)-ATPase activity (1).

In the KHCO\(_3\) trial the hyperkalemia was associated with increased renal U\(_{Na}\)\(^{-}\) despite the 15% reduction in plasma volume and decrease in plasma [Na\(^{+}\)]. Hyperkalemia has been shown to inhibit Na\(^{+}\) and water absorption by the proximal tubule, resulting in a diuresis and natriuresis (6, 7) without change in plasma renin (30, 37, 38) and atrial natriuretic peptide (37). Increased GFR was associated with elevated distal tubule Na\(^{+}\) delivery with minimal increase in Na\(^{+}\) fractional excretion. There appears to be minimal evidence for decreased Na\(^{+}\) reabsorption in the diuretic and natriuretic responses to KHCO\(_3\) ingestion. This finding is in contrast to the natriuresis that occurs with
KCl ingestion (38), indicating that the accompanying anion plays a role in modulating tubular excretion and reabsorption of Na⁺ (22). The later decline in renal U Na⁺-V (from 120 min onward) is attributed to the strong antinatriuretic action of aldosterone and the ensuing increase in tubular Na⁺ reabsorption (31, 37, 38, 41). This effect and associated decreases in GFR, UFR, and Cl⁻ excretion are consistent with the effects of aldosterone occurring 1–2 h after it begins to increase in the blood (12, 41). It is concluded that a K⁺-stimulated natriuresis was responsible for the observed hyponatremia.

K⁺ excretion. NaHCO₃ ingestion resulted in a small, although not statistically significant, increase in U K⁺-V, a tendency (Fig. 4) that was associated with a modest hypokalemia. A tendency (P < 0.1) toward increased U K⁺-V is consistent with increased delivery and net reabsorption of Na⁺, but not Cl⁻, at the distal tubules; this tendency establishes a negative electrochemical gradient that favors modest increases in U K⁺-V (16, 39). Alkalosis has also been reported to stimulate Na⁺-K⁺-ATPase-mediated uptake of K⁺ into principal cells, resulting in enhanced K⁺ secretion (34). An increased delivery of HCO₃⁻ to the distal nephron, in the presence of increased aldosterone, may also stimulate U K⁺-V during alkalosis (34).

In the KHCO₃ trial, increased excretion of K⁺ above basal levels accounted for 26 ± 5% of ingested K⁺. Over the course of the experiment, total U K⁺-V accounted for 34 ± 6% (about 1.2 mmol/kg) of ingested K⁺, representing about 17% of the normal kidneys' daily capacity of 7 mmol/kg (31). The incomplete renal excretion of all ingested K⁺ agrees with the observation that about 64% of ingested K⁺ had entered cells by 270 min and was thus removed from the ECF and the circulatory system (27).

The rapid, fivefold increase in renal U K⁺-V was biphasic in time course, peaking at 90 min before decreasing (Fig. 3C), and paralleled increases in plasma [K⁺] and aldosterone concentration (Fig. 1). The early rise in U K⁺-V preceded the kaliuretic action of increased plasma aldosterone concentration but coincided with the increase in filtered K⁺ load, perhaps indicating a direct kaliuretic effect of increased plasma [K⁺] (30). In contrast, the fractional excretion of K⁺ progressively increased over time, peaking at 71 ± 12% of the filtered load at 270 min, consistent with the peak effects of aldosterone occurring 1–2 h after it increases (12, 41). These results are consistent with previous studies of K⁺ loading in humans (9, 30, 37, 38) and other animals (3, 6, 7, 21, 32, 41). It is likely that elevated plasma [K⁺] and aldosterone concentration independently contributed to the kaliuresis (9, 31) by increasing principal cell Na⁺-K⁺-ATPase activity (34) and intracellular [K⁺] in the distal tubule and cortical collecting duct (13, 15).

Also, the presence of anions that are relatively impermeant to distal tubule reabsorption (such as bicarbonate and sulphate) increases luminal electronegativity and may have contributed to the increase in K⁺ secretion (39). An increased flow of fluid through the distal tubule and cortical collecting duct also stimulates K⁺ secretion by these segments (16, 26).

Cl⁻ excretion. In the NaHCO₃ trial, as may be expected with increased HCO₃⁻ delivery to the tubules, there occurred a 146 meq/l decrease in urine [Cl⁻] and a modest increase (not statistically significant but appearing to be of physiological importance) in tubular Cl⁻ reabsorption (Fig. 3F). This response is similar to that seen occurring after acute lactate loading caused by high-intensity exercise (28); there appears to be a preferential reabsorption of Cl⁻ over HCO₃⁻ and lactate. Overall, though, the NaHCO₃ load had only a small effect on renal Cl⁻ transport, similar to the absence of effect of NaCl loading on renal Cl⁻ excretion (17, 37).

The renal Cl⁻ response to KHCO₃ ingestion, however, is in marked contrast to that seen in the NaHCO₃ trial. Cl⁻ excretion markedly increased equimolar with the increased excretion of Na⁺, resulting in similar cumulative excretions of Cl⁻ and Na⁺. Similar responses to KHCO₃ loading in humans have previously been reported (37), and increased HCO₃⁻ delivery has been suggested to reduce net Cl⁻ reabsorption by the proximal tubules and increase Cl⁻ excretion (37). The absence of a similar result in the NaHCO₃ trial may be explained by the absence of the rapid and very large increase in GFR seen in the KHCO₃ trial. Thus the marked increases in both Cl⁻ and Na⁺ excretion seen after KHCO₃ ingestion appear to be associated with mechanisms for acute regulation of plasma [K⁺] (10, 25, 37). The decrease in Cl⁻ excretion late in the experiment (180–270 min) was similar to that seen for Na⁺ and is consistent with Na⁺-dependent Cl⁻ absorption mechanisms responding to elevated plasma aldosterone concentration (10, 17).

Renal Ca²⁺ and P₃ regulation. The ingestion of NaHCO₃ and KHCO₃ did not significantly affect renal Ca²⁺ and P₃ excretion. In both trials, the decreases in urine [Ca²⁺] and [P₃] were due solely to the accompanying diuresis, consistent with the absence of significant change in plasma Ca²⁺ content (27).

Implications for exercise performance. NaHCO₃ loading is widely practiced in human and equine athletic competition as a means of reducing the severity of extra- and intracellular acidosis resulting from the performance of high-intensity exercise (19). Indeed, the dose of NaHCO₃ administered in the present study consistently results in performance-enhancing effects in humans (19). It is also noteworthy that NaHCO₃ loading resulted in an ~1-liter expansion of plasma volume that persisted in excess of 3 h after ingestion of the solution. This result indicates that the gastrointestinal tract may be used as a reservoir of readily available water and Na⁺ for maintaining extracellular volume during prolonged exercise. On the negative side, there was a twofold increase in UFR during the first 2 h after ingestion that may compromise exercise performance.

High-intensity exercise results in the rapid loss of K⁺ from contracting skeletal muscle, and the resulting decrease in intracellular [K⁺] is thought to contribute
to skeletal muscle fatigue (see Ref. 27). The rationale for providing subjects with oral KHCO$_3$, at a dose equivalent to the performance-enhancing effect of NaHCO$_3$, was twofold. The first was to provide a similar magnitude alkalosis to offset exercise-induced acidosis, with the idea that K$^+$ being predominantly intracellular would provide further protection against intracellular acidosis. The second was to provide additional K$^+$ to skeletal muscles so as to better maintain intracellular [K$^+$] and delay the onset of fatigue in the face of contraction.

However, the results of the present study indicate that KHCO$_3$ loading should not be considered for the enhancement of exercise performance. Ingestion of this quantity of K$^+$ poses safety concerns, both at rest and particularly if subjects are contemplating exercise. Ingestion of more than 150 mmol (about 16 g) of KHCO$_3$ results in a rapid increase in plasma [K$^+$] that may require prompt treatment for hyperkalemia (see Ref. 27). Two hours after ingestion of KHCO$_3$, subjects maintained an average plasma [K$^+$] of about 6 meq/l, which, with high-intensity exercise, could result in life-threatening increases in plasma [K$^+$]. Also, it is likely that the rapid and pronounced decrease in plasma volume that occurred with KHCO$_3$ ingestion may impose additional stress on the cardiovascular and intestinal systems during exercise.

Conclusions. Renal responses to ingested NaHCO$_3$ and KHCO$_3$ solutions are more rapid and of greater magnitude than previously appreciated. In both trials, excreted Na$^+$ and K$^+$ accounted for 25–40% of the ingested ion and, in the KHCO$_3$ trial, cumulative urine volume over 270 min equalled the ingested volume load. In both trials, the GFR and UFR responses were transient and largely normalized by 210 min postingestion. The neural and cellular mechanisms for the rapid up- and downregulation of GFR and UFR in the NaHCO$_3$ trial are not well understood. The rapidity of the downregulation suggests either that, after some time, the regulatory systems become tolerant of the remaining fluid imbalance or that there may be feedback mechanisms for preventing overadjustment of fluid and Na$^+$ balance. In the KHCO$_3$ compared with the NaHCO$_3$ trial, renal ion excretions occurred with greater rapidity, were of greater magnitude, and resulted in an increased osmotic clearance. In both trials, increases in base excretion were sustained until the end of the experimental period. It is also noteworthy that, although the plasma acid-base disturbances had markedly different physicochemical origins (27), the renal acid-base responses were similar with respect to excretion of base. The rapidity and magnitude with which the kidneys responded to the NaHCO$_3$ and KHCO$_3$ loading demonstrate their capacity, and physiological importance, for restoring body fluid homeostasis in the face of large, acute disturbances in water, ion, and acid-base balance.

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