

The place of THAM in the management of acidemia in clinical practice

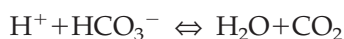
M. H:SON HOLMDAHL¹, L. WIKLUND¹, T. WETTERBERG², S. STREAT³, S. WAHLANDER⁴, K. SUTIN⁴ and G. NAHAS⁴

¹Department of Anesthesiology, Uppsala University, Sweden, ²King Faisal Research Center, Riyadh, Saudi Arabia, ³Department of Critical Care, Auckland Hospital, New Zealand, ⁴Department of Anesthesiology and Critical Care, New York University Medical Center, USA

TITRATING agents should only be used to correct acidemia after attempts to correct the underlying causes of this life-threatening condition have failed. This requires optimization of: ventilation CO₂ removal, circulation to promote blood-tissue exchange, metabolic status (in, for example, diabetes) urinary function with hemodialysis if necessary. If these measures are ineffective, one can use buffers to normalize pH until homeostasis is restored. For example, non-bicarbonate buffers are indicated in severe bronchospasm (status asthmaticus) to reduce PaCO₂ and restore adrenergic mediated bronchodilatation (1).

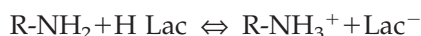
Which buffers should be used?

Sodium bicarbonate has been the drug of choice in all protracted cases of acidemia. The salts of weak acids, such as sodium citrate, lactate, or acetate which are bicarbonate precursors, have also been used. To be effective, these precursors depend on metabolic conversion to bicarbonate, which occurs slowly in the state of shock or acidemia. Sodium bicarbonate titrates CO₂ according to the following reaction, and it is catalyzed by carbonic anhydrase found mainly in erythrocytes and renal tubules:



This is a reaction which generates free CO₂ and will aggravate acidemia when CO₂ elimination from tissues or lungs is hindered, as in heart failure, hemorrhagic shock, or pulmonary failure (e.g. ARDS, Adult Respiratory Distress Syndrome).

THAM, Tris-Hydroxymethyl-Amino-Methane, introduced in clinical practice in 1959 (2, 3), titrates (e.g. lactic acid or CO₂) according to the following reaction:



THAM is a proton acceptor that generates NH₃⁺/HCO₃⁻ without generating CO₂, and the protonated R-NH₃⁺ is eliminated by the kidneys. THAM is the buffer of choice in the situation where CO₂ elimination is impaired (in which case NaHCO₃ cannot correct acidemia), and to avoid a Na⁺ load. THAM was first used experimentally in animals to keep pH normal during apneic oxygenation with complete retention of CO₂, whereas CO₂-generating bicarbonate was ineffective. Even during short intervals of apneic oxygenation when CO₂ elimination is curtailed, THAM, but not bicarbonate, will maintain a normal arterial pH. This is the reason why THAM should be used when CO₂ elimination is impaired. An additional reason is to avoid the Na⁺ overload of bicarbonate.

Two reviews published in 1966 and 1998 questioned the use of THAM in acidemia because of "its toxicity and general lack of clinical indications" (4, 5) and concluded that sodium bicarbonate is the only acceptable buffer in clinical medicine. This paper is based on the first-hand experience gathered in intensive care and emergency medicine units, where THAM solutions were developed over the past three decades and are still routinely used. The results of our studies, and of many others, were published in a 1998 review "Guidelines for the treatment of acidemia with THAM" (6). This article, which contains 280 references, may be summarized as follows:

THAM (trometamol); Tris-hydroxymethyl amino-methane is a biologically inert amino alcohol of low toxicity, which buffers carbon dioxide and acids *in vitro* and *in vivo*. At 37°C, the pK (the pH at which the weak conjugate acid or base in the solution is 50% ionized) of THAM is 7.8, making it a more effective buffer than bicarbonate in the physiological range of blood pH. THAM is a proton acceptor with a stoichio-

metric equivalence of titrating 1 proton per molecule.

In vivo, THAM supplements the buffering capacity of the blood bicarbonate system, accepting a proton, generating bicarbonate and decreasing the partial pressure of carbon dioxide in arterial blood (PaCO₂). It promptly distributes through the extracellular space and slowly penetrates the intracellular space, except for erythrocytes and hepatocytes. THAM is excreted by the kidney in its protonated form at a rate that slightly exceeds creatinine clearance. Unlike bicarbonate, which requires an open system for carbon dioxide elimination, THAM is effective in a closed or semi-closed system and maintains its buffering power in the presence of hypothermia.

THAM rapidly restores pH and acid-base regulation in acidemia caused by carbon dioxide retention or metabolic acid accumulation, which have the potential to impair cardiac function. Tissue irritation and venous thrombosis at the site of administration occur with THAM base (pH 10.4) administered through a peripheral or umbilical vein; however, THAM acetate

300 mmol/L (pH 8.6) (Abbott Laboratories), the only formulation available in the USA, is well tolerated by peripheral or umbilical vein.

In Scandinavia, two THAM preparations are used. Addex-THAM and Tribonate Fresenius Kabi. Addex-THAM contains THAM 20 g (165 mmol) in a 50 mL vial titrated with hydrochloric acid to a final pH of 9.2. Like other Addex-preparations, this vial is added to a 1 L glucose solution. Two vials added will result in a 0.3 M THAM concentration. Tribonate Fresenius Kabi, contains THAM 300 mmol/L, acetate 200 mmol/L, Na⁺ 210 mmol/L, pH of the solution is 8.1 and osmolality 800 mOsmol/L. Tribonate and Addex solutions are also well tolerated by peripheral veins, even if Addex solutions preferably should be administered through central venous catheters.

The initial loading dose of THAM acetate 0.3 mol/L to correct acute acidemia in a volume approximating extra cellular space may be estimated as follows:

THAM (ml 0.3 mol/L solution)=lean bodyweight (kg)×base deficit (mmol/L).

The maximum daily dose is 15 mmol/kg for an adult (3.5 L of a 0.3 mol/L solution in a 70 kg patient). In large doses, especially when given rapidly, THAM may induce respiratory depression and hypoglycemia, which will require ventilatory assistance, glucose monitoring and possible supplementation.

When initial organ failure, especially of the heart or lung, results in severe hypercapnic or metabolic acidemia (pH<7.20), the use of THAM within a 'therapeutic window' has proven an effective therapy. It restores the plasma and intracellular pH and corrects the body's own acid-base homeostatic mechanisms. For example, in the treatment of respiratory failure, THAM has been used effectively (6, 7) in conjunction with hypothermia and controlled hypercapnia, Fig. 1.

Other applications of THAM include management of renal acidosis, salicylate intoxication, and increased intracranial pressure associated with cerebral trauma (8). THAM is also used in cardioplegia solutions (9) and in cardiac resuscitation (6). The usefulness of THAM in Infant Respiratory Distress Syndrome (IRDS) and asphyxia neonatorum, documented in the neonatal non-human primate (10), deserves renewed evaluation (11, 12). THAM possesses also non-buffering antioxidant properties which require further investigation, especially in the management of brain injury (13).

In ARDS, THAM-buffer has been successfully used in addition to permissive hypercapnia (7). Permissive hypercapnia may reduce overexpansion of injured lung and THAM minimizes the resulting acidemia. (From our perspective, respiratory depression associ-

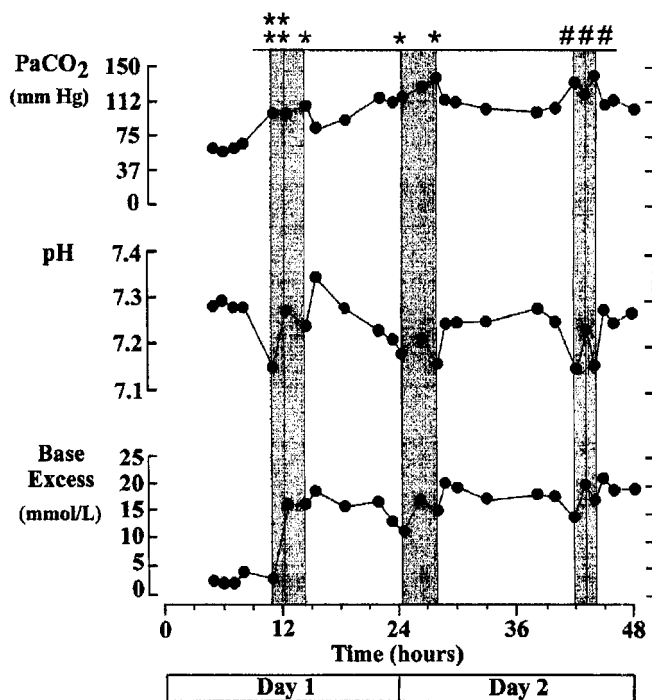


Fig. 1. Administration of THAM in a patient with post-traumatic adult respiratory distress syndrome and pneumonia (7). He was treated with a combination of controlled hypercapnia, hypothermia (35–36°C), chemical paralysis and sedation. In order to maintain the pH of arterial blood at >7.20, a total of 1370 mmol of THAM was administered as either Tribonate 125 mmol (*), Tribonate 250 mmol (**), or Addex 165 mmol (#) over a 2-day period, during the "therapeutic windows" indicated by the shaded areas. Onset of the therapeutic window for THAM administration occurs when the pH decreases to <7.20.

ated with administration of THAM base through a central catheter is not a problem since our patients have ventilator support). The foregoing clinical observations conflict with the conclusions of other authors, who claim that there is no place for THAM in the treatment of acidemia (4, 5).

According to Bleich and Schwartz (4), the use of THAM for pH correction in situations of cardiovascular collapse or severe bronchoconstriction is limited by quantitative considerations which "restrict the potential therapeutic value of tris buffer." It has never been claimed that THAM administration could substitute for CO₂ elimination, but it may over short periods become a significant adjunct to H⁺ buffering and kidney elimination of protonated THAM. In a period of 24 h, the maximal daily dose of 1200 mmol THAM will titrate an equivalent amount of CO₂ or organic acid. In the treatment of metabolic acidosis, Bleich and Schwartz (4) consider that THAM is not of therapeutic value in removing carbon dioxide, particularly "since compensatory hyperventilation ordinarily produces an effective and sustained reduction in PCO₂". This does not apply to patients with respiratory failure or with a reduced cardiac output, which causes venous hypercapnia: while NaHCO₃ worsens venous hypercapnia, THAM corrects this disorder (6).

Thirty-two years later in their review of 1998 on the management of life-threatening acid-base disorders (pH<7.20) (5), Adrogué and Madias repeat the same argument when they write "The use of THAM has been suggested in patients with chronic hypercapnia, because of its 'theoretical' potential to decrease the partial pressure of carbon dioxide. However, this explanation has not been borne out. The resultant decrease in alveolar ventilation worsens hypoxemia and offsets the disposal of carbonic acid that is due to the buffering effect of THAM (5)." Such a statement is incorrect. The buffering of CO₂ by THAM is not theoretical; it is a fact established 40 years ago (2) and the guidelines for its clinical use (6) are being ignored once again by Adrogué and Madias. They nevertheless recognize that "during acute exacerbation of chronic hypercapnia with the patients on a ventilator treatment alkali therapy is indicated, as it is in ventilated patients who have acidemia and severe bronchospasm from any cause, by restoring the responsiveness of the bronchial musculature to beta-adrenergic agonist as well as in patients treated with controlled hyperventilation." However, these authors still reject the use of THAM in such conditions, referring to its alleged toxicity and to the "depression" of alveolar ventilation. How can this happen in patients receiving THAM and who are on controlled mechanical ventilation?

Unfortunately, the opinions of these authors which uncritically duplicate those much earlier expressed (4) appear to have been adopted by many uninformed clinicians. Yet in recommended doses, according to clinical guidelines carefully drawn up (6), THAM can be used safely and effectively to correct acidemia of respiratory or metabolic origin in a transient but effective fashion.

The reviews on THAM published by the New England Journal of Medicine were written by professors of medicine, while the reviews describing the clinical use of this compound were by university anesthesiologists and pharmacologists. Such a different professional orientation might explain some of the discrepancies in the opinions expressed by these reviewers. It is time for a reference journal like the New England Journal of Medicine to consider a multidisciplinary approach to the management of acid-base disorders which will take into account the molecular mechanism of THAM, and HCO₃⁻, and the experience of anesthesiologists.

Conclusion

THAM is a weak base that provides a temporary surrogate buffer to the extracellular fluid, which is effective even when carbon dioxide elimination is impaired. THAM stoichiometrically accepts H⁺, which is excreted by the kidney as R-NH₃⁺. When disturbance of vital functions results in severe acidemia (pHa<7.20), proper use of THAM has proven to be an effective titrating medication. THAM administration may restore the pH of the internal milieu long enough to permit the homeostatic mechanisms of acid-base regulation to assume again their vital function. This treatment should not be withheld from the care of patients who might benefit from its use.

References

1. Holmdahl MH, Hedstrand U, Parrow A, Korkeila J, Telivuo L, Matell G. Association of artificial respiration and THAM in the treatment of status asthmaticus. *Presse Med* 1967; **75**: 957-960.
2. Nahas G. Use of an organic carbon dioxide buffer *in vivo*. *Science* 1959; **129**: 782-783.
3. Nahas G. The pharmacology of THAM. *Pharmacol Rev* 1962; **14**: 447-472.
4. Bleich H, Schwartz W. Tris buffer (Tham): An appraisal of its physiologic effects and clinical usefulness. *N Engl J Med* 1966; **274**: 782-787.
5. Adrogué AJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998; **338**: 26-34.
6. Nahas G, Sutin K, Fermon H, Streat S, Wiklund L, Wahlander S et al. Guidelines for the treatment of acidemia with THAM. *Drugs* 1998; **55**: 181-224.
7. Wetterberg T, Steen S. Combined use of hypothermia and

- buffering in the treatment of critical respiratory failure. *Acta Anaesthesiol Scand* 1992; **36**: 490–494.
8. Wolf A, Levi L, Marmarou A, Ward JD, Muizelaar PJ, Choi S et al. Effect of THAM upon outcome in severe head injury: a randomized prospective clinical trial. *J Neurosurg* 1993; **78**: 54–59.
 9. Fermon C. Buffer capacity of THAM. Use in cardioplegia in Guidelines for the treatment of acidemia with THAM. *Drugs* 1998; **55**: 194–196, 212–214.
 10. Adamsoms Jr K, Behrman R, Dawes G, James L, Koford C. Resuscitation by positive pressure ventilation and tris-hydroxymethylaminomethane of rhesus monkeys asphyxiated at birth. *J Pediatrics* 1964; **65**: 807–818.
 11. Helwig H. *Metabolic effects of Trometamol with special references to pediatrics*. New York: Springer-Verlag, 1974.
 12. Yellin P. Infant Respiratory Distress Syndrome in Guidelines for the treatment of acidemia with THAM. *Drugs* 1998; **55**: 207–211.
 13. Nagao S, Kitaoka T, Fyita K, Kuyama H, Ohkawa M. Effect of tris-(hydroxymethyl)aminomethane on experimental focal cerebral ischemia. *Exp Brain Res* 1996; **111**: 51–56.

Address:
M. H:son Holmdahl
Department of Anaesthesiology and Intensive Care
University Hospital
751 85 Uppsala, Sweden
e-mail: Martin.Holmdahl@anestisi.uu.se