

The Treatment of Acidosis in Acute Lung Injury with Tris-Hydroxymethyl Aminomethane (THAM)

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Mechanical hyperventilation of acidemic patients with acute lung injury (ALI) requires the use of high volumes and pressures that may worsen lung injury. However, permissive hypercapnia in the presence of shock, metabolic acidosis, and multi-organ system dysfunction may compromise normal cellular function. Tris-hydroxymethyl aminomethane (THAM) may be an effective method to control acidosis in this circumstance. Protonated THAM is excreted by the kidneys, so that carbon dioxide production is not raised. In an uncontrolled study, we administered THAM to 10 patients with acidosis (mean pH = 7.14) and ALI (mean lung injury score = 3.28) in whom adequate control of arterial pH could not be maintained during either eucapnic ventilation or permissive hypercapnic ventilation. THAM was given at a mean dose of 0.55 mmol/kg/h. Administration of THAM was associated with significant improvements in arterial pH and base deficit, and a decrease in arterial carbon dioxide tension that could not be fully accounted for by ventilation. Although further studies are needed to confirm these observations, THAM appears to be an effective alternative to sodium bicarbonate for treating acidosis during ALI.

Permissive hypercapnia is recommended to treat patients with acute lung injury (ALI) (1). However, permissive hypercapnia requires patient tolerance of respiratory acidosis for hours or days until renal compensation can correct arterial pH. ALI that develops as a consequence of sepsis and trauma commonly occurs with severe metabolic acidosis, shock, and multi-organ system dysfunction. In this situation, induced respiratory acidosis may compromise normal cellular function. Using high minute ventilation (\dot{V}_E), with or without sodium bicarbonate, to treat acidosis requires a ventilation strategy that may cause further structural damage to the lungs and deterioration in pulmonary gas exchange function, because some combination of high tidal volume (V_T), respiratory rate, and airway pressure (Paw) is required (2, 3). In addition, controlled studies using sodium bicarbonate to treat metabolic acidosis have not shown significant hemodynamic effects and have demonstrated conflicting effects on tissue oxygenation (4–7).

Tris-hydroxymethyl aminomethane (THAM), a weak base amino-alcohol, may be superior to sodium bicarbonate for the treatment of metabolic acidosis (8). THAM has a greater buffering capacity than bicarbonate (pK of 7.82 versus 6.1, respectively) (9), and is effective in buffering both metabolic and respiratory acidosis (10). Protonated THAM is excreted by the kidneys (11) so that CO_2 production is not raised, thus eliminating the need to increase \dot{V}_E in order to correct arterial pH. In respiratory acidosis, THAM lowers CO_2 while producing bi-

carbonate (12). Although THAM is commonly used in pediatric/neonatal critical care practice, its use in adults, as an alternative to sodium bicarbonate therapy, has been viewed with skepticism (13). We administered THAM to 10 patients with ALI and severe acidosis. In these patients respiratory compensation with mechanical ventilation was avoided because of the risk of severe pulmonary barotrauma and worsening lung injury.

METHODS

Patients consisted of all patients with ALI who received THAM between March 1, 1994 and March 1, 1999 at San Francisco General Hospital. The patients were not part of a randomized, prospective study, and the decision to administer THAM was made by the patient's treating physician; therefore, informed consent was not sought. THAM (0.3 M solution; Abbott Laboratories, Abbott Park, IL) was used to treat severe acidosis during either eucapnic ventilation or permissive hypercapnic ventilation in patients with ALI. In six of these patients adequate control of pH could not be achieved with sodium bicarbonate therapy. We have summarized the clinical circumstances and laboratory findings that compelled us to use THAM in these patients (Table 1), along with the severity of their ALI (Table 2). Lung injury scores were computed using the method described by Murray and colleagues (14) using data from the day therapy with THAM was initiated. Quasi-static respiratory system compliance was calculated from the expired V_T divided by the end-inspiratory plateau pressure minus positive end-expiratory pressure (PEEP) (15). In five cases (Patients 2, 5, 6, 9, and 10) the physiologic deadspace to tidal volume ratio (V_D/V_T) was determined by the Eghoff modification of the Bohr equation, using a 5-min expired gas collection with a bedside metabolic monitor (16). Alveolar minute ventilation (\dot{V}_A) was calculated by subtracting the portion of minute ventilation occupied by physiologic deadspace from total \dot{V}_E . All cases were complicated either by the presence of barotrauma (Patients 2 and 3), chest wall restriction (Patients 1, 6, 7, and 8), profound acidosis and shock (Patients 1, 4, 5, and 8–10), or pulmonary gas trapping (Patients 2, 4–6, 9, and 10).

THAM was used 13 times in 10 patients and was administered on two occasions in three cases (Patients 1, 6, and 7). In seven of our patients THAM was infused at a mean rate of 0.55 mmol/kg/h. The average length of treatment in these patients was 39 h (range of 2 to 96 h). In three cases with severe shock (Patients 5, 9, and 10) THAM was rapidly administered as a single dose (150 to 200 mEq) over 30 min to 1 h as rescue therapy. The pH, Pa_{CO_2} , and base deficit data were obtained 1 h prior to THAM infusion and within 2 h after the infusion commenced (Table 3). During this period, no other significant hemodynamic or metabolic interventions occurred. In the six patients who received both THAM and sodium bicarbonate therapies, the bicarbonate therapy had ceased at least 4 h before commencement of THAM infusion. The mean dose of sodium bicarbonate received was 82.5 mEq/dl (Table 4). We compared the effects of both THAM and sodium bicarbonate on arterial pH, Pa_{CO_2} , and base deficit using Wilcoxon signed rank tests. Findings were considered to be statistically significant if $p < 0.05$.

RESULTS

Administration of THAM always was associated with an improvement in arterial pH and a reduction in base deficit (Ta-

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TABLE 1
DESCRIPTION OF PATIENTS REQUIRING TREATMENT OF ACIDOSIS WITH THAM

Case	Subject	Management Problems
1	22-yr-old man with necrotizing pancreatitis, and septic shock	Severe ascites. Systolic BP = 70 mm Hg with epinephrine, dobutamine, norepinephrine. HCO ₃ = 21 mEq/dl, anion gap = 15, creatinine = 0.4 mg/dl. Second episode of septic shock, V̇ _E = 25.8 L/min produced an arterial pH = 7.12, Pa _{CO₂} = 86 mm Hg
2	34-yr-old female with severe inhalation injury	Severe oxygen desaturation (< 80%) hypercarbia (Pa _{CO₂} > 90 mm Hg) despite very high levels of sedation and paralysis. Multiple tension pneumothoraces and bronchopleural fistulas. Intrinsic PEEP levels of 20 cm H ₂ O. HCO ₃ = 38 mEq/dl, anion gap = 9, creatinine 0.8 mg/dl
3	28-yr-old female, with necrotizing pneumonia and septic shock	Multiple tension pneumothoraces and bronchopleural fistulas. Peak alveolar pressures = 39 cm H ₂ O, V _T = 5 ml/kg, V̇ _E = 15.6 L/min. HCO ₃ = 17 mEq/dl, anion gap = 13, creatinine = 0.9 mg/dl
4	55-yr-old female with neurogenic pulmonary edema and multi-organ system failure	Dopamine, dobutamine, and phenylephrine needed to maintain CPP > 60 mm Hg. ICP = 20 mm Hg despite continuous drainage. V̇ _E = 18.5 L/min, intrinsic PEEP = 23 cm H ₂ O. Serum HCO ₃ = 22 mEq/dl, anion gap = 15, creatinine = 1.3 mg/dl
5	58-yr-old female with septic shock and pneumococcal pneumonia	Mean arterial pressure = 60 mm Hg with dopamine, norepinephrine, phenylephrine. V̇ _E = 16.6 L/min, intrinsic PEEP = 19 cm H ₂ O. Peak alveolar pressure = 45 cm H ₂ O. HCO ₃ = 14 mEq/dl, anion gap = 25, creatinine = 1.7 mg/dl
6	45-yr-old man with abdominal gunshot wound, ascites, asthma and septic shock	Pulmonary hypertension (mean pulmonary arterial pressure = 58 mm Hg). Severe bronchospasm with V̇ _E = 18 L/min and intrinsic PEEP = 18 cm H ₂ O. Mean arterial pressure = 70 mm Hg with norepinephrine and dopamine. HCO ₃ = 23 mEq/dl, anion gap = 9, serum creatinine = 2.0 mg/dl
7	33-yr-old male with abdominal gunshot wound, ascites, and septic shock	Peak alveolar pressure = 54 cm H ₂ O, PEEP = 14 cm H ₂ O, inspiratory:expiratory ratio = 1:1. V̇ _E = 18.2 L/min. HCO ₃ = 27 mEq/dl, anion gap = 5, creatinine = 1.1 mg/dl
8	42-yr-old male with necrotic pancreatitis and septic shock	Mean arterial pressure = 51 mm Hg with dopamine, norepinephrine, epinephrine. Peak alveolar pressure = 44 cm H ₂ O, PEEP = 15 cm H ₂ O, V _T = 7 ml/kg. V̇ _E = 12.4 L/min. HCO ₃ = 15 mEq/dl, anion gap = 19, creatinine = 1.6 mg/dl
9	49-yr-old female with hepatic failure and septic shock	Mean arterial pressure = 55 mm Hg with dopamine, phenylephrine, norepinephrine. Peak alveolar pressure = 45 cm H ₂ O. V̇ _E = 19.3 L/min and intrinsic PEEP = 11 cm H ₂ O. HCO ₃ = 17 mEq/dl, anion gap = 7, serum creatinine = 1.4 mg/dl
10	34-yr-old man with AIDS and pneumococcal pneumonia	Dopamine, norepinephrine, and phenylephrine to maintain mean arterial pressure = 65 mm Hg. V̇ _E = 23.8 L/min and intrinsic PEEP = 20 cm H ₂ O. Peak alveolar pressure = 47 cm H ₂ O, V _T = 9 ml/kg. HCO ₃ = 22 mEq/dl, anion gap = 13, creatinine = 2.0 mg/dl

Definition of abbreviations: CPP = cerebral perfusion pressure; ICP = intracerebral pressure; PEEP = positive end-expiratory pressure.

ble 3). Although there was no control group, the differences in arterial pH, Pa_{CO₂}, and base deficit pre- and post-THAM infusion in individual patients were statistically significant (p < 0.01). In some patients, the buffering effect of THAM appeared to be sustained after the infusion was discontinued, although no patient developed an overshoot alkalosis.

TABLE 2
PHYSIOLOGIC CHARACTERISTICS OF ALL PATIENTS BEFORE THE START OF THAM

Case	Lung Injury Score*	Respiratory Rate (breaths/min)	V̇ _E (L/min)	V _D /V _T	Respiratory System Compliance (ml/cm H ₂ O)
1	3.25	28	14.0	ND	14
2	2.75	24	10.8	0.70	16
3	2.5	34	16.3	ND	10
4	3.75	26	18.5	ND	16
5	3.50	26	16.6	0.69	23
6	2.5	20	18.0	0.58	19
7	3.75	26	18.2	ND	16
8	3.75	20	12.4	ND	18
9	3.25	28	19.3	0.83	18
10	3.75	32	26.1	0.79	24
Mean ± SD	3.28 ± 0.55	26.4 ± 4.5	17.0 ± 4.2	0.72 ± 0.1	17.4 ± 4.1

Definition of abbreviations: ALI = acute lung injury; ND = not determined; V̇_E = minute ventilation; V_D/V_T = physiologic deadspace to tidal volume ratio.
* Reference 14.

THAM often was associated with a decrease in Pa_{CO₂} that could not be entirely accounted for by concomitant increases in V̇_E. In five cases, concurrent measurement of V_D/V_T allowed the determination of V_A. In these patients, Pa_{CO₂} was significantly lower after the start of THAM (65.4 ± 26.9 mm Hg before THAM and 52.8 ± 24.8 mm Hg afterwards; p < 0.05) at equivalent levels of V̇_A (12.9 ± 4.5 L/min before THAM and 11.5 L/min afterwards; p > 0.05). As in our sample, a marked decrease in P_{CO₂} (20 to 39 mm Hg) has been reported after the administration of THAM and appeared to be dose-dependent (17).

Six of the 10 patients received sodium bicarbonate before THAM as treatment for their acidosis (Table 4). The arterial pH decreased significantly and the Pa_{CO₂} increased significantly in these patients after the bicarbonate infusion (p < 0.05). These changes were opposite of those that occurred with THAM infusion. Other changes in the patients' clinical status did not occur that could explain these findings.

THAM has been reported to decrease blood glucose at high doses (18). Serum glucose tended to decrease mildly (10 to 30 mEq) after the start of therapy. However, a precipitous drop in glucose (from 125 to 24 mg/dl) occurred in one patient after rescue therapy with THAM (150 mEq over 30 min).

DISCUSSION

Using sodium bicarbonate to treat metabolic acidosis has been controversial (8). In patients who have impaired circulation from cardiac arrest, shock, or sepsis, lactic acid production is the primary cause of metabolic acidosis (8, 13). The adminis-

TABLE 3
DIFFERENCES IN pHa, Pa_{CO₂}, AND BASE EXCESS BEFORE AND AFTER
ADMINISTRATION OF THAM AMONG PATIENTS WITH ALI

Case	pHa Pre-THAM	pHa Post-THAM	Pa _{CO₂} Pre-THAM (mm Hg)	Pa _{CO₂} Post-THAM (mm Hg)	Base Deficit Pre-THAM (mEq/L)	Base Deficit Post-THAM (mEq/L)	THAM dose (mmol/kg/h)
1	7.10	7.31	64	38	-11.0	-7.0	0.45
1b*	7.12	7.25	86	54	-2.7	0.0	0.45
2	7.18	7.26	110	95	+13.1	+15.7	0.48
3	7.21	7.31	41	38	-11.3	-7.3	1.36
4	7.21	7.36	52	37	-8.0	-4.5	0.21
5 [†]	7.07	7.34	39	30	-18.3	-9.0	3.10
6	7.12	7.18	59	46	-10.4	-7.5	0.41
6b	7.14	7.26	66	51	-7.3	-4.5	0.62
7	7.16	7.23	67	59	-6.0	-3.8	0.39
7b	7.19	7.32	73	57	-1.7	+2.5	0.49
8	7.07	7.12	46	50	-16.3	-13.0	0.36
9 [†]	7.09	7.12	52	44	-14.4	-14.7	2.42
10 [†]	7.11	7.31	60	44	-10.9	-4.0	4.10
Mean ± SD	7.14 ± 0.05	7.26 ± 0.08 [‡]	63 ± 19	50 ± 16 [‡]	-8.1 ± 8.0	-4.4 ± 7.6 [‡]	1.07 ± 1.23

Definition of abbreviation: pHa = arterial pH.

* b denotes second trial of THAM therapy.

[†] Rescue therapy.

[‡] p < 0.05 by Wilcoxon signed rank test for comparison of pre- and post-THAM values.

tration of sodium bicarbonate under these conditions may lead to decreased cardiac output (19), venous hypercapnia with associated intracellular acidosis (20), increased lactate production (21), and tissue hypoxia (5). In our study, we found that sodium bicarbonate was not effective at increasing pH in the six patients who received it as treatment for acidosis associated with ALI before receiving THAM. In all six cases, administration of sodium bicarbonate resulted in an acute worsening of acidosis. Studies of patients with lactic acidosis have found conflicting results regarding the use of sodium bicarbonate (6, 7). Among the six patients in our study who had increased anion gap metabolic acidosis presumably owing to lactic acidosis, THAM infusion resulted in an increased pH. However, none of the three patients with an increased anion gap acidosis who received sodium bicarbonate demonstrated an increase in pH. Clearly, larger studies are needed to confirm these findings. Our study was too small to permit definitive conclusions regarding the use of sodium bicarbonate in patients having acidosis associated with ALI. Furthermore, studies having clinical endpoints are needed to determine whether the outcome is impacted by these changes.

Rapid intravenous administration of 50 mEq of sodium bicarbonate generates approximately one minute's worth of CO₂ gas (22). To prevent hypercapnia under normal conditions would require a transient doubling of alveolar ventilation (22). Yet, V_D/V_T is reported to be highly elevated in ALI, especially in association with septic shock (23). Therefore, compensation to produce a normal or subnormal Pa_{CO₂} after rapid administration with sodium bicarbonate would require a much greater increase in total ventilation.

The presence of shock and severe acidosis may compel the clinician to abandon permissive hypercapnia in order to restore arterial pH. However, mechanical hyperventilation during shock may paradoxically worsen both respiratory and lactic acidosis by diminishing the effectiveness of pulmonary CO₂ gas exchange and further exacerbating systemic hypoperfusion. High levels of V_E tend to cause gas trapping and intrinsic PEEP (24). This increase in end-expiratory lung volume may diminish the perfusion of normal lung tissue (especially during shock) as alveolar pressure would exceed pulmonary arterial pressure during all or part of the respiratory cycle (West Zone 1) resulting in an increase in V_D/V_T (25). Suter and colleagues

TABLE 4
DIFFERENCES IN pHa, Pa_{CO₂}, AND BASE EXCESS BEFORE AND AFTER ADMINISTRATION
OF SODIUM BICARBONATE (NaHCO₃) AMONG PATIENTS WITH ALI

Case	pHa Pre- NaHCO ₃	pHa Post- NaHCO ₃	Pa _{CO₂} Pre- NaHCO ₃ (mm Hg)	Pa _{CO₂} Post- NaHCO ₃ (mm Hg)	Base Deficit Pre- NaHCO ₃ (mEq/L)	Base Deficit Post- NaHCO ₃ (mEq/L)	NaHCO ₃ Dose (mEq)
1	7.17	7.10	58	64	-7.8	-11.0	50
2	7.23	7.18	93	108	11.6	12.5	50
3	7.14	7.08	33	48	-16.8	-15.6	200
5	7.27	7.05	38	40	-9.2	-18.7	115
9	7.27	7.09	46	52	-6.5	-14.4	50
10	7.17	7.11	50	59	-9.9	-10.9	30
Mean ± SD	7.21 ± 0.06	7.10 ± 0.04*	53 ± 19	62 ± 24*	-6.4 ± 9.5	-9.7 ± 11.3	82.5 ± 64.5

* p < 0.05 Wilcoxon signed rank test for comparison of pre- and post-NaHCO₃ values.

(26, 27) demonstrated that even moderate levels of both PEEP (9 cm H₂O) and V_T (10 ml/kg) resulted in overdistension of normal lung tissue and an increase in V_D/V_T. Mechanical ventilation with PEEP decreases cardiac output (28) and particularly may impair hepatic, renal, and splanchnic perfusion from the effects of increased abdominal pressure on vascular outflow resistance (29). Because this effect is more pronounced during inspiration (30) mechanical hyperventilation may potentiate systemic hypoperfusion. Gattinoni and colleagues (31) demonstrated a 26% increase in cardiac output and a 28% decrease in pulmonary vascular resistance with low frequency positive-pressure ventilation versus conventional ventilation at 16 breaths/min. In our sample, the mean respiratory frequency prior to THAM was 26 breaths/min (Table 2).

In some patients, the buffering effect of THAM was sustained after the infusion was discontinued. THAM rapidly distributes into a volume that approximately equals the extracellular space, and over time, its final distribution volume equals total body water (11). The rate of THAM excretion slightly exceeds creatinine clearance (11). Although 25% of THAM can be recovered from the urine within an hour after infusion (32), it may take between 24 to 72 h to achieve 80% excretion (9, 11). Brasch and colleagues (11) reported that the half-life of THAM was between 16 and 45 h in surgical patients with metabolic acidosis. In Cases 2, 3, and 5, where the patients received a one-time dose of THAM, the improvement in pH was maintained for at least 24 h. Other studies, however, have raised concern that although THAM may decrease arterial CO₂ and raise pH, it may also produce arterial vasodilator effects that can adversely affect outcome (33, 34).

It is recommended that THAM be administered with a loading dose of 2 to 4 mmol/kg over 20 min, followed by a constant infusion of 0.5 to 1.0 mmol/kg/h for 4 to 10 h (9). With the exception of the subjects who received THAM as rescue therapy, our mean infusion rate was similar (0.55 mmol/kg/h) but our average treatment duration was substantially longer (39 h). Yet, Nahas and colleagues (9) describe an unpublished case of acute respiratory distress syndrome (ARDS) where THAM was infused at 0.3 to 0.6 mmol/kg for 10 d. Wolf and colleagues (35) infused THAM at 0.3 mmol/kg/h over 5 d and found no difference in the incidence of complications compared with controls.

THAM was both effective and well tolerated in our patients even with prolonged use. In addition, rapid infusion of THAM in an emergency setting was very effective in correcting pH in two of the three cases when it was used. Although our study was uncontrolled, THAM appears to be an attractive therapeutic option to treat acidosis in the presence of ALI. Before recommending THAM as a primary treatment for acidosis associated with ALI, controlled, prospective studies are needed to determine both whether and how to best treat acidosis in this clinical setting.

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