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Safety and Tolerability of Long-Term Sodium Bicarbonate Consumption in Cancer Care

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Abstract

Objective: Pre-clinical studies have shown that chronic systemic buffering may have a beneficial impact in cancer care. This is a Phase 0/I clinical trial to determine if a sodium bicarbonate dose concentration of 0.5 g/kg/day is feasible and well tolerated as measured by the proportion of subjects with first evidence of adherence failure. The secondary objective was to determine if the dose concentration of 0.5 g/kg/day sodium bicarbonate is safe for long term consumption (90 days) as measured by vital signs and basic metabolic blood panels (BMP).

Methods: Healthy volunteers were recruited to consume 2-3 times per day a total maximum dose of 0.5 g/kg/day sodium bicarbonate. Volunteers were permitted to downward dose to find a tolerable dose they were willing to consume daily for 90 days. Volunteers returned to the clinic on day 10, 30, 60, and 90 to monitor vital signs, BMP, and urine pH. In between visits, the volunteers recorded their urine pH before and after sodium bicarbonate consumption. Volunteer journals and routine communication between clinical personnel and volunteers was maintained to monitor adherence and adverse events (AEs).

Results: The trial accrued 15 volunteers, 11 women and 4 men. The average age of volunteer was 55 years. The average daily dose was 0.17 ± 0.03 g/kg. Most adverse events were Grade 1. Two AEs were Grade 2. Most symptoms were gastrointestinal in nature. Two subjects withdrew from the study before the 90 day time point. One incidence of metabolic alkalosis occurred and was resolved by downward dose adjustment.

Conclusions: The study demonstrates that voluntary long-term consumption of sodium bicarbonate is feasible and safe, but the predicted upward tolerable dose was too high for healthy volunteers.

Keywords: Sodium bicarbonate; Feasibility; Safety; Clinical trial; Buffering; Cancer

Abbreviations: AE: Adverse Event; AG: Anion Gap; BMP: Basic Metabolic Blood Panels; BUN: Blood Urea Nitrogen; CTCAE: Common Terminology Criteria for Adverse Events; DCIS: Ductal Carcinoma *in situ*; GFR: Glomerular Filtration Rate; NEAP: Net Endogenous Acid Production

Introduction

Invasive cancer develops from solid tumors cycling through multiple stages of somatic evolution. Heritable changes are driven by the hostile microenvironment [1]. Low extracellular pH or acidity (pH 6.5-6.7) is a major hallmark of the hostile tumor microenvironment, and a driver of metastatic potential in solid tumors such as breast and prostate [2-4]. Several studies in mouse models for cancer have demonstrated that tumor acidity can be raised or buffered to physiological pH (7.2) through oral administration of a buffering agent [5-7]. The effect of systemic buffering has been shown to reduce tumor aggression in these animal models, by preventing the spread of metastases [7,8], improving disease-free survival [7,8], inhibiting pH-sensitive invasion enzymes [7,9,10], reducing the number of circulating tumor cells [9], and reducing tumor macroautophagy [11]. In most of these animal studies the buffer treatment was sodium bicarbonate.

There are no comprehensive findings discussing the effect of systemic buffering or sodium bicarbonate as a treatment for cancer in humans. Sodium bicarbonate has been used in combination with intravenous DMSO in the palliative care of cancer patients with metastatic prostate cancer [12,13]. Other studies have tested sodium bicarbonate consumption in late-stage cancer patients to determine feasibility and effectiveness, but were stalled by adherence issues due to low tolerance for the regimen (0.6 g/kg/day) [14,15]. Chronic sodium bicarbonate consumption may have a greater feasibility in relatively healthy individuals. We tested this concept in a Phase 0/I safety and feasibility trial in healthy human subjects. We predicted that volunteers would tolerate concentrations similar to the recent sodium bicarbonate consumption trials in cancer patients better and tolerably sustain a sodium bicarbonate regimen safely for 90 days. Our predictions are based on mathematical models that calculate the highest safe dose for chronic usage in humans as 0.5 g/kg/day. Amounts higher than this pose an increased risk for metabolic alkalosis [16]. The findings of this trial are being reported to provide safety guidance to the public and advance or contribute to the scientific discussion about buffering in cancer care.

Human Subjects and Methods

Human subjects

Eligible volunteers were healthy adults aged 18 to 80. Subjects had normal renal function (creatinine clearance: 88-128 mL/min; GFR:

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>90 mL/min/1.7 m^2) and did not exhibit uncontrolled hypertension (systolic pressure>140 and diastolic pressure>90) despite maximal antihypertensive therapy. Participants with a history of controlled hypertension with medication were not excluded.

Trial design

The study was divided into 2 phases: (1) Run in/adjustment- From baseline, time 0 to day 10 which was the first clinic visit after the baseline clinic visit. (2) Long term - From day 10 to day 90, consisting of 5 visits to the clinic. Volunteers were asked to return 30 days later after the end of the study for an off-treatment post-study clinic visit (Table 1). The maximum proposed starting dose was 0.5 g/kg/day. To find a tolerable daily range, volunteers were instructed to adjust their dosing downward by as much as half the starting dose if necessary, and continue downward dosing in the following days until a tolerable regimen is achieved. The volunteers consumed sodium bicarbonate doses 2-3 times per day on an empty stomach. Each dose was dissolved in 500 mL (~17 oz.) of water. Subjects were advised to consume the sodium bicarbonate in less than 20 min on an empty stomach for the most rapid and uninhibited absorption. Drug holidays (up to 7 consecutive days) were allowed. Urine pH measurements were assessed at all study visits. Volunteers also measured urine pH in between clinic visits with study provided commercial pH strips marketed for home testing (pHydrion®, MicroEssential Laboratory, Brooklyn, NY) before and 20-30 minutes after consumption. Subjects recorded daily urine pH measurements, and included information about dosage, timing of consumption, regimen consistency, and regimen deviations. To follow-up on their regimens, the volunteers were contacted by phone or email every 2-3 days within the first 10 days of the trial and once every 2 weeks afterwards until day 90. Journal entries containing daily dosing amounts and time taken, drug holidays, AEs and urine pH were collected from the subjects at study completion. Trial overview is described in Table 1.

Clinic visits

On days 0 (consent/baseline), 10, 30, 60, and 90 urine was collected for pH measurement. Blood pressure and resting pulse rate was recorded. A 3.5 mL blood sample was collected for basic metabolic panel (BMP). BMPs reported on changes in levels of key cations and anions in the blood. The test included measurements of serum sodium (Na^+), potassium (K^+), chloride (Cl^-), carbon dioxide (CO_2), anion gap (AG), blood urea nitrogen (BUN), creatinine, calcium (Ca^{++}), and glomerular filtration rate (GFR).

Dosing

After eligibility determination, screening was completed and subjects were consented and instructed to start the trial. On the day of consent, subjects were weighed to determine the maximum dosing limit for the 90 day daily consumption trial of 0.5 g/kg. If they experienced any acute symptoms possibly related to sodium bicarbonate consumption (i.e. headache, stomach discomfort, dizziness), the subjects were instructed to contact study personnel and reduce dose by as much as 50%. Dose reduction was continued until a daily tolerable dose was reached.

Safety

Study subject safety monitoring was conducted at every clinic visit. Blood pressure, pulse rate and blood pH were measured and BMP was used to assess subjects for adverse signs of chronic sodium bicarbonate consumption, including decreased kidney function, hypertension, and metabolic alkalosis. Reporting on symptoms of discomfort or adverse events (AEs) associated with the regimen was annotated at clinical visits and from between contact intervals. An AE is any untoward medical occurrence in a subject administered an investigational product even if not causally related to the treatment. All AEs were documented from subject consent until 30 days after study treatment was discontinued, using Common Terminology Criteria for Adverse Events (CTCAE) version 3. All AEs were followed to resolution where possible.

Endpoints

The primary objective of the study was to determine if the dose concentration of 0.5 g/kg/day sodium bicarbonate is feasible and well tolerated as measured by the proportion of subjects with first evidence of adherence failure. The secondary objective was to determine if the dose concentration of 0.5 g/kg/day sodium bicarbonate is safe for long-term consumption (90 days) as measured by blood pressure, resting pulse rate, and basic metabolic panels to assess metabolic alkalosis.

Statistical methods

All statistical calculations were carried out with GraphPad Prism version 4.03 for Windows (GraphPad Software, San Diego CA, http://www.graphpad.com). Linear regression was applied to measure the slope deviation from the zero. A paired t-test was applied to compare pH values in subjects before and after sodium bicarbonate consumption. A p-value of less than 0.05 was considered statistically significant. Mean data set values are presented with ± SD. Since this was a Phase 0/I feasibility study, the sample size was necessarily limited. All statistical analyses are considered exploratory.

Results

Patient characteristics

The study enrolled a total of 15 subjects, 11 female and 4 male. The median subject age at time of enrollment was 59 years old (mean was 55). The range of volunteer ages spanned from 18 to 73.

Subject dosing regimen and adherence

Thirteen volunteers out of 15 completed all 90 days of the trial. Two subjects withdrew from the study because they did not tolerate the investigational product. One (1001) withdrew 5 days after registration from stomach discomfort. This subject was lost to post-study follow-up. The other subject (1008) who withdrew from the trial before day 90 did so 25 days after registration reporting stomach discomfort, which continued throughout their participation in the study. This subject returned 31 days later for post-study (off treatment) clinic visit for blood tests and vitals. Two other volunteers (1003 and 1016) completed the 90 day trial, but did not complete all clinic visits. One subject (1003) completed the regimen schedule, but was lost to follow-up for the last day (day 90) clinic visit. Their journal was recovered 2 months later after their scheduled (but missed) final clinic visit. Another subject

Visit	Trial phase	Time (day)	Assessments/Outcome Measures/ Labs/Procedures	
1	1	0	vitals/blood/urine pH	consent
2	1	10	vitals/blood/urine pH	
3	2	30	vitals/blood/urine pH	
4	2	60	vitals/blood/urine pH	
5	2	90 (off treatment)	vitals/blood/urine pH	journals
6	study end	120	vitals/blood	

Table 1: Trial overview is described in Table 1.

(1016) completed all clinic visits, but was lost to follow-up for the post-study (off treatment) clinic visit.

Thirteen volunteers consumed sodium bicarbonate twice a day. Two of the volunteers chose to consume their daily regimen divided up into three times a day. Volunteers consumed a daily average of 0.17 ± 0.03 g/kg/day. The average amount consumed was 12.7 ± 2 g/day or approximately 2.5 teaspoons/day (Table 2). Nine of the volunteers used drug holidays to assist in their adherence in the full trial. Five of the participants did not report any drug holidays. The volunteer (1001) who withdrew within the first 5 days of the study did not take a drug holiday and is not included in the analysis. The subjects took an average of 7-8 drug holidays during the trial. Sixteen of the drug holidays taken by volunteers were 1 day intervals, 11 were 2 day intervals. Drug holidays that went longer than 2 days occurred 5 times amongst the study participants. Drug holidays that lasted longer than 5 days were directly consistent with travel periods and the end of the year holiday season (Table 2).

Adverse events

Adverse events were reported in 14 of the 15 volunteers. Most AEs were Grade 1 (mild; asymptomatic or mild symptoms; clinical or diagnostic observations only) and lacked severity to disincline further participation in the study. Grade 2 AEs (moderate and temporarily limiting activities of daily living) were reported by subject 1001 ("stomach cramping" and "migraine headache") who withdrew from the study after 5 days on the investigational product. A grade 2 AE was reported in one other subject (1011 experienced vomiting). This subject completed the study. In total, the subjects reported 189 instances of symptoms that were 'possibly' or 'probably' related to the consumption of sodium bicarbonate. Most of the AEs (67.7%) were related to intestinal issues (bloating, gassiness, appetite loss, indigestion, loose stools, diarrhea, nausea, vomiting, abdominal discomfort, and stomach cramping). The other most common AE (29.6%) was related to pressure in the head (dizziness, swelling, flushing, and headache). There were other reports of fatigue, weakness, insomnia, and dehydration which accounted for 2.6% of the overall AEs (Table 3). The average number of AE's per subject was 14 ± 4 (median = 8) (Table 2).

We evaluated the relationship between individual AE reporting and dosing (g/kg) using a linear regression model. We found a significant relationship ($p<0.02$) between AE reporting and dosing in individual subjects. Dosing amounts were considered a low predictor of AEs because the r^2 value from this analysis was 0.382 (Figure 1a). We note in this analysis that in all but, 2 cases (1003 and 1004), downward dosing was associated with reports of discomfort, but reports of discomfort did not cause downward dosing in subjects. The drug holiday intervals were not related to the dosage of daily sodium bicarbonate per individual (Figure 1b) or AE reporting (Figure 1c).

Urine pH

Urine pH is a reflection of acid-base balance and elevated urine pH is indicative of systemic bicarbonate excess. Urine pH is not a direct measure of systemic bicarbonate since other factors such as kidney function, and diet will also strongly influence urine pH measurements. For the purposes of this study, urine pH serves as a surrogate marker primarily to verify adherence. The mean urine pH baseline of all study participants was 6.39 ± 0.24, ranging from 5.06 - 7.82. There was no difference in urine pH values between male and female participants. Urine pH values were recorded by two methods. It was collected and measured at each of the clinic visits, and the subjects measured before and after (20-30 min) sodium bicarbonate consumption. The pH measurements were recorded in journals provided to the volunteers. In subsequent clinic visits, urine pH values were either increased or unchanged from baseline pH from the first visit, with the exception of two volunteers, 1005 and 1011. Urine pH in subject 1005 measured lower than baseline at visit 5, from 7.05 to 6.06. Urine pH in subject 1011 measured lower than baseline (7.01) at visits 4 (5.66) and visit 5 (5.88). Figure 2 shows urine pH measurements at clinic visits for each subject. In the overall volunteer population, urine pH was significantly higher ($p<0.02$) than baseline with the exception of visit 5 which was

Subject	mean dose (g)	mean dose (g/kg)	Drug holiday	Drug holiday (intervals)	reported AEs*
1001	9.3 ± 1.9	0.21 ± 0.04	-	-	2
1002	24.6 ± 4.3	0.24 ± 0.04	4	1,2	3
1003	11.3 ± 3.5	0.14 ± 0.04	-	-	
1004	29.1 ± 10.0	0.37 ± 0.1	-	-	37
1005	3.0 ± 2.2	0.04 ± 0.03	17	8†,7†,2	6
1008	1.43 ± 0.9	0.025 ± 0.02	6	6†	10
1009	19.3 ± 7.1	0.18 ± 0.07	-	-	2
1010	5.6 ± 2.8	0.09 ± 0.05	3	1,1,1	11
1011	4.9 ± 0.65	0.07 ± 0.01	4	2,2	17
1012	14.0 ± 4.3	0.26 ± 0.08	4	1,1,1,1	35
1013	17.1 ± 5.8	0.19 ± 0.07	10	3,2,1,1,1,1,1	2
1014	10.2 ± 1.5	0.17 ± 0.02	-	-	1
1015	19.7 ± 1.7	0.32 ± .0.03	5	1,1,2,1	40
1016	9.9 ± 0.5	0.12 ± 0.01	-	-	1
1017	11.4 ± 4.3	0.17 ± 0.06	15	5,2,2,2,2,2	22
mean	12.7 ± 8.0	0.17 ± 0.1	8 ± 5	-	14 ± 14

Table 2: Sodium bicarbonate dosing amounts (total grams and g/kg), drug holidays per volunteer, and volunteer adverse event reporting. Mean values with standard of deviation (SD) are expressed for each subject and in bottom rows for all subjects. *Only AEs that were considered 'likely', 'probably', or 'possibly' related to sodium bicarbonate consumption are listed. † Drug holiday intervals directly associated with extensive travel of volunteers.

	overall reporting	number of subjects
Intestinal Issues		
bloating/gassiness	12	4
appetite loss	1	1
indigestion	1	1
loose stool/diarrhea	82	9
nausea/vomiting	8	4
stomach upset/discomfort/abdominal pain/ cramping	24	6
	128	
Head Issues		
dizziness	6	3
pressure in head	1	1
swelling/swollen sinuses/sinus edema	23	2
flushing	2	2
headache	24	3
	56	
Other Issues		
insomnia	1	1
dehydration	2	1
weakness/fatigue	2	2
	5	

Table 3: List of adverse events experienced by the volunteers in the study. AEs are grouped as intestinal issues, Head issues, and Other. The sums of these groups are tallied in the bottom of the group column.

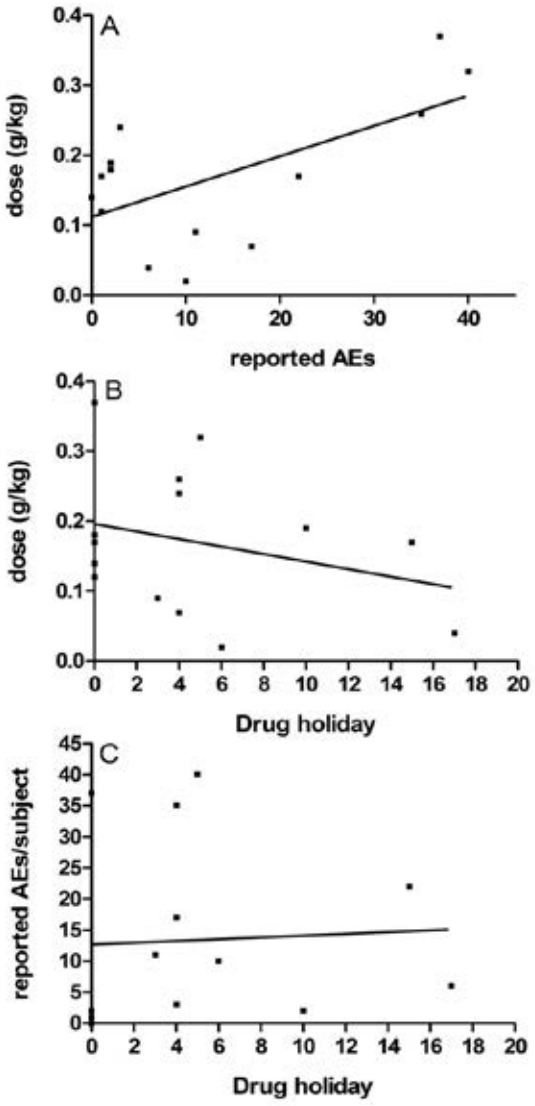

Figure 1: Linear regression analysis comparing subject sodium bicarbonate dosing (g/kg), subject adverse event (AE) reporting, and subject drug holidays. (A) Subject dosing vs. reported AEs. The mean dosing amount per subject in g/kg was compared to total subject AE reporting. The linear regression analysis reports a significant deviation from 0 ($p<0.0185$) with an r^2 value of 0.3822. (B) Subject dosing vs. drug holidays. The mean dosing amount per subject in g/kg was compared to total subject drug holidays. The linear regression analysis reports no significant deviation from 0 ($p = 0.392$). (C) Reported AEs vs. drug holidays. Total subject AE reporting was compared to total subject drug holidays. The linear regression analysis reports no significant deviation from 0 ($p = 0.392$).

the final clinic visit and coincided with the final day of volunteer bicarbonate dosing. We compared the fold pH change from baseline at each subsequent clinical visit to the amount of sodium bicarbonate being consumed by the subjects at the time of the visit. This analysis showed that there was no correlation between change in urine pH and bicarbonate dosing. Urine pH values appeared to either increase with dose or remain the same (Figure 3a). This outcome appears to be impacted by the urine pH of subjects who had more alkaline baseline urine pH. When baseline urine pH was compared to the mean fold change in urine pH per volunteer there was a significant trend ($p<0.0001$) suggesting that baseline urine pH was a factor ($r^2 =0.82$) influencing the urine pH to dose concentration analysis (Figure 3b). Urine pH measurements from journal entries were collected from 11 of the subjects. The urine pH reporting by the volunteers also showed a consistent alkaline flux from daily dosing. Although pH fluctuations varied, the overall urine pH changes from before to after bicarbonate dosing increased significantly in each volunteer (Figure 4).

Clinical outcomes

Kidney function: Basic metabolic blood panels were collected at each clinic visit to monitor kidney function, test for metabolic alkalosis, and to test for risk of hypertension from consuming higher amounts of sodium. The panels measured serum sodium (Na^+), potassium (K^+), chloride (Cl^-), carbon dioxide (CO_2), anion gap (AG), blood urea nitrogen (BUN), creatinine, calcium (Ca^{++}), and glomerular filtration rate (GFR). Measuring GFR, calcium, creatinine, and BUN in the metabolic panels assessed kidney function. Throughout the study from baseline to off-treatment, all subjects had normal range GFR levels (between 90 and 174 mL/min/1.73 m^2) and normal range Ca^{++} levels (between 8.6 and 10.3 mg/dL), indicating healthy kidney function. Serum creatinine levels were slightly below normal range (by 0.1 mg/dL) in two of the subjects (1004 and 1011) during the study, but normal overall in all of the volunteers. The lower serum creatinine levels did not appear to coincide with AEs nor were they related to sodium bicarbonate dosing changes in the subjects. BUN levels were always higher than normal in subject 1016. BUN levels were higher than normal in 4 out of 5 clinic visits in 1002 and 1004 (including baseline visit). Higher BUN levels were measured once or twice in five other subjects (1001, 1009, 1012, 1014, and 1015). Two higher than normal BUN levels were measured at baseline (1001 and 1009). Subject 1001 withdrew from the study. Normal BUN levels were measured in 1009 after the high BUN baseline measurement. There did not appear to be any correlation between out-of-range BUN levels and AEs or sodium bicarbonate dosing changes (data not shown).

Metabolic alkalosis: The primary risk for a study of this nature is the development of metabolic alkalosis defined as persistently higher concentrations of serum [HCO_3^-]. Serum [HCO_3^-] was calculated by subtracting Cl^- and AG concentrations from Na^+ levels. We observed one occurrence of elevated serum [HCO_3^-] consistent with metabolic alkalosis and subsequent sodium bicarbonate consumption. The subject was instructed to cut the study dose in half. Blood panels from this subject did not show evidence of high serum [HCO_3^-] in later clinic visits. Two other subjects had elevated serum [HCO_3^-] levels at baseline; however these levels were in the normal range during on-treatment clinic visits. Low serum [HCO_3^-] levels were detected in four of the subjects during the trial, 3 at the 'day 90' clinic visit (1002, 1011, 1016) and 1 on day 10 of the study (1017) (data not shown).

Higher serum CO_2 levels can be associated with metabolic alkalosis. Elevated CO_2 levels were observed in 8 of the volunteers during the study. Three volunteers (1005, 1008, and 1009) exhibited CO_2 levels greater than 30 mmol/L on the day 0 baseline visit before consuming sodium bicarbonate. Subsequent CO_2 measurements in these volunteers decreased over the course of the trial despite daily sodium bicarbonate consumption. Two volunteers (1004 and 1015) exhibited elevated CO_2 levels during the trial. The increase over normal CO_2 levels in these individuals was modest (less than 3-7%) and follow-up measurements remained in the normal range during the course of the study. The CO_2 fluctuations observed in these volunteers was not associated with changes in sodium bicarbonate dosing or any AEs. Three of the volunteers (1003, 1010, and 1017) exhibited increased CO_2 levels above the normal range during the trial that were 10-28% higher

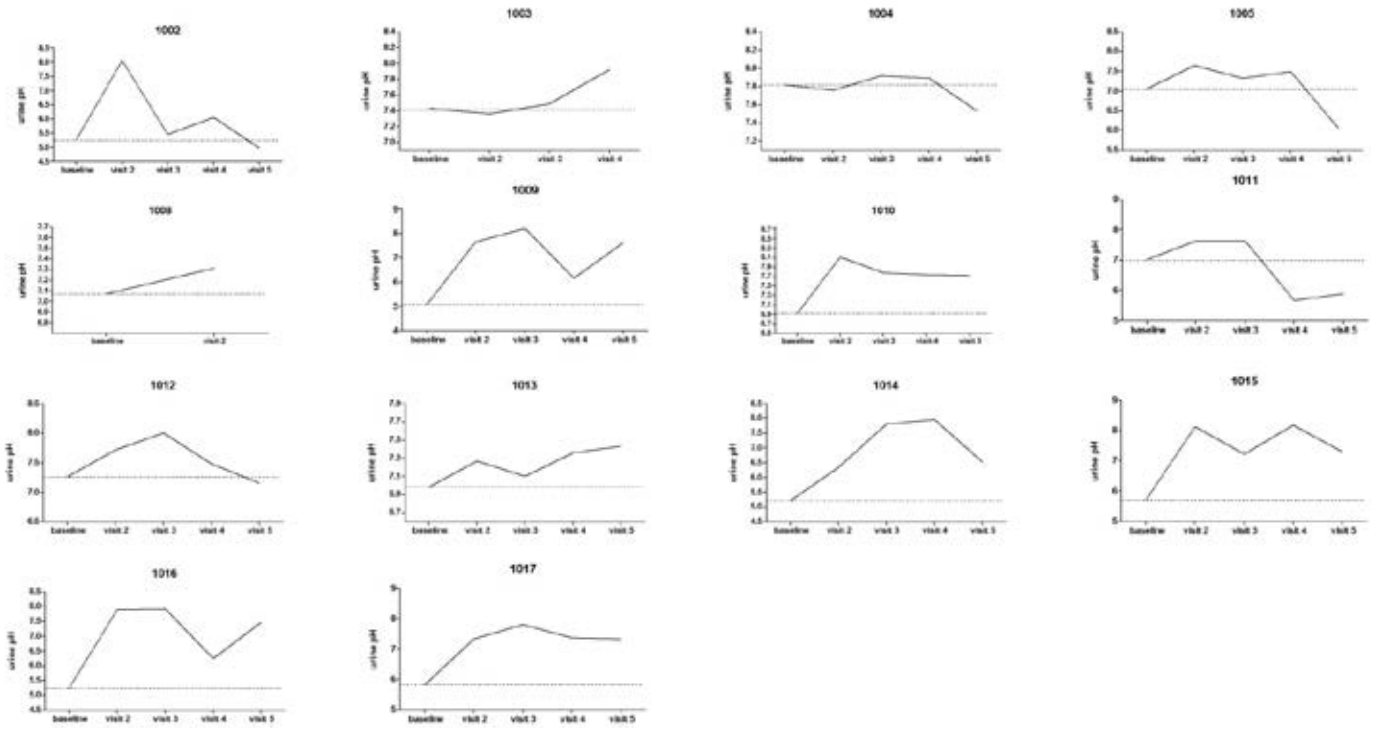

Figure 2: Urine pH of individual subjects at each clinic visit. Dashed line represents baseline urine pH.

than CO_2 levels at baseline. Elevated CO_2 in these individuals was concomitant with serum bicarbonate increases, implicating the sodium bicarbonate dosing as a potential cause of these fluctuations. Subject 1003 was the only volunteer who developed higher than normal levels of CO_2 and [HCO_3^-]. Although subject 1003 did not report any AEs, they were instructed nonetheless to reduce their dose by half. The dose reduction was followed by a reduction in CO_2 and [HCO_3^-] levels in all of the follow-up clinic visits. Although bicarbonate levels increased in association with CO_2 in subjects 1010 and 1017, these levels were still in the normal range (20-30 mmol/L). The increase in CO_2 and [HCO_3^-] in subject 1010 was observed 10 days after they had started the trial. Four days later they reduced their daily dose by half due to headaches and dizziness. Subject 1010 had normal CO_2 and bicarbonate levels in all follow up clinic visits. Subject 1017 exhibited higher than normal levels of CO_2 with an increase in serum [HCO_3^-] 30 days into the trial. This participant reported a sensation of sinus swelling since day 10 and subsequently reduced their study dose by one third (data not shown).

Low potassium levels could also be an indicator for metabolic alkalosis, but no subjects measured for serum potassium levels below the normal range. Subject 1005 exhibited higher than normal potassium levels on the 'Day 60' clinic visit. This measurement did not appear to be associated with other markers, symptoms, or sodium bicarbonate dosing (data not shown).

Serum sodium and hypertension: One teaspoon (about 5 grams) of sodium bicarbonate equals 1000 mg of sodium, indicating hypertension as a potential risk factor in sodium bicarbonate consumption. Higher than normal range serum Na^+ was measured in 10/15 volunteers during various clinical time points. In 5 of these cases (1002, 1010, 1013, and 1015), higher than normal serum Na^+ values were measured at baseline. In 4 of these cases (1002, 1004, 1014, 1015, and 1016), higher than normal serum Na^+ values were measured

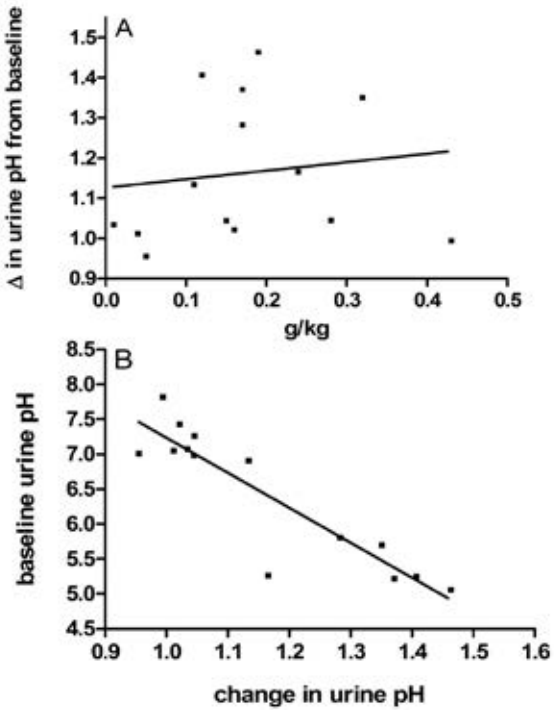

Figure 3: Clinical visit urine pH measurements in subjects compared to mean sodium bicarbonate dose and fold urine pH change from baseline urine pH. (A) Overall fold change in urine pH at each clinic visit after baseline vs. mean g/kg sodium bicarbonate. The linear regression analysis reports no significant deviation from 0 ($p=0.484$). (B) Baseline urine pH values compared to overall fold change in urine pH in each subject. The linear regression analysis reports a significant deviation from 0 ($p<0.0001$) with an r^2 value of 0.8204.

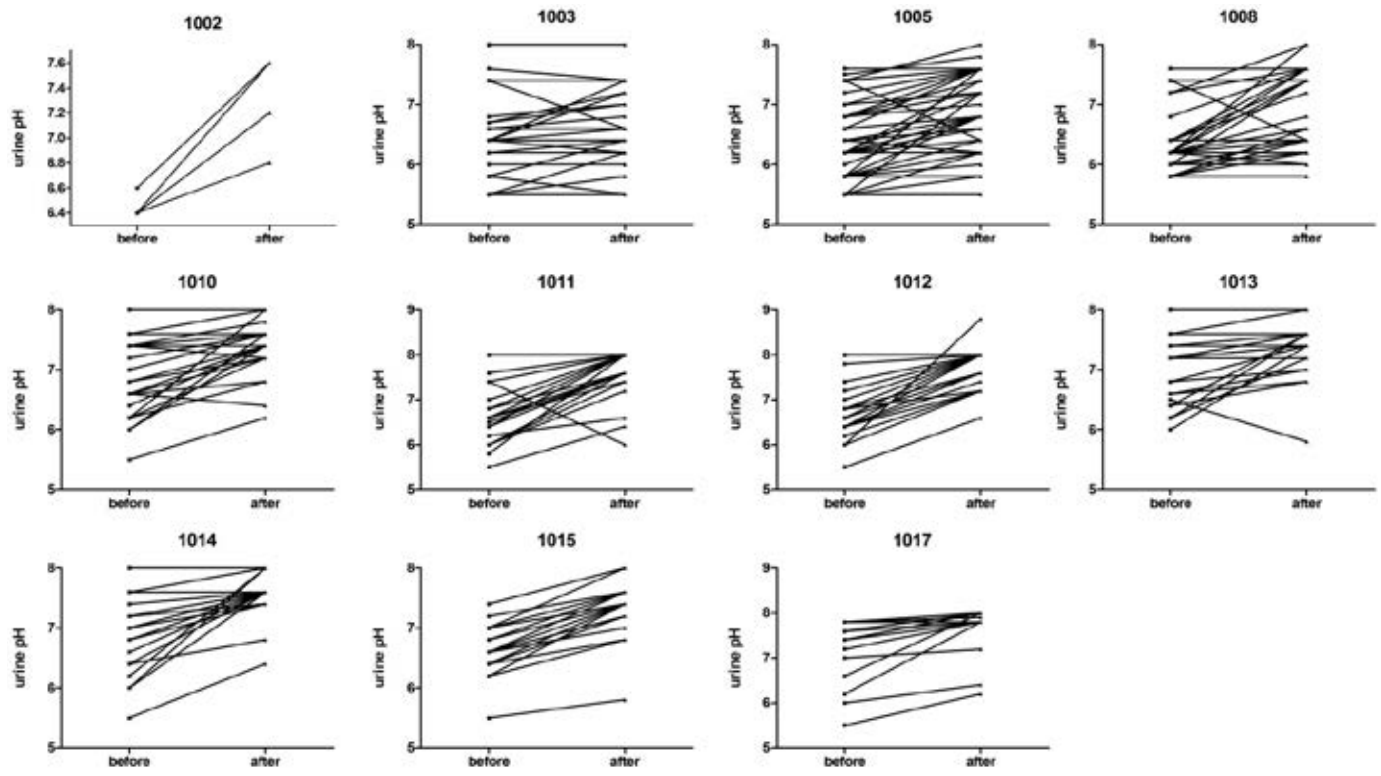

Figure 4: Subject urine pH measurements from journal entries. Subjects measured urine pH just prior to sodium bicarbonate consumption, then again 20-30 minutes after consumption. All values are paired. Differences between 'before' and 'after' measurements were significant ($p<0.01$) by paired t-test.

after 30 days off treatment (data not shown). On average, serum Na^+ values were 1.2% above the normal range. There was no correlation between serum Na^+ values and sodium bicarbonate dosing in any of the volunteers. Blood pressure and pulse were measured at the clinic visits. Pulse rates were normal in all subjects (data not shown). Fourteen of the volunteers exhibited a normal blood pressure range at baseline and throughout the trial. Subject 1003 had a blood pressure approaching stage 1 hypertension (150/86). At the day 10 clinic visit, subject 1003 had a blood pressure consistent with Stage 1 hypertension (162/91) (data not shown).

Discussion

In pre-clinical studies, captive 25 g mice will consume sodium bicarbonate drinking water at a concentration of 200 mM *ad libitum* at ~4-5 mL every 24 hours. The amount of sodium bicarbonate taken in during this period is about 68 mg. Dose translation for humans based on body surface area is approximately 12.5-15 g/day or slightly less than half the daily dose proposed for a 70 kg volunteer participating in the study (0.17-0.21 g/kg/day) [17]. Mathematical simulations carried out by Martin et al. argue that this dosing range in humans would have a '*substantially lower*' quantitative effect on buffering tumor pH than it does in the mouse models. The example provided states the sodium bicarbonate dose raises tumor pH in mice to 7.07, but only to 7.04 in humans [16]. Assuming a tumor with a proton output of 100 μmol/h/g tumor weight, it is predicted this dose of sodium bicarbonate would counteract the acid load of a 15 mg tumor [7].

It should be noted that effectiveness of this type of intervention would be dependent on a combination of several factors including the size of the tumor and the proton production rate of the tumor which is regulated by numerous membrane pumps and exchangers on the cell surface [18]. Age may also play a role in the effectiveness of the sodium bicarbonate dose. Renal efficiency declines due to nephron death during age progression. As GFR dips below 80 mL/min/1.73 m^2, blood pH decreases due to a retention or increase in $[H^+]$ concentration. Reduced acid secretion rate translates to improved therapeutic efficacy of the buffering treatment primarily because higher doses would be better tolerated [16].

The findings from this trial challenge us to refine strategies and determine patient populations where buffering would have optimal impact in cancer care. Auxiliary agents to reduce kidney function (GFR inhibitors) or reduce tumor proton production (dichloroacetate) have been proposed [16]. These agents have only been tested to a very limited extent in the context of cancer and extracellular pH modulation [8], and therefore it is unknown if buffer combination strategies will improve anticancer therapy. Alternative buffers IEPA and free-base lysine have been tested in mouse tumor models with favorable outcomes [19-22]. These buffers have higher buffering capacity than sodium bicarbonate due to higher pKa values that are equal to or higher than physiological pH [16,24].

Dietary intake may also serve as a buffering strategy. The metabolic constituents of foods contribute to acid-base balance in the body. Fruits and vegetables are net-base producing foods, yielding anion precursors such as citrate, succinate, malate, and conjugate bases of carboxylic acid. Animal proteins and cereal grains comprised of sulfur-containing amino acids (methionine and cysteine) are typically oxidized into sulfuric acid and drive net-acid balance [25,26]. Various dietary constituents contribute to Net Endogenous Acid Production (NEAP) or the acid load from dietary content of acid precursors relative to alkali

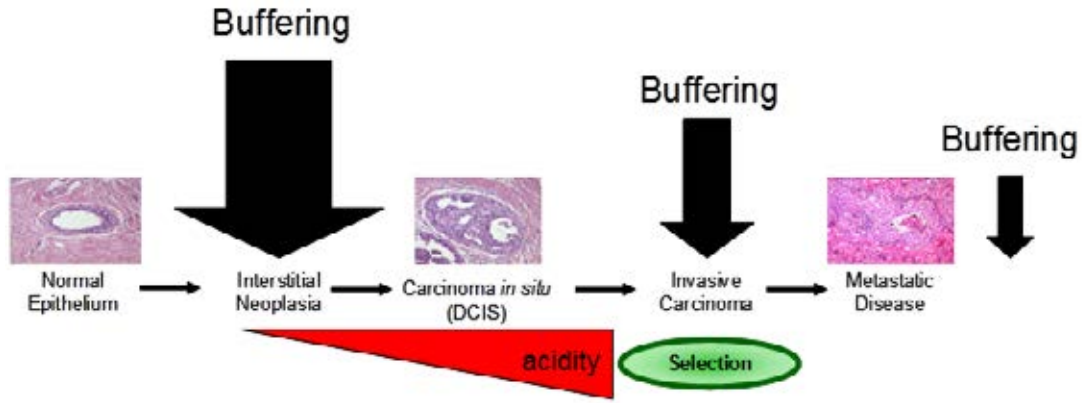

Figure 5: Buffering is proposed to have greater impact early in tumor progression before acidity selects for malignant tumor populations.

precursors. A recent report has also shown that systemic buffering can occur during digestion. Acidification of food in the stomach mediated on the apical side by parietal cells results in counteracting bicarbonate production at the basolateral membrane. The digestion phase yields a buffering impact that is distinct from acid-base balance mediated by NEAP [21].

Despite the low predicted tumor pH buffering impact of the doses consumed by the subjects in this trial, there is still evidence of significant systemic buffering as indicated from the urine data (Figures 2 and 4). Therefore, it is worth exploring if chronic maintenance of these buffering levels, whether by sodium bicarbonate or some an alternate approach is sufficient as a preventative approach for some types of solid tumors. The rationale for this concept was addressed in a study of a mouse model for spontaneous prostate cancer where animals treated with sodium bicarbonate drinking water before 6 weeks of age did not develop cancer, indicating that buffering alone was sufficient in prevention of malignancy [23]. The study outcomes may be explained by evidence demonstrating extracellular acidity, which becomes more prominent at the DCIS stage, is a driving micro-evolutionary aspect in promoting tumor progression [2,3]. In brief, early tumor exposure to acidic metabolites from hypoxia-induced glycolysis serves as a selective pressure for new generations of tumor cells to constitutively upregulate factors crucial for the maintenance of tumor survival. One of these factors, carbonic anhydrase IX (CA-IX), is responsible for regulating intracellular pH and in turn, aggravating extracellular acidification. It is an especially relevant factor given its strong association with increased tumor migration, invasion, focal adhesion, destabilization of intercellular contacts, tumor-stroma crosstalk, signal transduction, and resistance to therapy [27]. CA-IX was concurrently expressed at lower levels in mice treated with sodium bicarbonate drinking water before 6 weeks of age indicating its importance as a potential functional marker of transition from tumor indolence to aggression [23]. Elevated CA-IX expression is associated with the BRCA1 mutation [28]. The perceived benefits of early buffering therapy serve as an alternate paradigm for the application of chronic buffering in cancer care and may play an effective role in reducing cancer incidence in higher risk individuals such as those with the BRCA1 mutation (Figure 5). In developing future buffering strategies for patients, it should be taken into consideration that this approach will have little to no effect in some cancers that do not rely on extracellular acidity to metastasize [22].

Conclusions

The study results suggest that the predicted daily dose of 0.5 g/kg in healthy human subjects for 90 days is too high to be feasible in healthy individuals. The median level of daily consumption per volunteer was 0.17 g/kg. Adherence to the regimen was high (13 out of 15 subjects completed all 90 days) after the volunteers made tolerable dosing adjustments. AEs were restricted to mostly intestinal grade I type. While alternative buffers may have greater impact than sodium bicarbonate in cancer interventions, we hypothesize that moderate sodium bicarbonate supplementation or diets favoring net-base or higher systemic bicarbonate levels may have value as an approach to maintain constant neutral buffering in the interstitial spaces where tumors can occur in high risk individuals, in order to prevent acid-selected tumor progression.

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