Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis

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ABSTRACT: ***Background:*** **Sodium bicarbonate is despite its side effects, considered the standard alkali therapy in metabolic acidosis. THAM is an alternative alkalizing agent; however, there are limited data on the use of THAM in metabolic acidosis. The aim of this study was to compare the efficacy and adverse effects of a single dose of sodium bicarbonate and THAM in intensive care unit (ICU) patients with mild metabolic acidosis.**

Methods: **18 adult ICU patients with mild metabolic acidosis (serum bicarbonate <20 mmol/L) were randomized to a single dose of either sodium bicarbonate or THAM, administered over a 1-hour period, and titrated to buffer the excess of acid load.**

Results: **Sodium bicarbonate and THAM had equivalent alkalinizing effect during the infusion period. This was still present 4 hours after start of infusion of sodium bicarbonate, and until 3 hours after start of infusion of THAM. Serum potassium levels decreased after sodium bicarbonate infusion, and remained unchanged after THAM. After sodium bicarbonate, sodium increased, and after THAM, serum sodium decreased.**

Conclusions: **Sodium bicarbonate and THAM had a similar alkalinizing effect in patients with mild metabolic acidosis; however, the effect of sodium bicarbonate was longer lasting. Sodium bicarbonate did decrease serum potassium, and THAM did not; THAM is therefore not recommended in patient with hyperkalemia. As sodium bicarbonate leads to an increase of serum sodium and THAM to a decrease, THAM may be the alkalinizing agent of choice in patients with hypernatremia. Similarly, because sodium bicarbonate increases $PaCO_2$ and THAM may even decrease $PaCO_2$, sodium bicarbonate is contraindicated and THAM preferred in patients with mixed acidosis with high $PaCO_2$ levels.**

Key words: *Acidosis, Tromethamine, Sodium bicarbonate, Critical illness, Randomized controlled trials, Adverse effects, Hyperkalemia, Hypernatremia*

INTRODUCTION

Sodium bicarbonate is the recommended therapy for patients with severe acidemia (1). However, alkali therapy with sodium bicarbonate has also specific side effects. It can lead to hypernatremia, hyperosmolality, and volume overload. CO_2 may rise due to buffering of protons by bicarbonate ($HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$), and this may even lead to intracellular acidosis by diffusion of $PaCO_2$ into the cytoplasm (2-4).

THAM (trometamol or tris-hydroxymethyl aminomethane), a weak base with a pK of 7.8 has been proposed as an alternative alkalinizing agent (5, 6). THAM can bind both carbon dioxide and metabolic acids ($R\text{-}NH_2$ = unprotonated THAM, and $R\text{-}NH_3^+$ = protonated THAM):

$R\text{-}NH_2 + H_2O + CO_2 \leftrightarrow R\text{-}NH_3^+ + HCO_3^-$

$R\text{-}NH_2 + H^+ \leftrightarrow R\text{-}NH_3^+$

Protonated THAM is excreted by the kidney through glomerular filtration together with HCO_3^- or another anion, e.g. Ct. Because of these favorable buffer properties, THAM has been propagated as an effective alkalinizing effect in non-oliguric patients with either respiratory acidosis or metabolic acidosis (e.g. hyperchloremic acidosis) (5-8).

Toxic effects of THAM, observed after administration of high doses to healthy volunteers, were respiratory depression, hypoglycemia, hyperkalemia, vomiting and hypotension. Furthermore, vasospasm, and tissue necrosis were observed after administration of the THAM solution with a pH of 10.2, a solution currently no longer available (1, 6).

There is controversy in the literature regarding the optimal alkalinizing agent in severe acidosis. The use of THAM has been contraindicated because of the limited documentation of clinical effectiveness and the reported adverse effects (1, 9), while the use of sodium bicarbonate has also been questioned (10-15). There are to the best of our knowledge no studies in

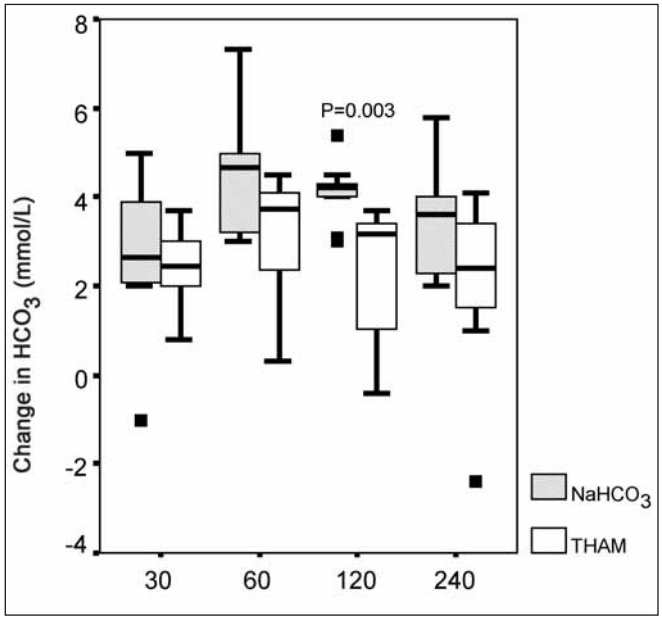

Fig. 1 - Change in serum bicarbonate after infusion of either sodium bicarbonate or THAM, expressed as the proportional change of the baseline value. The boxes represent the interquartile range, and the solid line in the box the median. The error bars represent the 95% confidence interval. Outliers are illustrated by ■.

critically ill patients with metabolic acidosis comparing the effects of sodium bicarbonate and THAM. Because of this paucity of data on the use of THAM in life threatening metabolic acidosis, we decided to evaluate its *in vivo* effect in patients with less severe metabolic acidosis. The aim of this study was therefore, to study the physiologic and adverse effects of a single dose of sodium bicarbonate or THAM in critically ill patients with mild metabolic acidosis.

Material and methods

The study was conducted in the 20-bed surgical ICU for adult patients in the Ghent University Hospital. Patients older than 18 years were included when serum bicarbonate was <20 mmol/L and base deficit >4 mmol/L (16-18), serum creatinine was <2 mg/dL, and when they had an arterial line for blood sampling. Patients were randomized to a single dose intervention with either sodium bicarbonate (Sodium bicarbonate 8.4%, B.Braun Medical N.V., Diegem, Belgium) or THAM (THAM Acetate, Rhone-Poulenc, France), using a randomization system with numbered, sealed, and opaque envelopes. The THAM preparation had a concentration of 300 mmol/L; sodium bicarbonate had a concentration of 1 mmol/mL.

The amount of base administered to the patients was titrated to correct acidemia. For this an empirical formula was used, calculated to correct an acid load in a volume exceeding the extracellular fluid volume by 10% (30% instead of 20% of body weight): 0.3 x bodyweight x base deficit (mEq/L) (6). As the patients' weight could not be measured, the predicted body weight was calculated for each patient. The predicted body weight for male patients was calculated as 50+0.91 (cm of height–152.4), and for female patients as 45.5+0.91 (cm of height–152.4) (16). The volume administered will be greater in the THAM group as the concentration of sodium bicarbonate was greater than that of THAM (1 mmol/mL versus 0.3 mmol/mL). The calculated buffer volume was administered over a 1 hour period: a loading dose of 25% of the calculated volume was administered over a 10 minute period, and the residual infusion volume over the next 50 minutes, according to the recommendations for administration of THAM. Ventilation settings remained unchanged during the study period in patients who were mechanically ventilated, in order to prevent respiratory modification of metabolic acid-base status.

The hemodynamic status of the patient, and biochemical parameters were recorded immediately before administration of the buffer, and 30, 60, 120, and 240 minutes after start of administration. The anion gap was calculated for each patient as $Na^+ + K^+ - Cl^- -$ bicarbonate. Whole blood samples were obtained from the arterial catheter, and analysed immediately on the blood gas analyser available on the ward (ABL 715, Radiometer Medical, Copenhagen, Denmark). Data were evaluated for efficacy and side effects.

Statistical analysis

Data are presented as mean ± standard deviation or proportion. Comparisons between both groups were done with the Mann-Whitney U test and the Fisher exact test. The evolution of parameters within each group was analyzed with the Friedman test; when this test demonstrated significant changes over the observation period for a specific parameter, the individual observations were evaluated for significant changes with the Wilcoxon signed ranks test. A double sided P value of <0.05 was considered significant. Analysis was performed with the statistical software package SPSS 11.0.1 (SPSS Inc. Chicago, Ill, USA).

Results

A convenience sample of 18 critically ill patients (13 male and 5 female), with a mean age of 62±10.3 years, and APACHE II score of 21±7.8 was included in the study.

The study patients were in a state of mild metabolic acidosis as evidenced by the baseline pH of 7.34±0.046, serum level of bicarbonate of 18±1.3 mmol/L, and base deficit of 7.5±1.31. Serum lactate was increased in 7 patients (38.9%). Although marked renal dysfunction (serum creatinine >2 mg/dL) was an exclusion criterion, decreased renal function could have contributed to metabolic acidosis, as evidenced by the serum creatinine level of 1.4±0.62 mg/dL.
Eight patients (44.4%) were treated with vaso-active therapy during the study period: 5 with norepinephrine, 2 with vasopressin, and one with a combination of vasopressin and norepinephrine. Ten patients (55.6%) were mechanically ventilated during the study period.

Efficacy of a single dose of sodium bicarbonate compared to THAM

Eight patients (44.4%) were randomized to a single dose intervention with THAM, and 10 (55.6%) to sodium bicarbonate. There were no differences in baseline characteristics of the patients between both groups.
Volume of infusion was significantly higher for patients who were randomized to THAM compared to those randomized to sodium bicarbonate (463±140.3 mL versus 152±28.8 mL, P<0.001).
During the infusion period both groups had the same increase in serum bicarbonate (Fig. 1). There was however, a longer lasting alkalinizing effect of sodium

TABLE I - EVOLUTION OF BIOCHEMICAL AND PATIENT PARAMETERS DURING THE STUDY PERIOD

	Baseline	T=30'	T=60'	T=120'	T=240'
a) Patients who received sodium bicarbonate					
pH	7.34±0.05	7.39±0.06*	7.42±0.06*	7.41±0.06*	7.41±0.05*
HCO_3^- (mmol/L)	17±1.5	20±1.7*	22±2.1*	21±1.5*	21±2.1*
Base deficit	8±1.1	4±1.7*	2±1.8*	2±1.6*	4±1.7*
$PaCO_2$ (mmHg)					
Spontaneous breathing (n=3)	26±2.1	29±3.0	29±4.8	28±1.3	26±4.1
$PaCO_2$ (mmHg)					
Mechanical ventilated (n=7)	33±7.0	35±6.4	36±6.6	35±6.3	34±6.0
PaO_2 (mmHg)	116±66.9	114±58.1	107±48.7	108±47.6	116±43.5
Na^+ (mmol/L)	137±8.9	138±9.1	140±9.1**	140±8.6*	140±8.9**
K^+ (mmol/L)	4.5±1.09	4.2±0.95**	4.1±0.93*	4.1±0.89*	4.1±0.90*
Cl^- (mmol/L)	114±10.6	115±10.6	114±10.0	114±10.3	114±10.5
Lactate (mmol/L)	2.5±1.81	2.4±1.67	2.6±1.74	2.5±1.55	2.5±1.60
Anion gap (mmol/L)	10.0±6.08	7.9±5.29	8.6±5.64	9.5±5.67	9.6±5.94
b) Patients who received THAM					
pH	7.35±0.04	7.39±0.03**	7.41±0.03**	7.39±0.05	7.37±0.07
HCO_3^- (mmol/L)	18±0.7	21±1.0**	22±1.3**	21±1.4**	20±1.9
Base deficit	7±1.5	4±1.4**	3±1.2**	4±1.5**	4±2.5
$PaCO_2$ (mmHg)					
Spontaneous breathing (n=5)	31±2.2	34±1.2	33±4.0	34±3.9	35±5.0
$PaCO_2$ (mmHg)					
Mechanical ventilated (n=3)	35±1.5	33±0.2	32±0.5	34±1.4	34±2.0
PaO_2 (mmHg)	118±29.8	102±27.9	96±28.1	109±29.4	111±33.0
Na^+ (mmol/L)	132±4.1	129±4.3**	129±4.2**	130±3.8**	130±3.9**
K^+ (mmol/L)	3.8±0.47	4.0±0.50	3.8±0.52	3.9±0.47	4.0±0.44
Cl^- (mmol/L)	112±4.7	111±4.6**	109±5.0**	110±5.0**	111±4.7**
Lactate (mmol/L)	1.6±0.84	1.7±0.79	1.7±0.81	1.6±0.66	1.6±0.68
Anion gap (mmol/L)	5.0±1.73	0.9±1.65	1.4±3.73	2.5±3.46	1.0±1.05

T=30-240' is respectively 30-240 minutes after start of administration of either sodium bicarbonate or THAM
The p values represent the statistical significance of the comparison of T=30-240 minutes versus baseline (Wilcoxon signed ranks test; this comparison was only performed when there was a significant change for the variable during the whole observation period (Friedman test)).
** is p<0.01 and ** is p<0.05.*

bicarbonate compared to THAM: 2 hours after start of infusion, the proportional increase in serum bicarbonate, was significantly higher in patients who received sodium bicarbonate compared to THAM patients (Fig. 1). The longer lasting alkalinizing effect was also illustrated by the evolution of pH, serum bicarbonate, and base deficit: all 3 variables significantly changed during the whole study period in patients who received sodium bicarbonate (Tab. I). In patients who received THAM the change in pH was no longer significant 2 hours after start of infusion, and the change in serum bicarbonate and base deficit was no longer significant 4 hours after start of infusion (Tab. I). The more sustained alkalizing effect of serum bicarbonate could not be explained by a change in serum lactate during the study period. In both groups blood pressure had a tendency to increase, although this was statistically not significant.

Adverse effects of sodium bicarbonate compared to THAM.

Patients who received sodium bicarbonate had a transient increase of arterial CO_2 concentration ($PaCO_2$) at the end of infusion (Tab. I). $PaCO_2$ did not change in patients who received THAM.
Sodium load was 13±2.4 g in patients who received sodium bicarbonate therapy. Not surprisingly, serum sodium consequently increased in this group. In those who were treated with THAM, sodium and chloride concentration decreased (Tab. I).
Potassium decreased in patients who received sodium bicarbonate in contrast to those who received THAM. Serum lactate, glucose, and PaO_2 remained unchanged in both groups. Central venous pressure also remained unchanged in both groups, despite the greater fluid load in the THAM group.

Discussion

In patients with mild metabolic acidosis short term infusion of sodium bicarbonate and THAM had comparable buffering effects. The effects of sodium bicarbonate were however more sustained compared to THAM. Furthermore, sodium bicarbonate therapy resulted in a decrease in potassium levels, whereas THAM had no effect on potassium. In case of associated hyperkalemia, sodium bicarbonate is therefore preferred over THAM.
The sodium load associated with sodium bicarbonate therapy lead to an increase in serum sodium. In contrast to this, THAM therapy resulted in a decrease of serum sodium. This may be explained by dilutional effect of the greater volume of water administered during THAM administration. Also, osmotic diuresis induced by THAM, and as a consequence of this an increased urinary sodium and chloride excretion (17) may explain decreased sodium levels.
Although the rise in $PaCO_2$ was small, it was significant in patients who received sodium bicarbonate. This may limit its use in patients with hypercapnia. In contrast, THAM had no effect on $PaCO_2$ in our study population. THAM seems, therefore, preferable to sodium bicarbonate in situations of mixed acid base disorders where $PaCO_2$ levels are increased, or in pure respiratory acidosis, as has been demonstrated in patients with acute lung injury (7).
THAM is eliminated by the kidneys, with a renal clearance that is approximately equal to the creatinine clearance (21). THAM can therefore accumulate in patients with kidney insufficiency, leading to pseudohyponatremia and an increased osmol gap. The use of THAM has, therefore, its limitations in patients with kidney insufficiency. Because kidney insufficiency is frequent in ICU patients and often under diagnosed (22), it is recommended to monitor osmolality when administering THAM. Also, its use is contraindicated in patients with severe kidney insufficiency, oliguria or anuria.
In conclusion, in this trial in critically ill patients with mild metabolic acidosis where a single dose of sodium bicarbonate and THAM were compared, sodium bicarbonate had a longer lasting buffering effect, and was effective in decreasing serum potassium levels, this in contrast to THAM. When there is an elevated serum sodium level and/or $PaCO_2$, THAM may offer an alternative for sodium bicarbonate. Other adverse effects of THAM, as previously reported, were not observed. The present data were obtained in mild metabolic acidosis and should therefore not automatically be extrapolated to patients with more severe acidosis.

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