REVIEW ARTICLE

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Guidelines for the Treatment of Acidaemia with THAM

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Contents

Summary

THAM (trometamol; tris-hydroxymethyl aminomethane) 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% ionised) 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 stoichiometric 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 ($paCO_2$). It rapidly distributes through the extracellular space and slowly penetrates the intracellular space, except for erythrocytes and hepatocytes, and it 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 in order to exert its buffering effect, THAM is effective in a closed or semiclosed system, and maintains its buffering power in the presence of hypothermia.

THAM rapidly restores pH and acid-base regulation in acidaemia caused by carbon dioxide retention or metabolic acid accumulation, which have the potential to impair organ function.

Tissue irritation and venous thrombosis at the site of administration occurs with THAM base (pH 10.4) administered through a peripheral or umbilical vein; THAM acetate 0.3 mol/L (pH 8.6) is well tolerated, does not cause tissue or venous irritation and is the only formulation available in the US. In large doses, THAM may induce respiratory depression and hypoglycaemia, which will require ventilatory assistance and glucose administration.

The initial loading dose of THAM acetate 0.3 mol/L in the treatment of acidaemia may be estimated as follows: THAM (ml of 0.3 mol/L solution) = lean bodyweight (kg) × base deficit (mmol/L). The maximum daily dose is 15 mmol/kg for an adult (3.5L of a 0.3 mol/L solution in a 70kg patient).

When disturbances result in severe hypercapnic or metabolic acidaemia, which overwhelms the capacity of normal pH homeostatic mechanisms (pH ≤7.20), the use of THAM within a 'therapeutic window' is an effective therapy. It may restore the pH of the internal milieu, thus permitting the homeostatic mechanisms of acid-base regulation to assume their normal function. In the treatment of respiratory failure, THAM has been used in conjunction with hypother-

mia and controlled hypercapnia. Other indications are diabetic or renal acidosis, salicylate or barbiturate intoxication, and increased intracranial pressure associated with cerebral trauma. THAM is also used in cardioplegic solutions, during liver transplantation and for chemolysis of renal calculi.

THAM administration must follow established guidelines, along with concurrent monitoring of acid-base status (blood gas analysis), ventilation, and plasma electrolytes and glucose.

There are few acid-salt buffer systems suitable for the regulation of pH in the physiological range of 7.3 to 7.5. Bicarbonate has a pK [the pH at which the weak conjugate acid (pKa) or base (pKb) in the solution is 50% ionised] of 6.1, below the physiological range, and should only be used in an open system, which allows carbon dioxide to be eliminated into the atmosphere. It also carries a sodium load in an amount equivalent to the administered bicarbonate.

In 1946, Gomori[1] suggested that THAM [trometamol; tris-hydroxymethyl aminomethane; $(CH_2OH)_3C\text{-}NH_2$] was the most effective amine compound for pH control in the physiological range. It is a white crystalline solid with a molecular weight of 121, is stable at room temperature for periods of up to 12 years, is easily prepared in a pure state and is available as a hydrochloride salt. Its physicochemical properties have been extensively reviewed.[2-4]

The dissociation constant ($K_b \times 10^6$) of THAM in water is 1.202 at 25°C. It is highly soluble in water (550 mg/ml), and has low lipid solubility.[4] The hydrogen atoms of THAM are bonded intramolecularly,[5] which accounts for its high degree of chemical stability.

Since its introduction as an *in vitro* titrating agent in biochemistry, this compound has been referred to by various names (e.g. trometamol, 2-amino-2-hydroxymethyl-1,3-propanediol, tris buffer, tromethamine);[4] THAM, which corresponds to one of its chemical descriptions, has been chosen for this review.

THAM has been widely used in clinical medicine, since its introduction in 1959 as an *in vivo* carbon dioxide buffer.[6] There are over 2000 references to THAM in MEDLINE® from 1966 to 1997, and several hundred articles before 1966. The 0.3 mol/L preparation of THAM base (pH 10.2), first used clinically for the correction of acidaemia, was replaced in the US in 1977 by a 0.3 mol/L solution titrated with acetic acid to pH 8.6 (THAM acetate).

The pharmacological properties of THAM have been extensively reviewed in several comprehensive articles.[7-11] The present review defines general guidelines for the clinical use of THAM, based on past and current literature.

1. Physicochemical Properties and Mechanisms of Action

1.1 Carbon Dioxide Buffering and Proton Acceptance

Pardee[12] and Krebs[13] first reported that *in vitro* carbon dioxide organic buffers can maintain the partial pressure of carbon dioxide in arterial blood ($paCO_2$) constant in the gas phase of a manometer, according to the reaction ($R\text{-}NH_2$ indicates unprotonated THAM and $R\text{-}NH_3^+$ indicates protonated THAM):

$$R\text{-}NH_2 + H_2O + CO_2 \Leftrightarrow R\text{-}NH_3^+ + HCO_3^- \qquad \text{(Eq. 1)}$$

Nahas[14] demonstrated that a similar reaction occurred *in vivo* in a closed system, where the major source of H^+ to be titrated is carbon dioxide, which THAM buffers in generating bicarbonate.

The other source of H^+ in body fluids is that of metabolic acids such as lactic acid, which is titrated by THAM[15] according to the reaction (La^- indicates lactate):

$$R\text{-}NH_2 + H^+ + La^- \Leftrightarrow R\text{-}NH_3^+ + La^- \qquad \text{(Eq. 2)}$$

1.1.1 Buffer Capacity of THAM

The buffer capacity of THAM is described in terms of 'buffer value'.[16] The buffer value or buffering power (β) is the amount of acid or base (mmol) that must be added to 1L of buffered solution to produce a 1-unit decrease or increase, respectively, in pH.[17] For a solution containing several buffers, such as blood, the total buffering power is calculated as the sum of the individual buffer powers.[17]

Jorgensen and Astrup[18] studied the effect of THAM on blood buffering capacity and reported that the addition of ≤50 mmol/L of THAM to plasma did not change the pK value (6.10) of carbonic acid. A buffer is most effective when the solution pH is within 1 pH unit, in either direction, of the buffer pK. The buffering capacity of a solution is determined by the buffer pK (which is a function of temperature), the pH of the buffer solution, and the concentration of the buffer in the solution.

1.1.2 Effects of Temperature on Buffering Capacity

The pK of buffers, and therefore their buffering power, varies with temperature. Cooling increases the pK of water (pKw) and increases the pH of electrochemical equivalence of water [the pH of neutrality (pN), the pH at which the ratio $H^+ : OH^- = 1$]. The pN of water is 6.80 at 37°C and increases to 7.00 at 25°C, an increase of 0.20 units. In a similar fashion, the pK of THAM also increases with cooling. At 37°C, the pK of THAM is 7.82, but increases to 8.08 at 25°C.[8]

The temperature coefficient of THAM is –0.028 pH units/°C, which approximately parallels the temperature-induced changes of the pN of water, the pK of histidine and the pH of blood.[19,20] With cooling, the pK of the α-imidazole group of histidine, the primary blood buffer, increases in parallel with the pK of water.[21] In contrast, with cooling, the pK of bicarbonate and phosphate does not change to the same extent as that of water and their pK values move further away from their buffering range.[21] The buffer capacity of 27 mEq/L of bicarbonate at 27°C is negligible in a closed system and 2 mEq/L/pH unit in an open system (table I).

1.1.3 Buffers in Hypothermic Solutions

Kresh[22] compared the buffering capacity of bicarbonate 27 mmol/L (open system), THAM 27 mmol/L (closed system) and histidine 161 mmol/L (closed system) cardioplegia solutions. (fig. 1). At 27°C and a pH of 8.0, the buffering capacity of the THAM solution was approximately 15 mmol HCl/L/pH unit and that of histidine was approximately 20 mmol HCl/L/pH unit. Thus, at pH 8.0, the buffering capacity of THAM was 75% that of the buffering capacity of histidine, even though it was present at less than 20% the concentration of histidine. This is because the pK of histidine is 6.04,[24] which is much less than that of THAM.

1.2 pH Homeostasis: Bicarbonate and THAM

The reactions of THAM or bicarbonate with a proton can be described by the Henderson-Hasselbach equation.

Table I. Buffer composition of cardioplegic solutions (standardised pH 7.8 at 27°C). Values for buffering capacity of THAM, bicarbonate and histidine were obtained by Kresh et al.[22] Haemoglobin buffering values are estimates based on an analysis by Gunn.[23] The concentrations of the components of the Buckberg solution assume a formula for the crystalloid portion: citrate phosphate dextrose 200ml, THAM acetate 0.3 mol/L 200ml, NaCl (0.2% in 5% dextrose) 500ml, KCl (120 mEq/60ml) 60ml, dextrose (5%) 40ml; this is then diluted 1: 4 with blood from the bypass pump

Buffer	THAM-based blood cardioplegia solution (Buckberg solution)		Histidine crystalloid solution		Bicarbonate solution	
	concentration	capacity (mmol HCl/L/pH unit)	concentration (mmol/L)	capacity (mmol HCl/L/pH unit)	concentration (mmol/L)	capacity (mmol HCl/L/pH unit)
Bicarbonate	16 mmol/L	0; –1.2[a]			27	0; –2[a]
THAM	12 mmol/L	–6.6				
Histidine			161	–20		
Haemoglobin	4.2g/100ml	–8.68				

a Values for: closed system; open system.

For THAM:

$$pH = 7.82 + Log\left(\frac{\text{concentration of } R\text{-}NH_2}{\text{concentration of } R\text{-}NH_3^+}\right) \quad \text{(Eq. 3)}$$

For bicarbonate:

$$pH = 6.1 + Log\left(\frac{HCO_3^-}{0.03 \times paCO_2}\right) \quad \text{(Eq. 4)}$$

1.2.1 The Bicarbonate Buffering System

Elimination of carbon dioxide is the principal mode of acid elimination from the body. The bicarbonate system is responsible for transporting the 15 000 mEq of carbon dioxide generated each day and expired by the lung. In contrast, proton elimination by the kidney amounts to 1 to 2 mEq/kg/day. Bicarbonate functions as a proton shuttle, rather than a blood buffer. The histidine moieties of haemoglobin are the most important blood buffer and represent the primary immediate mechanism by which a continuous source of protons is buffered.

Each ampoule (44.6 mmol) of 7.5% sodium bicarbonate administered intravenously will generate about 1000ml of carbon dioxide gas, which must be eliminated by the lung and necessitates a transient doubling of alveolar ventilation for several minutes in order to prevent hypercapnia.[25] When ventilation or organ perfusion are impaired, and tissue carbon dioxide elimination is decreased, the plasma alkalinising effect of sodium bicarbonate is reduced, and an increase in plasma carbon dioxide will cause an elevation of tissue pCO_2 (partial pressure of carbon dioxide). In the case of lactic acid accumulation and carbon dioxide retention (see section 6.1.3), bicarbonate administration will be ineffective, because of the following reaction:

$H^+ + HCO_3 \Leftrightarrow H_2O + CO_2$ (tissue retention).

1.2.2 Indications for Sodium Bicarbonate

The indications for sodium bicarbonate have been described in several reviews.[25,26] The most important are: (a) replacement of bicarbonate loss secondary to enteric and renal loss; (b) treatment of renal tubular acidosis following renal transplantation; (c) hyperkalaemia;[27-29] and (d) the treatment of tricyclic antidepressant overdose.[30-35]

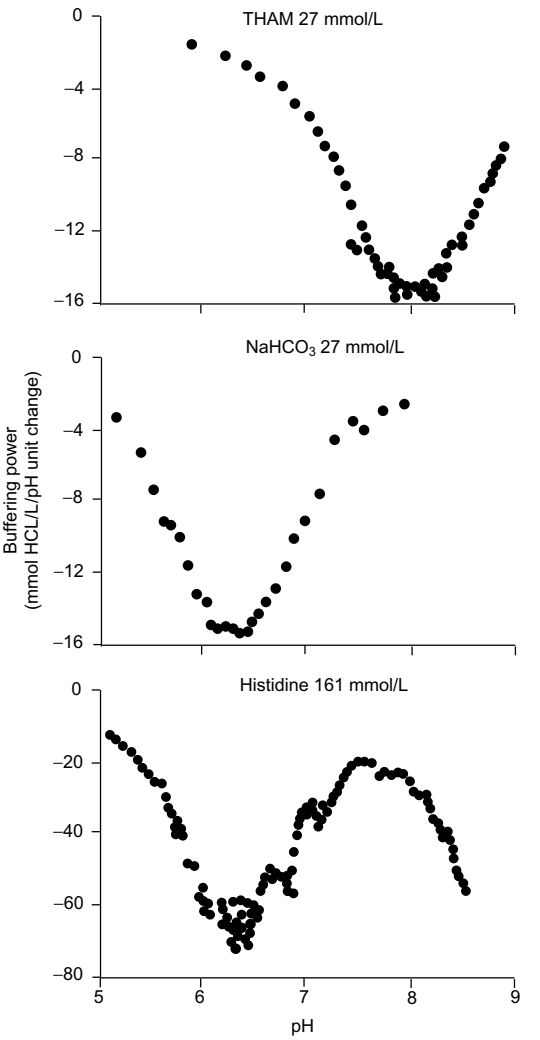

Fig. 1. Relative buffering power (mmol HCl/L/pH unit) at 27°C of THAM (trometamol) [top], sodium bicarbonate ($NaHCO_3$) [constant $paCO_2$] (middle) and histidine (bottom). Note that the concentration of histidine employed was 6 times greater than that of the 2 other buffers (after Kresh,[22] with permission). *Abbreviation:* $paCO_2$ = partial pressure of carbon dioxide in arterial blood.

1.2.3 Adverse Effects of Bicarbonate

The adverse effects of bicarbonate when used to correct acidaemia, especially when carbon dioxide elimination is impaired, include: (a) arterial and, especially, venous hypercarbia and diminished plasma alkalinising effect, when tissue perfusion

or pulmonary ventilation are impaired;[25,36-45] (b) increased myocardial hypercarbia[46] (myocardial acidosis impairs myocardial contractility and cardiac output[36,43,47-50]); (c) myocardial ischaemia in patients with acute heart failure;[37] (d) decreased systemic vascular resistance and coronary artery perfusion pressure, especially during cardiac arrest;[51] (e) decreased systemic oxygen consumption;[37,52] (f) fluid overload in patients with heart failure;[53] (g) hepatic intracellular acidosis;[36,40] (h) increased gut lactate production, decreased hepatic lactate extraction, and an increase in systemic lactate levels;[36,37,40,52-54] (i) decreased partial pressure of oxygen in arterial blood (paO_2),[37,55] and decreased P50 (partial pressure of oxygen at which 50% of haemoglobin is in the form of HbO_2);[37,55] (j) hypernatraemia,[53,56] and increased risk of intracranial haemorrhage in neonates;[53] (k) hyperosmolarity;[51,53] (l) decreased ionised calcium; and (m) paradoxical CSF hypercapnia and acidosis.[57]

1.2.4 THAM as a Surrogate Buffer System During Acidaemia

THAM (in the form of R-NH_2) is a proton acceptor. With a pK of 7.8, it is an effective buffer that helps to maintain the pH of body fluids (see equation 3)

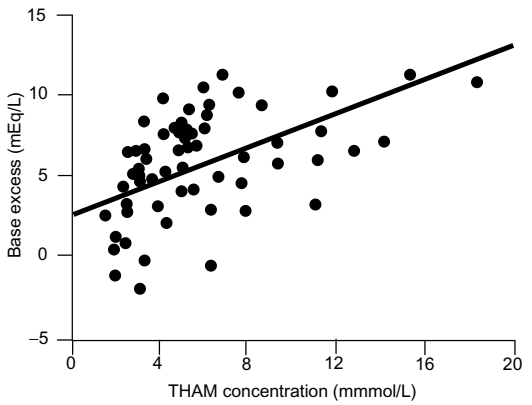

Fig. 2. Relationship between changes in base excess and THAM (trometamol) plasma concentration during experimental hypercapnic controlled ventilation in piglets. During hypercapnia, THAM acetate 0.3 mol/L (1.65 ml/kg/h) maintained normal pH. Base excess and THAM plasma concentration were positively correlated ($r = 0.63$, $p < 0.001$) [from Schneiderman, et al.,[58] with permission]

THAM is a titrating agent in the presence of either a metabolic acid or respiratory acidosis (equations 1 and 2). In the presence of carbon dioxide, THAM will generate bicarbonate (base excess) [fig. 2].

THAM, in the form of R-NH_3^+, is excreted by the kidney, through glomerular filtration, as a nonreabsorbable cation paired with an anion, mainly in the form of bicarbonate, but also with chloride.[58] Thus, THAM will exert an optimal buffering effect when renal function is intact.

1.3 pH Maintenance in Closed Biological Systems

An open buffer system is one in which a member of the buffer pair equilibrates with the environment.[17] In a closed system, stoichiometric buffering of strong acid by bicarbonate yields H_2CO_3, which is not removed by proper aeration so the pH decreases. THAM was first extensively used as a titrating agent *in vitro* in closed or semiclosed biological systems such as enzyme studies,[59] bacteriological media,[60] protozoan nutrition,[61] tissue culture,[62,63] yeast studies,[64] blood coagulation studies,[65] preservation and storage of bovine and human sperm,[66] and *in vitro* fertilisation. THAM is also used *in vivo* as a carbon dioxide buffer in closed biological systems to titrate carbon dioxide production, such as transport of live fish in sealed containers,[67] fluid breathing with hyperbaric saline,[68] or perfluorocarbon,[15,69], total carbon dioxide retention in mammals (section 4.1),[14] and cardioplegia (section 6.3).

1.4 Nontitrating Properties of THAM

Some enzyme-catalysed reactions[57,59,70] are altered *in vitro* by THAM. THAM also reacts with hydroxyl free radicals *in vitro*.[71,72] Trace amounts of THAM are metabolised by oxidation in hepatocytes.[73,74] The interaction of THAM with enzyme systems *in vitro* is limited by its slow intracellular penetration and by the rapid renal excretion of its protonated moiety. Some of these intracellular re-

actions (anti-oxidant) might have a beneficial effect. THAM is effective in preventing cellular damage resulting from hypoxia in liver cells[75] and cerebral tissue.[76,77]

1.5 Methods of Assay

THAM is extremely hydrophilic, not easily extracted from the aqueous phase and not amenable to traditional assay techniques. Current methods of assay include high performance liquid chromatography (HPLC) or gas chromatography,[78-81] and reversed-phase HPLC.[79,81]

2. Pharmacokinetics

2.1 Absorption After Oral Administration

After oral administration, THAM alkalinises body fluids,[82] but it is unpalatable and produces diarrhoea. To improve gastrointestinal tolerability, a THAM citrate solution was designed.[83] In humans, daily administration of THAM citrate syrup 3 to 6 mmol/kg will produce urinary alkalinisation (pH increasing from 5.6-6.8 to 7.2-7.3).[9]

2.2 Distribution

Following an intravenous bolus or short term infusion, THAM rapidly distributes into a volume approximating the extracellular space; at steady-state, it distributes into a volume slightly in excess of total body water.[78,84] THAM penetrates slowly into cells, and intracellular uptake is increased at a more alkaline pH, when more THAM is unprotonated. The α absorption-phase half-life ($t_{½\alpha}$) is 1.2 hours and the β elimination half-life ($t_{½\beta}$) is 5.6 hours (fig. 3).

2.3 Tissue Uptake

THAM equilibrates in an apparent volume of distribution equal to total body water, suggesting intracellular drug penetration and direct intracellular buffering.[8,9,11,84-87] However, renal drug elimination occurs rapidly, in contrast to the slow rate at which THAM permeates most cells:[78,88] 50% equilibrium takes 3 minutes in liver, 170 minutes in spleen, 24 hours for heart and muscle, and over 24 hours for brain. Intracellular uptake is therefore limited to a small fraction of the administered dose.[78,88,89]

The primary mechanism by which THAM produces an immediate intracellular alkalinising effect is the reduction of capillary and interstitial pCO_2, which causes the rapid diffusion of carbon dioxide out of the cell.[86,90,91] This is probably the only significant mechanism by which THAM increases intracellular pH in organs such as the brain, and skeletal or cardiac muscle, into which tissue uptake of THAM is very slow.[88,89]

In humans,[78] erythrocyte concentration peaked 20 minutes after the end of a 30-minute infusion of THAM 1 mmol/kg and remained elevated above plasma concentration. The concentration of intracellular THAM rose more rapidly and reached a higher level at a more alkaline initial plasma pH.

In individuals with normal renal function, most of the buffering effect of THAM will take place in the extracellular space, where THAM acts as a proton acceptor for H_2CO_3 or other acid metabolites. Hepatocytes[88] and, to a lesser extent, erythrocytes,[78] are the only cells in which THAM may exert a significant intracellular buffering effect. In other cells, because of slow intracellular penetration and rapid kidney excretion, THAM exerts minimal buffering effect.

2.4 Metabolism

In dogs administered ^{14}C-labelled THAM, no $^{14}CO_2$ was detected in expired air.[84] In rats administered the same compound, peak $^{14}CO_2$ exhalation was detected within 15 minutes after administration and amounted to 0.12% of the administered dose after 2 hours.[74] Metabolism of THAM appears to be minimal in humans, and only accounts for small fraction of its elimination (≤1%).[78,88,89]

2.5 Renal Excretion

Nahas et al.[92] studied acid excretion in dogs during administration of THAM 0.3 mol/L containing ^{14}C-labelled THAM under conditions of constant carbon dioxide load (apnoeic oxygena-

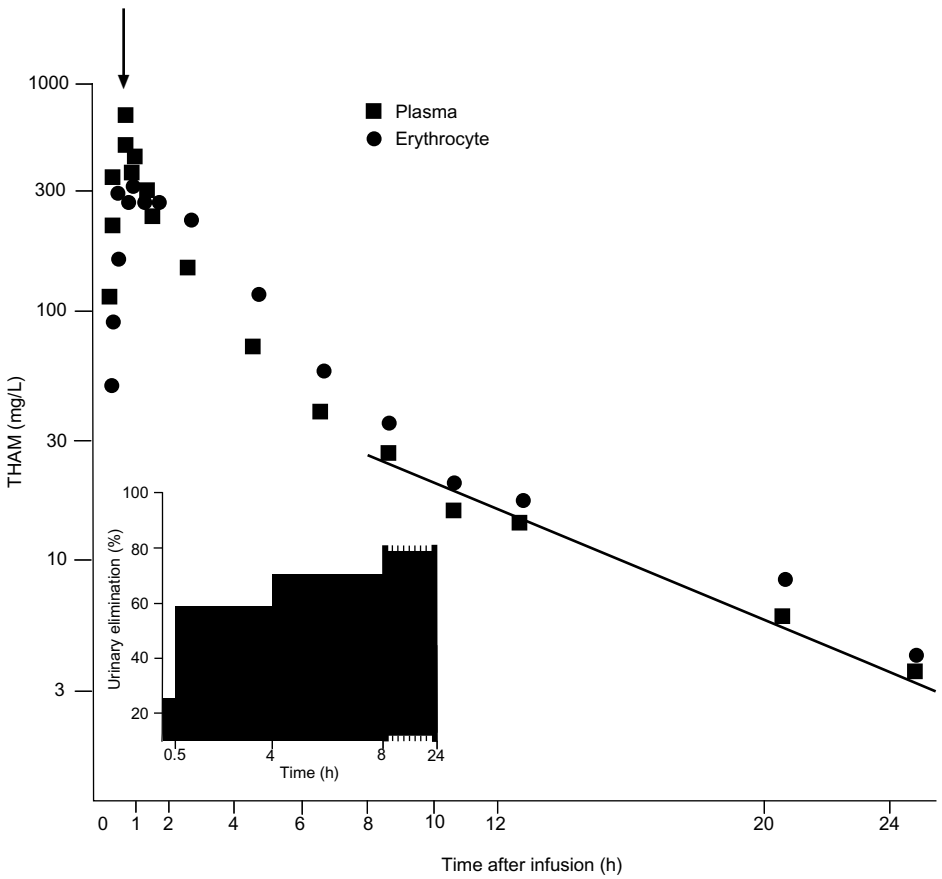

Fig. 3. Time curve of THAM (trometamol) concentration in plasma and erythrocytes in healthy adults, following intravenous administration of THAM 1.0 mmol/kg over 30 minutes. The end of the infusion is indicated by the arrow. THAM was assayed by gas chromatography. The line represents the β elimination from the plasma [half-life ($t_{1/2\beta}$) = 5.6 hours].[78]

tion) and normal blood pH. The osmotic diuretic activity of THAM was apparent because: urine osmolality was close to plasma osmolality; the rate of diuresis and Na^+ excretion were parallel; the rapid elimination of THAM (75% or more after 8 hours) was similar to that of other osmotic diuretics. The administration of THAM during hypercapnic acidosis was accompanied by a marked increase in H^+ excretion, as calculated by following formula:

$$UV_{H^+} = UV_{NH_4^+} + UV_{TA} + UV_{R\text{-}NH_3^+} + UV_{HCO_3^-} \quad \text{(Eq. 5)}$$

where UV = urine concentration × urine volume. *The concentration of R-NH_3^+ in the urine measured with ^{14}C-labelled THAM equalled the cationic deficit calculated in the urine* (fig. 4).

In healthy volunteers[78] administered THAM 0.3 mol/L solution intravenously, 25% of the drug was excreted in the urine within 30 minutes, and 82% after 24 hours. From a 2-compartment pharmacokinetic model, it was estimated that at 24 hours, 97% of the drug was eliminated from the plasma. This discrepancy of 15% at 24 hours could result from tissue binding and/or intracellular uptake of drug. In this study,[78] the clearance of drug

from the plasma (ml/kg/h) was estimated as: 1.02 × creatinine clearance (ml/kg/h) + 16.5 (renal clearance of THAM is 2% greater than that for creatinine).

3. Toxicity

A dose of THAM 3 to 5 mmol/kg administered intravenously to 10 healthy volunteers for 30 to 60 minutes was well tolerated in all instances.[93] Despite a fall in ventilation, increased $paCO_2$ and a decrease in oxygen saturation, no immediate or delayed adverse reaction was noted. An equivalent intravenous dose administered to 3 healthy young men resulted in similar observations.[94] Toxic manifestations were observed after the administration of 8.8 mmol/kg over a period of 60 minutes; these included transient but severe hypoglycaemia, respiratory depression, retching, vomiting and hypotension, which persisted for 24 hours.

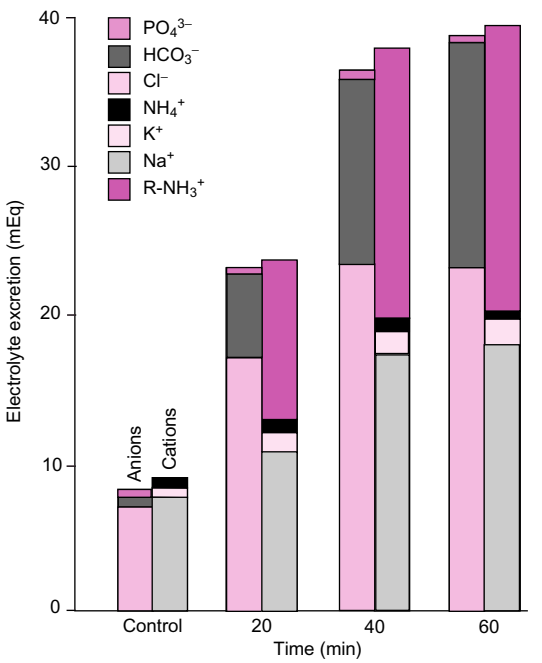

Fig. 4. Urine electrolyte excretion in dogs treated with THAM (trometamol) 0.3 mol/L during one hour of apnoeic oxygenation. Each period indicated represents 20 minutes of collection. The amount of THAM excreted in the urine was measured with ^{14}C-THAM. Most of the THAM excreted is in the protonated ($R\text{-}NH_3^+$) form.[92]

Venospasm of small veins has been reported following administration of THAM base 0.3 mol/L.[82,95,96] Hepatic necrosis has been described in infants given THAM solution (pH 10.2) through umbilical vein catheters.[97] Tissue necrosis was also noted[98] when THAM base was instilled into the urinary bladder. However, neither venous irritation nor tissue necrosis were observed when THAM 0.3 mol/L titrated to pH 8.80 was administered via a peripheral or umbilical vein, or the urinary bladder.[93,99]

4. Effects on Physiological Functions

4.1 Acid-Base Regulation and Electrolyte Balance

4.1.1 Acid-Base Regulation

THAM was first used in a 0.33 mol/L solution as a carbon dioxide buffer *in vivo* to titrate total carbon dioxide retention in the course of 1 hour of apnoeic oxygenation in dogs.[14,100] Arterial blood pH remained constant, bicarbonate level increased, and the untoward effects associated with severe hypercapnia (intracranial hypertension, bradycardia, hypertension followed by circulatory collapse, anuria and elevation of plasma catecholamine levels) did not occur.[101] Up to 28% of the estimated carbon dioxide produced during apnoea was excreted by the kidney, in the form of bicarbonate. It was concluded that a concentration of carbon dioxide over twice its normal level is well tolerated when its 2 fractions, bicarbonate and H_2CO_3, are in suitable proportion to maintain the biological 'neutrality of the internal environment' (see equation 4).[14,102,103]

Besides titrating carbon dioxide during apnoeic oxygenation, THAM also titrates acidaemia produced by infusion of lactic acid.[91,95,104-106]

4.1.2 Electrolyte Balance

During apnoeic oxygenation and THAM administration, the kidney functions as an outlet for protonated THAM. Renal excretion of THAM occurs mostly in the form of $R\text{-}NH_3^+$. As much as

28% of carbon dioxide production may be eliminated by the kidney within 1 hour as bicarbonate,[6,92] paired mostly with protonated THAM ($R\text{-}NH_3^+$) THAM causes a brisk osmotic diuresis with electrolyte loss. Excretion of Na^+ and Cl^- was increased by THAM. Plasma K^+ level remained constant, despite high levels of elimination, indicating a shift of K^+ out of the cells, which, in patients with renal impairment, could result in hyperkalaemia. Plasma osmolality, however, remained constant because of the increase in bicarbonate and the presence of protonated THAM. Osmotic diuresis was protective in a toxic dehydration animal model of acute renal failure.[107]

Hyperkalaemia may occur after rapid correction of severe and prolonged hypercapnic acidosis, as a result of movement of K^+ from cells into the extracellular fluid.[90] After bilateral ureteric ligation in dogs, administration of 18 mmol/kg of THAM 0.3 mol/L was associated with marked hyperkalaemia.[108] Such marked shifts have not been observed during clinical studies,[109] in which the amount of THAM administered was 5 to 8 mmol/kg. Electrolytes may be added to THAM solution (NaCl 30 mEq/L and KCl 5 mEq/L) to compensate for urinary loss.

4.2 Glucose Metabolism

In healthy volunteers, a fall in blood glucose level, associated with a fall in plasma phosphate level, was significant when doses in excess of THAM 500 mg/kg (4 mmol/kg) were administered over 1 hour.[110,111] In experimental studies, the hypoglycaemic activity of THAM was related to its nonprotonated fraction ($R\text{-}NH_2$), which penetrates into intracellular compartments. The hypoglycaemic effect of THAM results from increased insulin release[112-114] and activity.[42,115-116]

4.3 Cardiovascular Function

4.3.1 Myocardial Function

THAM was more effective than sodium bicarbonate or sodium lactate in restoring the myocardial response to catecholamines in dogs.[117-120] Moreover, it appears that intracellular pH is the critical determinant of myocardial performance during derangements of acid-base balance, and that is better maintained with THAM than with bicarbonate.[119] THAM significantly improves contractility and relaxation of the isolated heart impaired by metabolic acidaemia.[121]

Cline et al.[122] studied cardiac conduction in dogs with chronically implanted electrodes. They observed that THAM enhanced conduction through the atrioventricular (AV) node, but slowed conduction in Purkinje tissue and ventricular muscle, while excitability and fibrillation threshold was increased. THAM also abolished tachyarrhythmias induced by ouabain and quinidine intoxication. They concluded that THAM exerts an action on cardiac tissues similar to that of other commonly used antiarrhythmic drugs.

4.3.2 Coronary Circulation

THAM 0.3 mol/L (1.5 mmol/kg) administered to anaesthetised open-chest dogs during acidaemia produced an immediate and marked increase in coronary sinus blood flow and a slight increase in myocardial contractility, with no effect on cardiac output or blood pressure.[123] A rise in pH and a fall in $paCO_2$ of the coronary sinus blood and an increase in coronary oxygen arterial-venous difference were reported. Equivalent amounts of sodium bicarbonate administered in the same situation did not alter coronary sinus flow.

After total venous inflow occlusion, at either 37 or 25°C, dogs treated with THAM were able to tolerate a significantly longer period of circulatory arrest, relative to treatment with saline or bicarbonate solutions, with complete restoration of myocardial activity.[104,124]

4.4 Ventilation

Ventilatory depression associated with THAM has been reported in experimental preparations[116,125-127] and in humans.[128-131] A rapid increase in arterial pH with THAM administration can decrease spontaneous ventilation[130] and result in severe hypoxaemia, as reported in 2 nonventilated patients with cardiogenic shock after myocar-

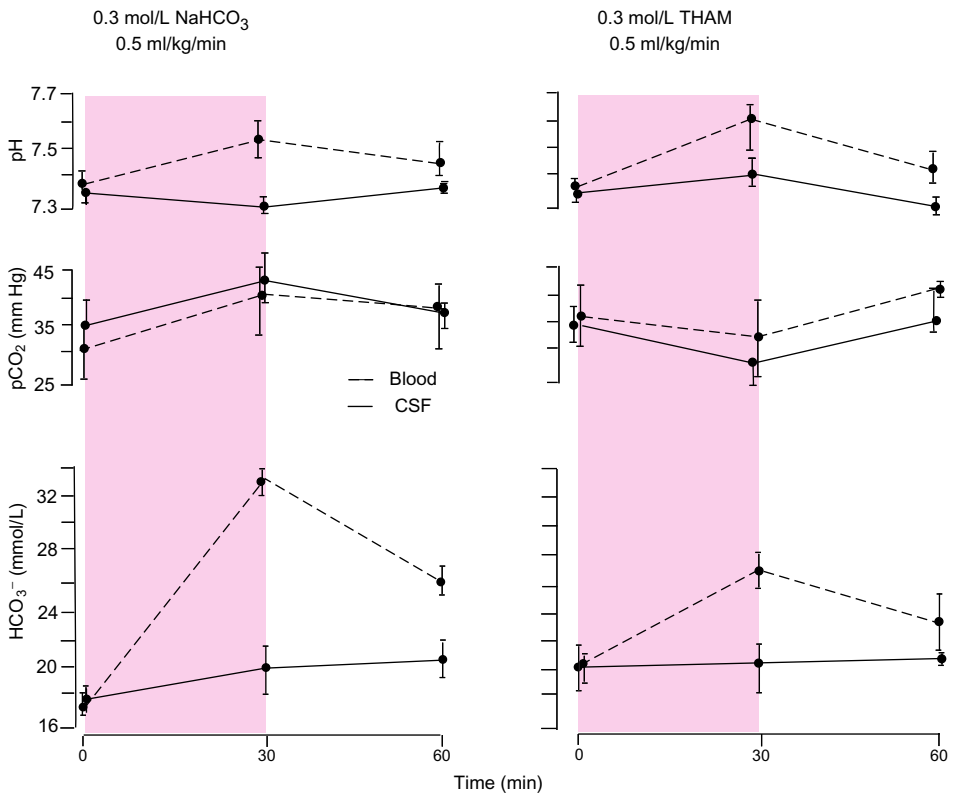

Fig. 5. Acid-base changes in blood and CSF after administration of sodium bicarbonate or THAM (trometamol) in dogs mechanically ventilated at constant volume.[57] Measurements were taken during mechanical ventilation with constant volume. The shaded area indicates the period of buffer administration. *Abbreviation:* pCO_2 = partial pressure of carbon dioxide in blood or CSF.

dial infarction.[132] Respiratory depression is not a concern in mechanically ventilated patients.

4.5 Sympatho-Adrenal System

Hypercapnic acidosis increases plasma catecholamine concentration and blood pressure.[133] Correction of hypercapnic acidosis with THAM rapidly restores plasma catecholamines to normal levels.[134]

4.6 CSF and Cerebral Circulation

Unlike bicarbonate, THAM produces an immediate decrease in the CSF $paCO_2$ (fig. 5) and a rise in pH.[57,135] The administration of THAM also prevents the increase in CSF pressure associated with hypercapnic acidaemia.[114,135,136]

THAM slowly crosses the intact blood-brain barrier to enter the CSF,[84,88,89] but rapidly decreases intracranial pressure (ICP),[57,137] most likely by decreasing $paCO_2$. CSF pH rapidly adjusts to changes in arterial $paCO_2$, but is slower to respond to alterations in arterial bicarbonate levels.[138-140] It is likely that THAM penetrates the traumatically injured, inflamed or disrupted blood-brain barrier faster than when it is intact.

In experimental studies, THAM (0.3 to 0.6 mol/L solution) blunted the increase in ICP induced by inflation of a subdural balloon[135] or blunt head trauma,[141,142] and after cryogenic brain injury.[143]

Table II. Chemical composition of buffer solutions currently in use

Compound/property	Sodium bicarbonate	THAM acetate	THAM E®[a]	Addex®[b]	Tribonate®
THAM base (mmol/L)		300	300	3300	300
Sodium (mmol/L)	892		30		210
Potassium (mmol/L)			5		
Chloride (mmol/L)			35		
Bicarbonate (mmol/L)	892				160
Phosphate (mmol/L)					20
Acetic acid (mmol/L)		100			200
Buffering capacity (mmol/L)	892	300 + 100[c]	300	3300 + 300[c]	460 + 200[c]
pH	7.8	8.6	10.2	9.2	8.1
pK	6.1	7.82	7.82	7.82	7.60
$paCO_2$ (mm Hg)	85				70
Osmolality (mOsm/L)	1800	380	370	650	800
Vial size (ml)	50	500	1000[d]	50	250 or 500
Buffering capacity per vial (mmol/L)	44.6	100	300	3300	165 or 330

a Discontinued in 1977.

b Available in Germany and Sweden. Titrated with hydrochloric acid to pH 9.2. Must be diluted before use.

c After lyophilised THAM E diluted in 1L of water.

Abbreviations: $paCO_2$ = partial pressure of carbon dioxide in arterial blood; pK = the pH at which the weak conjugate acid or base in the solution is 50% ionised.

5. Clinical Management of Acidaemia with THAM

5.1 THAM Preparations for Parenteral Administration

Parenteral THAM solutions (table II) are made from a pharmaceutically pure grade of THAM. The alkalinity of the pure base solution erodes ordinary glass and requires alkaline-resistant glass.

The first preparation available in the US was lyophilised THAM base with electrolytes (THAM E®: Na^+ 30 mEq/L, K^+ 5 mEq/L, Cl^- 35 mEq/L). It was prepared by adding 1 litre of water to THAM-E® 36g to produce a 300 mmol/L THAM solution with a final pH of 10.2. Its use was discontinued in 1977 because of complications related to peripheral intravenous administration (venospasm, phlebothrombosis, hepatic necrosis and soft tissue necrosis following extravasation). THAM base was replaced by THAM 0.3 mol/L titrated with acetic acid to pH 8.6 (THAM acetate), which is well tolerated when administered through a peripheral vein or umbilical artery. *In vivo*, acetate is metabolised by the liver and converted to acetyl coenzyme A in the Krebs cycle, resulting in the removal of a proton.

Addex® solution contains THAM 20g (165 mmol) in a 50ml vial (3300 mmol/L) titrated with hydrochloric acid to a final pH of 9.2. It can be further diluted with different electrolyte or glucose solutions.

Tribonate® contains THAM 300 mmol/L, acetate 200 mmol/L, sodium bicarbonate 160 mmol/L and disodium phosphate 20 mmol/L. It has a final sodium concentration of 210 mmol/L, a pH of 8.1 and an osmolality of 800 mOsm/L.

As described in section 5.3.4, THAM solutions may be added to preparations used for peritoneal dialysis and will cause alkalinisation of the plasma.

5.2 Preparations for Oral Administration

The composition of a preparation of THAM citrate in cherry syrup, suitable for oral administration[83] and urine alkalinisation is shown in table III. Incidentally, a salt of THAM, ketorolac tromethamine, is a nonsteroidal anti-inflammatory drug available for oral or intramuscular administration.

5.3 Mode of Administration and Dosage Guidelines

5.3.1 Acute Intravenous Administration

The THAM acetate solution in common use has a concentration of 0.3 mol/L and is titrated to pH 8.4 with acetic acid. This titrated solution may be safely administered through a peripheral vein. THAM base, pH 10.4, should only be administered through a central venous catheter. The amount of THAM 0.3 mol/L required to correct acidaemia is estimated by an empirical formula, calculated to correct an acid load in a volume exceeding extracellular fluid volume by 10% (30% instead of 20% bodyweight).[9] The same formula is used for THAM acetate.

$$\text{Volume of 0.3 mol/L THAM (ml)} = \text{bodyweight (kg)} \times \text{base deficit (mEq/L)} \quad \text{(Eq. 6)}$$

A loading dose of 25 to 50% of the calculated dose is given intravenously over 5 to 10 minutes, and the balance is administered over 1 hour.

In order to prevent rapid changes in plasma glucose or potassium levels, the rate of THAM administration should not exceed 2 mmol/kg in 30 minutes or 5 mmol/kg in 1 hour (see section 5.4).

5.3.2 Intravenous Administration Over Several Days

THAM has been used in the treatment of adult and infant respiratory distress syndromes, and in the management of increased ICP after trauma, over periods of several days.

The 24-hour dosage of THAM should be limited to 15 mmol/kg or 3.5L of 0.3 mol/L solution in a 50kg adult patient with normal creatinine clearance (see section 5.4).

Table III. Composition of a preparation of THAM citrate in cherry syrup (pH 8.5 at 37°C, 1870 mOsm/L, base equivalent 1.8 mol/L)

Compound	Amount	
	g	mmol
THAM	200	1650
Citric acid	42	220
Ethyl alcohol (as vehicle)	20	–
Water (with cherry syrup, as vehicle)	1000	–

5.3.3 Oral Administration

The daily dose of THAM citrate syrup is 1.5 to 9 mmol/kg of THAM for renal acidosis, adjusted to maintain urinary pH, and from 40 to 80 mmol for chemolysis of renal calculi in 3 or 4 fractionated doses.[83]

5.3.4 Peritoneal Dialysis

Approximately 60% of a THAM 0.15 mol/L dialysate administered into the peritoneal cavity will be absorbed after 1 hour, and it was established that 11 mmol/kg was the maximum amount to be administered in 24 hours.[144] The total amount of THAM to be administered daily in a dialysate containing 150 mmol/L should not exceed 18 mmol/kg/24h or 120 ml/kg/24h of a 0.15 mol/L solution in a 70kg patient.[144]

This volume of dialysate represents 8.4L or 4 exchanges of 2.1L, each of 1 hour's duration. Peritoneal dialysis with THAM has been mostly used for the treatment of intoxication with salicylates, barbiturates and methyl alcohol (methanol) [see section 6.10].

5.4 Monitoring

THAM is primarily eliminated from the plasma by renal filtration of its protonated form.[78] THAM can accumulate in patients with renal insufficiency, and produce an 'osmolar gap' with pseudohyponatraemia. Serial measurements of serum osmolality or THAM concentrations[81] are recommended if therapy lasts for several days, or if renal function is impaired. Renal clearance of THAM is 2% greater than that for creatinine.[78] At steady-state, if there is no drug accumulation, the rate of THAM elimination must equal the rate of THAM infusion (IR_{THAM}).

The steady-state plasma THAM concentration (P_{THAM}) can be estimated from the infusion rate (IR_{THAM}) and the creatinine clearance (CL_{CR}) according to the formula:

$$P_{THAM}\,(\text{mmol/L}) = 16.67 \times \frac{IR_{THAM}\,(\text{mmol/h})}{CL_{CR}\,(\text{ml/min})} \quad \text{(Eq. 7)}$$

Also, for a desired P_{THAM}, it is possible to estimate the desired IR_{THAM}:

$$IR_{THAM}\ (mmol/h) = 0.06 \times CL_{CR}\ (ml/min) \times P_{THAM}\ (mmol/L) \quad \text{(Eq. 8)}$$

It is recommended that plasma THAM concentrations be maintained at ≤6 mmol/L. If the CL_{CR} is 100 ml/min, the maximum THAM infusion rate should be 40 mmol/h to keep the plasma THAM concentration in that range. This would deliver a dosage of 960 mmol/24h, or slightly less than 15 mmol/kg/24h for a 70kg person (which is the maximum recommended daily dosage).

6. Clinical Indications

6.1 Respiratory Failure

6.1.1 Induced Acute Hypercapnia (Apnoeic Oxygenation)

Apnoeic oxygenation was first used in humans during bronchoscopy.[145] In the course of 10 bronchoscopic procedures intravenous THAM 0.3 mol/L (0.53 ml/kg/min or 1.6 mmol/kg/min) was administered to balance carbon dioxide production during 6 minutes of apnoeic oxygenation. Arterial blood pH remained constant during THAM administration, as did blood pressure and heart rate. The amount of THAM infused was slightly greater than that predicted on the basis of the stoichiometric reaction between THAM and carbon dioxide.

These results were duplicated using THAM acetate 0.3 mol/L (pH 8.4) [table IV]. Therapeutic guidelines for the use of THAM during bronchoscopy are as follows.

1. The patient must be completely paralysed and ventilated for 15 minutes with 100% oxygen.

2. Intratracheal insufflation with 100% oxygen at 5 L/min is performed through a catheter or bronchoscope.

3. During apnoea, THAM acetate 0.3 mol/L is administered at a rate of 0.5 ml/kg/min for up to 10 minutes. Beyond that time, the rate of THAM infusion may be reduced by half, not to exceed 2 mmol/kg in 30 minutes or 5 mmol/kg in 1 hour.

THAM administration has been suggested (Streat S, unpublished observations) during the 10 to 15 minutes of apnoeic oxygenation required for organ collection from organ donors, in order to avoid the haemodynamic instability (with hypercapnia-induced hypertension and arrhythmia) that may arise in the course of the procedure.

6.1.2 Status Asthmaticus

Matell[146] and Holmdahl et al.[147] reported the successful management of severe respiratory acidosis associated with status asthmaticus in patients in whom mechanical ventilation was unable to correct hypercapnic acidosis. Previous authors have suggested the use of bicarbonate to correct respiratory acidaemia,[148] but this application is not effective.[44] Treatment of status asthmaticus has been supplemented with THAM acetate 0.3 mol/L in the

Table IV. THAM 0.3 mol/L administration (60 mmol) during a 6-min period of apnoeic oxygenation during bronchoscopy. Note maintenance of pH of arterial blood (pHa) and increase in bicarbonate level (Sutin KM, unpublished observations)

Time (min)	Ventilation mode	Heart rate	Mean arterial pressure (mm Hg)	pHa	$paCO_2$ (mm Hg)	paO_2 (mm Hg)	Plasma bicarbonate (mmol/L)	Base deficit (mmol/L)	Plasma sodium (mmol/L)
–60	Spontaneous, room air	120	93	7.43	38	96	25	0.9	140
–15	Controlled, 100% O_2	102	77	7.42	36	496	23	–1.6	141
0	Apnoeic oxygenation, 100% O_2 at 5 L/min	112	106	7.41	42	489	27	1.8	141
3	Apnoeic oxygenation, 100% O_2 at 5 L/min	102	108	7.40	49	521	30	5.1	136
6	Apnoeic oxygenation, 100% O_2 at 5 L/min	96	85	7.40	50	523	31	6.1	135
7	Controlled, 100% O_2	94	77	NR	NR	NR	NR	NR	NR
9	Controlled, 100% O_2	92	73	7.42	47	529	31	5.9	135
11	Controlled, 100% O_2	94	69	7.42	46	477	30	5.7	138

Abbreviations: NR = data not recorded at this time; $paCO_2$ = partial pressure of carbon dioxide in arterial blood; paO_2 = partial pressure of oxygen in arterial blood.

critical care unit of Auckland Hospital, New Zealand, resulting in an improved rate of survival (Streat S, unpublished observations).

The dose of THAM required is calculated according to the base deficit (equation 6, section 5.3.1). The initial rate of infusion is 8 ml/kg/min for 10 minutes, decreased to 5 ml/kg/min for 2 to 3 hours. The maximum dosage is 15 mmol/kg/24 hours in a patient with normal renal function (see section 5.4).

6.1.3 Respiratory Assistance and Septic Shock

Acidaemia, in the presence of optimal mechanical ventilation, is not uncommon in critically ill patients with sepsis. In the US, there are 500 000 cases of sepsis each year; about 50% of patients develop septic shock, and the mortality rate is 40 to 60%.[149] Supportive care for septic shock includes maintenance of blood pressure, organ perfusion, support of impaired cardiac function and use of measures to ameliorate organ dysfunction, including lung, gut, kidney and heart. Correction of metabolic acidaemia has not been emphasised by many intensive care specialists within the brief 'therapeutic window' available for this therapeutic intervention. The 'therapeutic window' refers to the brief interval during which a patient with life-threatening acidaemia (pH 7.1 to 7.2, $paCO_2$ <35mm Hg, lactic acidaemia >10 mEq/L) may be treated with THAM to transiently or permanently normalise acid-base status.

At the critical care unit of Auckland Hospital, THAM is used to correct severe metabolic acidosis [pH of arterial blood (pHa) 7.1 to 7.2] in patients who have not responded to optimal ventilatory support with mild hypocapnia ($paCO_2$ 30 to 35mm Hg), hypervolaemia and cardiovascular pressor agents.

THAM was administered to 18 of 42 patients with septic shock enrolled in a study of an anti-cytokine monoclonal antibody (median APACHE-II score 23.)[150] In the group of THAM-treated patients, the observed mortality was 40%, significantly lower than the predicted mortality (54%). A solution of THAM acetate 0.3 mol/L (pH 8.4) was administered via a central venous line, with a loading dose of 2 to 4 mmol THAM/kg bodyweight over 20 minutes, followed by a constant infusion of 0.5 to 1 mmol/kg/h for 4 to 10 hours. As a result, increases in arterial pH of 0.05 to 0.15 were observed without increases in $paCO_2$, and there was a brisk diuresis. Cardiovascular response was variable – some patients demonstrated a marked rise in blood pressure with reduction in pressor or inotropic support, some experienced vasodilation and tolerated further blood volume expansion, while others showed no haemodynamic response. Severe cardiac dysfunction with persistent hypotension was the most common cause of death occurring within the first 72 hours after the onset of sepsis.[151] Table V summarises the course of one patient treated with THAM at the intensive care unit of Bellevue Hospital, New York.

6.1.4 Adult Respiratory Distress Syndrome, Controlled Hypercapnia and Hypothermia

Hypercapnia during ventilatory support is uncommon early in the course of septic shock, except when severe adult respiratory distress syndrome (ARDS) is also present. ARDS more often develops following sepsis or another systemic insult, usually in association with other organ failure.[152] Controlled (permissive) hypercapnia,[1] often in conjunction with THAM infusion, has been used in the Auckland Hospital critical care unit for 20 years to treat asthma and ARDS, and results in lower rates of morbidity and mortality (Streat S, unpublished observations).

THAM, unlike bicarbonate, is an effective buffer during hypothermia (section 1.1.3). A 50% reduction in oxygen demand and carbon dioxide production can be expected when body temperature is decreased from 40 to 33°C.[154] Wetterberg et al.[155] reported on the combined use of mechanical ventilation, hypothermia to 33°C, and controlled hypercapnia and buffering with THAM; this pre-

1 Controlled hypercapnia[153] is induced by paralysing the patient and adjusting the ventilator to decrease tidal volume. this lowers inspiratory pressure and minimises the risk of traumatic distension of the lung. $paCO_2$ may increase to 140mm Hg or above, while pHa may decrease to 7.10 to 7.20.

vented the arterial pH falling below 7.16 (fig. 6) Without THAM buffering, it was estimated that the arterial pH would have fallen below 6.95 when the arterial $paCO_2$ reached 140mm Hg.

Hypothermia may also provide cerebral protection against hypoxia.[156] Brain perfusion with THAM through the carotid artery of hypothermic baboons during cardiac arrest prevents structural brain damage and neurological sequelae, which may still occur when bicarbonate is administered.[157] Combined use of buffering with THAM and hypothermia to treat hypercapnic hypoxaemia may complement new ventilatory approaches in ARDS, allowing controlled hypercapnia[154] while limiting reductions in arterial pH.[158]

Reduction of elevated pulmonary vascular resistance by THAM infusion may improve right heart failure. THAM avoids extreme acidaemia during controlled hypercapnia, without increasing carbon dioxide production and promotes extrapulmonary carbon dioxide removal via the kidney.[14]

A 40kg woman with pancreatitis was treated at Bellevue Hospital for severe ARDS. On pressure-control ventilation, with an inspiratory pressure of 25cm H_2O and 5cm H_2O peak end-expiratory pressure, her tidal volume was 200 to 300ml (compliance about 10 ml/cm H_2O). With an inspired fraction of oxygen (FiO_2) of 0.4 to 0.6, paO_2 was maintained between 70 and 80mm Hg. The patient was treated with a combination of controlled hypercapnia ($paCO_2$ 80 to 147mm Hg), mild hypothermia (35 to 36°C), and chemical paralysis and sedation; THAM acetate 0.3 mol/L was infused at a rate of 1 to 2 ml/kg/h to maintain arterial blood pH at ≥7.20. The patient was administered 7.2 to 14.4 mmol/kg/day of THAM acetate for 10 days (total of 15L of THAM acetate solution, or 4600 mmol of buffer) [Wahlander S, unpublished observations].

Table V. THAM acetate 0.3 mol/L administration during a 'therapeutic window' in a patient with sepsis following an intraoperative cardiac arrest. A total of 430 mmol of THAM acetate was administered over 14 hours. Restoration of acid-base balance and cardiac function was observed. The patient was mechanically ventilated. Vasopressors were titrated to maintain a mean arterial blood pressure of 60mm Hg. Note increased plasma sodium level after bicarbonate administration [Sutin KM, unpublished observations]

Time (h)	Therapy/ clinical situation	Stroke volume (ml)	FiO_2	pHa	$paCO_2$ (mm Hg)	paO_2 (mm Hg)	Plasma bicarbonate (mmol/L)	Plasma sodium (mmol/L)	Blood lactate (mmol/L)
Operating Room									
0		NR	0.5	7.05	49	77	14	141	14
3.5	$NaHCO_3$ 89.2 mmol	67	0.5	7.13	31	201	10	146	NR
4.25	$NaHCO_3$ 44.6 mmol	56	0.5	7.12	29	193	9.4	145	NR
5.3	Cardiac arrest	NR	0.5	7.05	47	370	13	150	NR
5.8	Atrial fibrillation	NR	0.5	6.94	53	139	11	149	NR
Recovery Room									
7.5	$NaHCO_3$ 44.6 mmol	22	1.0	7.14	27	255	9.3	148	NR
7.6	Cardioversion	26	1.0	NR	NR	NR	NR	NR	NR
8	$NaHCO_3$ 44.6 mmol	NR	1.0	7.29	24	284	11.4	150	16.5
8.5	THAM 125 mmol	42	1.0	7.34	25	356	13	153	NR
10	THAM 125 mmol	67	1.0	7.38	23	357	13	152	NR
11.8	THAM 15 mmol/h	65	1.0	7.32	34	154	16.4	149	NR
14	THAM 15 mmol/h	71	0.4	7.43	35	90	23	150	10.8
20	THAM 15 mmol/h	86	0.4	7.41	38	76	24	149	9.3
21.3	THAM off	NR	0.4	7.42	38	76	24	148	10.1
26		84	0.4	7.37	44	82	26	147	NR

Abbreviations: FiO2 = fraction of inspired oxygen; NR = data not recorded at this time; $paCO_2$ = partial pressure of carbon dioxide in arterial blood; paO_2 = partial pressure of oxygen in arterial blood; pHa = pH of arterial blood.

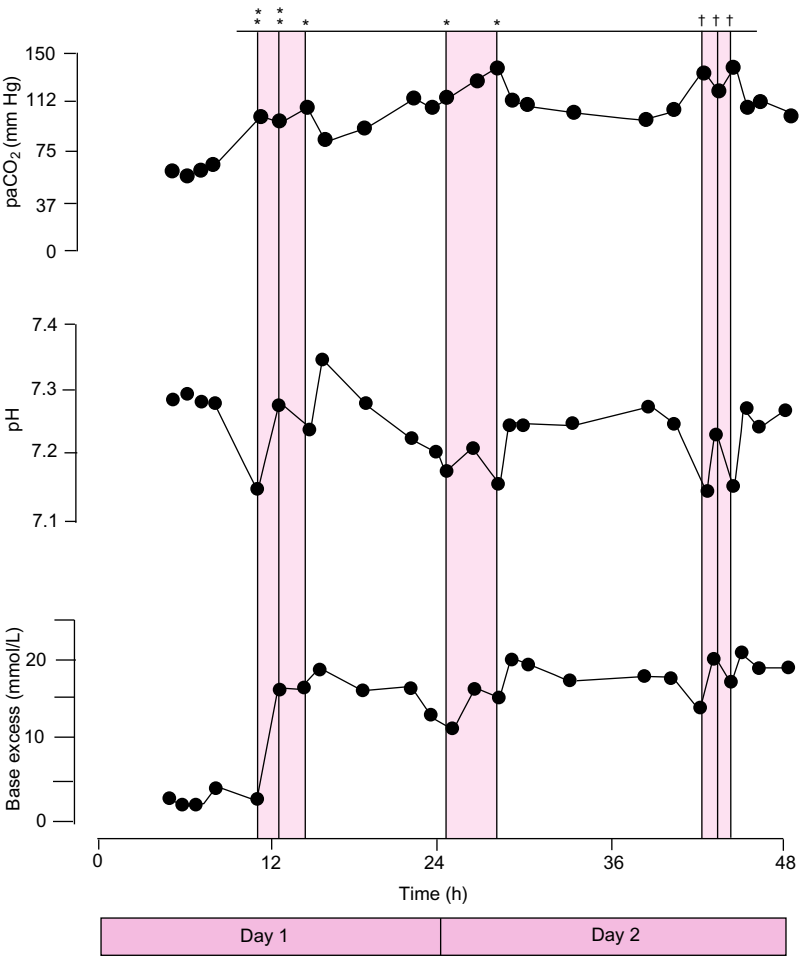

Fig. 6. Administration of THAM (trometamol) in a patient with post-traumatic adult respiratory distress syndrome and pneumonia.[155] He was treated with a combination of controlled hypercapnia, hypothermia (35 to 36°C), chemical paralysis and sedation. In order to maintain the pH of arterial blood at ≥7.20, a total of 1370 mmol of THAM was administered as either Tribonate® 125 mmol (*) or 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. *Abbreviation:* $paCO_2$ = partial pressure of carbon dioxide in arterial blood.

6.1.5 Infant Respiratory Distress Syndrome

The use of THAM in the treatment of asphyxia neonatorum or infant respiratory distress syndrome (IRDS) was one of the first applications suggested after animal studies reported the effectiveness of this carbon dioxide buffer in correcting the hypercapnic acidaemia of apnoeic oxygenation.[14,99,159,160] Experimental studies clearly show the superiority of THAM over bicarbonate in the resuscitation of fetal rhesus monkeys asphyxiated at birth.[99,159,160] The effectiveness of THAM in treating experimental pulmonary hypertension caused by hypoxaemia and acidaemia was striking (fig. 7).

THAM is particularly well suited to the treatment of acidaemia in neonates with respiratory distress syndrome or perinatal asphyxia, because there are usually respiratory and metabolic compo-

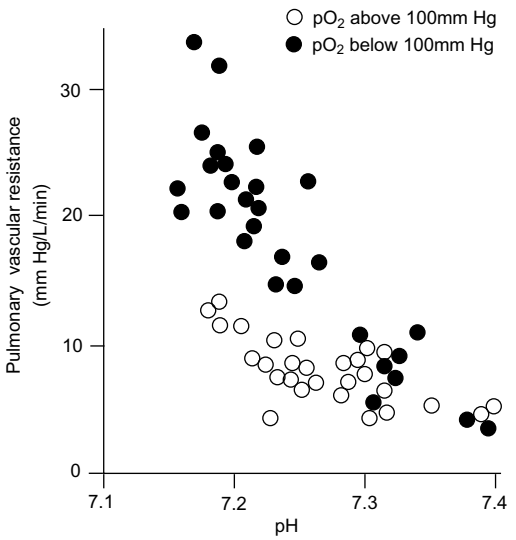

Fig. 7. Response of the pulmonary vasculature to changes in blood pH at different levels of arterial oxygen tension in 4 calves with ligated ductus arteriosus. Blood pH was altered by infusion of either lactic acid or THAM (from Rudolph and Yuan,[161] with permission).

nents.[9,162] In contrast, sodium bicarbonate will worsen hypercapnia in a closed system. Moreover, the use of repeated doses of sodium bicarbonate is limited by the risk of sodium overloading (table V). In addition, bicarbonate may cause CSF hypercarbia, leading to increased cerebral blood volume and intracranial pressure.[139]

Bicarbonate and Its Adverse Effects

Usher [163] described improved survival of infants with IRDS after intravenous bicarbonate and glucose administration. However, the effectiveness of sodium bicarbonate (0.9 mol/L solution) in correcting hypercapnic acidaemia in neonates remains controversial, despite its widespread use. Although one uncontrolled study indicated that earlier correction was more effective than late correction in improving pH, oxygenation and respiratory symptoms,[164] several randomised trials have also failed to demonstrate that sodium bicarbonate therapy is beneficial in the treatment of neonates with perinatal asphyxia or respiratory distress syndrome.[93,165-172] In addition, there have been no randomised trials to assess the efficacy of bicarbonate in the treatment of persistent pulmonary hypertension.

Use of sodium bicarbonate has been associated with adverse consequences, the most serious being the increased incidence of intraventricular haemorrhage in preterm neonates. This complication appears to be associated with the rapid infusion of hyperosmolar solutions, such as the standard paediatric sodium bicarbonate solution (900 mOsm/L). The current recommendations are that bicarbonate be diluted and administered slowly to minimise this problem. Nonetheless, concerns remain over the apparent relationship between bicarbonate treatment and intraventricular haemorrhage.[165,173-178]

When ventilation is restricted, bicarbonate administration is associated with a decrease in CSF pH, and an increase in intracranial pressure,[57] and CSF acidosis, cerebral hypoxia and decreased cerebral blood flow and associated neurological deterioration have been noted.[139,179,180]

The limited evidence for beneficial effects of bicarbonate therapy and the increasing evidence of its adverse effects have raised serious questions concerning its use in neonatal care, and it should be used with extreme caution,[181] if at all.[172]

Use of THAM

In view of the untoward effects of sodium bicarbonate in hypercapnic acidosis, the use of THAM in the management of asphyxia neonatorum and respiratory distress of the newborn should be reconsidered. THAM administration could be performed according to specific guidelines based on experimental and clinical observations.[7,93] The pharmacokinetics of THAM should be studied in neonates, especially in those born prematurely.

In the 1960s, a series of reports confirmed the effectiveness of THAM in the correction of acidaemia in neonates.[93,182] THAM administration corrected acidaemia in 13 infants with IRDS (pH 7.10 to 7.26, $paCO_2$ 56 to 80mm Hg), and resulted in transient or lasting improvement.[183] Gupta[93] reported THAM therapy in 58 infants with IRDS. A

solution of THAM 0.3 mol/L titrated with hydrochloric acid to pH 8.8 was used. An initial dose of 1 ml/kg was administered for each 0.1 of a pH unit below 7.40, at a rate of 1 ml/min. Further doses of THAM were given based on the observed changes in blood gases. Criteria for administration of THAM included arterial pH <7.25, $paCO_2$ >40 and paO_2 <100mm Hg. In most patients with IRDS, THAM administration was associated with a significant, but transient, improvement in pHa and paO_2. However, administration of THAM and correction of acid-base states was not always associated with survival (56% of babies survived) [fig. 8].

The life-threatening IRDS results from the combined failure of the cardiopulmonary system manifested by a deterioration of the vital signs and laboratory evidence of severe acidaemia (pH ≤7.20). Administration of THAM may cause only a transient improvement of acid-base balance, without improvement of the underlying cause or survival of the baby (fig. 8). To prove the benefit of THAM administration, studies similar to those on asphyxiated fetal rhesus monkeys[99,159,160] should be performed. In those randomised studies, infants with IRDS would be randomly treated with THAM, bicarbonate or saline, and the resulting outcomes compared. However, some might question the ethical aspect of such a study, referring to the favourable outcome of asphyxiated rhesus monkeys treated with THAM in contrast to those treated with bicarbonate.

Helwig[9] described the use of THAM acetate 0.3 mol/L in 135 infants with respiratory distress. The dose of THAM was calculated using the formula in equation 6 (section 5.3.1). During the first 2 years in which this study was conducted,[9] the dose of THAM was infused in 5% glucose over 3 to 5 hours. In the third year of the study, the dose was doubled and administered over 2 to 3 hours. The average dose administered was 6.2 ± 2.16 mmol/kg. Measurements of acid-base status were made at least 30 minutes after the end of the THAM infusion. Following the administration of THAM, acid-base status improved, but was not a predictor

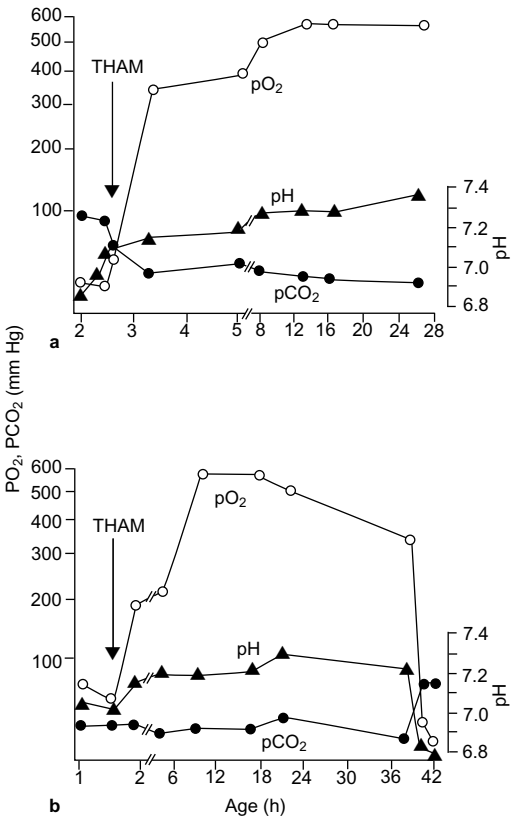

Fig. 8. Change in arterial pH (pHa), partial pressure of carbon dioxide ($paCO_2$) and oxygen (paO_2) in arterial blood, following the administration of THAM (trometamol) [indicated by arrow] in 2 neonates with infant respiratory distress syndrome. A solution of THAM 0.3 mol/L titrated with hydrochloric acid to ph 8.8 was administered at an initial dose of 1 ml/kg for each 0.1 pH unit below 7.40, at a rate of 1 ml/min. Further doses of THAM were administered based on the observed changes in blood gases (arterial blood pH <7.25, paCO2 >40mm Hg, paO_2 indicating 'considerable shunt'). Both neonates were apnoeic, cyanosed and limp at 1 minute after birth, and were intubated and given positive pressure respiration. After THAM administration, a marked improvement in pHa and paO_2 were observed. (**a**) At 2 hours of age, the child was cyanosed with a respiratory rate of 60 breaths/min. Following THAM administration, there was rapid improvement in the infant's condition: he started to cry and became pink, moved all extremities, the sternal retractions ceased and the child survived. (**b**) At 1 hour of age, the child developed respiratory distress with pHa 7.03 and paO_2 51mm Hg. Ten minutes after THAM administration, pHa was 7.13, paO_2 190mm Hg and $paCO_2$ unchanged at 30mm Hg. The child became more active and costal retractions diminished. At age 37 hours, the child became pale and limp, developed several apnoeic episodes and died after a precipitous fall in paO_2 and pHa, which were unaltered by THAM.[93]

Table VI. Average acid-base determination in 5 high-risk premature infants (bodyweight at the time of treatment 730-1540g, age 2-5 days) before and after exchange transfusion with acid citrate dextrose blood titrated with THAM (15 mmol of 0.3 mol/L solution) [from Ornato et al.,[190] with permission]

Parameter	Bank blood		Neonate		
	pre-THAM	post-THAM	pre-exchange	end of exchange	14-15h after exchange
pH	6.70	7.50	7.32	7.38	7.39
$paCO_2$ (mm Hg)	>150	27	74	58	48
Base excess (mEq/L)	–22.0	–5.3	+2.7	+6.0	+4.3
Bicarbonate (mEq/L)		18.4	37.1	34.4	29.3

Abbreviation: $paCO_2$ = partial pressure of carbon dioxide in arterial blood.

of survival, which remained low (26%). Adverse effects, such as ventilatory depression or osmotic diuresis, were related to dose and rate of administration and were not problematical. Helwig[9] concluded that in neonatal respiratory distress, the ultimate response to THAM therapy (in terms of survival) was limited by the severity of the underlying organ failure.

Other applications of THAM in paediatrics include treatment of gastroenteritis,[7,184,185] diabetic ketoacidosis,[7,186,187] renal acidosis,[7,188] and exchange transfusion[189] with acid citrate dextrose blood (table VI).

Reported Adverse Effects

The initial enthusiasm about the use of THAM in paediatric and neonatal care was tempered by reports of significant adverse effects and claims of limited clinical evidence for its superiority over sodium bicarbonate.[191] The most significant complication of THAM was respiratory depression. In one study,[192] hypoventilation or apnoea was observed in 17 of 100 babies who received 10ml of 0.3 mol/L or 0.6 mol/L THAM HCl (pH 8.6) in a single dose (3 to 6 mmol) through the umbilical vein over 2 to 3 minutes. These authors also observed that babies with a history of spontaneous apnoea appeared to have a greater sensitivity to the respiratory depressant effects of THAM. Although it is important for clinicians to be aware of the potential for respiratory depression, it is likely that most patients who require THAM will also require mechanical ventilation and, therefore, respiratory depression can be readily managed.

Other adverse effects associated with THAM have included hypokalaemia and hypoglycaemia, which occurred when THAM was administered either rapidly or in a large dose.[9,11,192,193] Hypoglycaemia was not observed when THAM was administered with 5% glucose.[7,99]

THAM base (pH 10.2) was observed to cause local venous irritation and sclerosis, and tissue infiltration can produce tissue necrosis (see section 3). Hepatic necrosis was observed in several patients who received this solution through umbilical venous catheters.[97] In addition, bladder necrosis was associated with infusion through umbilical arterial catheters.[98] These adverse effects of THAM are related to its alkalinity and hyperosmolality.[194,195] Use of the solution that is buffered to a final pH of 8.6 with acetic acid is not associated with these complications.[7,196]

As a result of these early criticisms, THAM has not been widely used in paediatrics or neonatology in the US. The composition, dosage and mode of administration of THAM were not clearly delineated, and its indications in the overall management of IRDS were not well defined.[182,192,197] In fact, there is little in the recent literature regarding the use of THAM in children, and it is mentioned only briefly, if at all, in most paediatric textbooks. Conversely, the use of sodium bicarbonate remains relatively commonplace, despite the usual concerns about it (see above).

Guidelines for the Use of THAM

Only THAM acetate 0.3 mol/L (pH 8.6) should be used in neonates, since it may be safely administered through a peripheral vein or an umbilical

vessel. Untitrated THAM base (pH 10.2) must not be used.[99] To avoid hypoglycaemia, a solution containing no less than 5% glucose should be administered simultaneously.

Equation 6 (section 5.3.1) may be used to calculate the dosage of THAM to correct acidaemia.[9] For example, a 2.0kg baby with a base deficit of 10 mEq/L should be administered $2.0 \times 10 = 20$ml of THAM 0.3 mol/L solution (6 mmol). A loading dose of 25% of the calculated dose (in this case 5ml), may be administered rapidly over 5 to 10 minutes through an umbilical or peripheral vein. The balance should be given by infusion over 1 hour (in this case, the remainder of the drug should be given at 15 ml/h).

Monitoring of blood gases, plasma electrolytes (especially potassium and glucose) and vital signs is important. The drug should be given only when means for ventilatory support are readily available. If the baby develops signs of ventilatory insufficiency or significant hypercapnia, ventilatory support must be provided as needed. In premature infants, THAM administration should be performed as a slow infusion over an hour.

The maximum daily dose of THAM to be administered to neonates must take renal function into account. In adults, the dosage of THAM is generally limited to 15 mmol/kg per 24 hours. Because the glomerular filtration rate of neonates is one-third to one-half that of the adult, the dosage in neonates with normal renal function should be limited to 5 to 7 mmol/kg/day to prevent drug accumulation.

6.2 Cardiac Failure

6.2.1 Open Heart Surgery

Since the inception of open heart surgery, THAM has been extensively used to titrate the perfusate when ACD blood was used, or to correct acid-base balance following surgery.[123,198-202]

6.2.2 Cardiopulmonary Resuscitation

Cardiac arrest and cardiopulmonary resuscitation (CPR) are associated with severe metabolic acidaemia of vital organs (brain and heart). Correction of acidaemia is recommended in order to promote successful resuscitation.[45,190,203-211]

Only one investigation has shown that the rate of hospital discharge is improved by correction of initial acid-base status with sodium bicarbonate.[205] Instead, restoration of adequate spontaneous circulation is considered the best means of correcting tissue acidosis, and it appears unlikely that sodium bicarbonate contributes to this end.[203] Since the 1980s, the adverse effects of sodium bicarbonate administered in larger amounts have been described (section 1.2.3), and the American Heart Association[212] cautions against systematic administration of sodium bicarbonate during CPR, except in cardiac arrest caused by hyperkalaemia or tricyclic antidepressant overdose. However, in experimental models, benefit from administration of sodium bicarbonate during CPR has been demonstrated[213-216] and no animal study has reported any detrimental outcome with small doses of sodium bicarbonate used in combination with epinephrine (adrenaline). It has also been shown in animals that large doses of sodium bicarbonate used after cardiac arrest impair resuscitation outcome.[211,217]

THAM has been used during CPR, and some authors have preferred this agent to sodium bicarbonate.[87] During cardiac arrest, the positive inotropic effect of THAM on the ischaemic myocardium,[218] and its buffering effect (which is independent of carbon dioxide elimination), contrast with the negative inotropic effect of sodium bicarbonate.[38,219,220]

During cardiac arrest treated with CPR, the effect of buffer administration on the rate of return of spontaneous circulation is marginal.[205,206,210,217] No pharmacological agent can be effective against tissue acidaemia while the total blood flow during closed-chest CPR is reduced to 10% of normal cardiac output.[209] Nevertheless, the rate of return of spontaneous circulation can be improved if arterial pH is kept in the range of 7.20 to 7.55.[205,206,210,216,217] Buffers may improve outcome if excessive acidosis occurs during CPR, in the course of reperfusion, or if arrest is associated

with hyperkalaemia or tricyclic antidepressant overdose.

The available evidence indicates that administration of titrating agents, bicarbonate or THAM, during CPR does not significantly improve outcome.[205-207,210] Such a result is likely because of the very limited perfusion of vital organs during closed-chest cardiac massage and the seriousness of the primary lesion responsible for organ failure. The initial emergency management of CPR does not require the use of titrating agents. However, after restoration of cardiac function, a loading dose of 0.5 mmol/kg of THAM has been advocated, followed by an infusion of 1 mmol/kg with pressor agents over 60 minutes, until pH and $paCO_2$ have been corrected. In this case, the use of a solution containing 600 mOsm of THAM acetate (pH 8.2), such as Tribonate®, has been recommended.[221]

6.3 Cardioplegia in Open Heart Surgery

During cardiopulmonary bypass, coronary blood flow is stopped and the heart is intermittently perfused with cold, hyperkalaemic solutions. Hyperkalaemia produces diastolic arrest and hypothermia decreases metabolic rate. Cardioplegic buffering with either haemoglobin (blood), histidine or THAM improves the tolerance of the heart to prolonged arrest.[222]

Irreversible myocardial injury occurs when the myocardial adenosine triphosphatase (ATP) content decreases by 30% from baseline (to the threshold of irreversible myocardial injury or t-ATP).[223] In normothermic chemically induced cardiac arrest, the t-ATP is reached after approximately 10 minutes. With cold cardioplegia–induced arrest, excitation and contraction are uncoupled, ATP stores are initially preserved, and membrane ATPases are inhibited. In this situation, the t-ATP may not be reached until 120 minutes (at 15°C).[223]

During cardioplegic arrest, anaerobic glycolysis predominates and less ATP is produced per mole of glucose metabolised than during aerobic metabolism.[224] Lactic acid production reduces the intracellular pH (pHi), and will inhibit glycolytic enzymes such as phosphofructokinase.[225] Buffered cardioplegic solutions increase pHi and preserve ATP stores more effectively than nonbuffered solutions.

Buffers used in cardioplegia should have the following characteristics: the buffer pK should be ±1 unit of the pH of the solution being buffered; the cooling-induced changes of the buffer pK should parallel those of the pK of water; the concentration of buffer should be below the toxic level and not alter myocardial function; and the buffer should be effective in a closed system (which approximates the conditions during cardioplegia).[226] Buckberg[226] has suggested that the optimal pH for myocardial metabolism at 28°C is 7.70. THAM fulfils these requirements, whereas at that temperature, bicarbonate has no buffering capacity in a closed system (table II).

Although THAM has been used extensively in humans[9] undergoing extracorporeal circulation, without reported adverse effects, some studies in animals have described a myocardial depressant effect.[24] One *in vitro* study[227] reported a reduced isometric tension in isolated rat aorta and portal vein at THAM concentrations of 5 to 30 mmol/L.[228] Another study showed that THAM inhibited the contractile response of an isolated rabbit heart preparation to vagal stimulation. The clinical significance of these experimental protocols is open to question in view of the well established clinical safety of THAM at recommended doses (section 5.3.1). In addition, several *in vivo* experimental studies have indicated that THAM has a positive cardiac inotropic and haemodynamic effect and improves coronary circulation, especially when given to counteract respiratory or metabolic acidosis.[119,121,123,218]

Used as a cardioplegia additive, THAM may also act as an intracellular buffer.[225] However, the immediate buffering effect of THAM on the myocardium results from its overall lowering of $paCO_2$.

THAM is an excellent buffer for use in cardioplegic solutions[112,226] because its pK is in the correct range to be effective and, with cooling, the change in pK with temperature parallels the change of the pN of water and the pH of physiological

Table VII. Composition of 1L of a blood-based cardioplegia solution used at the New York University Department of Surgery (Spencer, personal communication) before dilution with 4 litres of blood derived from the cardiac bypass circuit. This formula is based on that proposed by Buckberg[226]

Solution	Volume (ml)	Citrate (mmol)	Na^+ (mmol)	Cl^- (mmol)	K^+ (mmol)	Citric acid (mmol)	Dextrose (mmol)	THAM base (mmol)	Acetic acid (mmol)	HPO_4^- (mmol)
Citrate phosphate dextrose	200	20	68	3		3	28			4
5% dextrose in 0.2 NaCl	500		19	19			139			
THAM acetate	200							60	20	
Dextrose 50%	40						111			
Potassium chloride	60			120	120					

solutions. Unlike bicarbonate, THAM is effective in a closed system, and at equimolar concentrations, THAM has a higher buffering capacity than histidine. Moreover, THAM has no toxic effects at the concentrations currently in use (12 mmol/L or less). It has become an important component of the blood-based cardioplegia solutions used at New York University Medical Center (table VII). Vasodilators, such as nitroglycerin (glyceryl trinitrate) or a calcium antagonist, may be added.

6.4 Liver Transplantation

Lactic acidosis is a common and serious complication in patients with end-stage liver disease, and always occurs during the anhepatic and neohepatic phases of liver transplantation. Depending on the severity of the underlying pathophysiology, patients may also have a pre-existing metabolic acidosis (pH <7.35 and base deficit 3 to 7 mmol/L). During the anhepatic phase of liver transplantation, the plasma pH falls and the base deficit frequently exceeds 10 to 12 mmol/L.[229] Correcting the base deficit before unclamping the blood supply to the transplanted liver may help to prevent the complications of reperfusion (hyperkalaemia, metabolic acidosis, and release of myocardial depressant and vasoactive substances from the donor liver). These metabolic derangements may produce hypotension, bradycardia, arrhythmias, vascular collapse or cardiac arrest.[230]

Sodium bicarbonate or sodium dichloroacetate have been used to correct metabolic acidosis before reperfusion of the transplanted liver. However, the efficacy and use of sodium bicarbonate have been challenged (section 1.2.3). A possible advantage of THAM is that it promptly equilibrates with the hepatic intracellular space,[88] where it exerts a buffering effect and may protect hepatocytes against hypoxia.[75,88]

Correction of intraoperative acidosis with bicarbonate in liver transplantation can limit acidosis, but this frequently leads to intraoperative hypercarbia, hypernatraemia and postoperative rebound alkalosis.[231] The hypercarbia may be difficult to treat intraoperatively if there is underlying pulmonary pathology and restricted ventilation caused by the upper abdominal incision. Hypernatraemia related to the sodium load of bicarbonate might burden the kidney and increase the risk of central pontine myelinolysis.[232] Postoperative alkalosis often occurs as the new liver metabolises transfused citrate and residual lactate.

THAM acetate (pH 8.6) was used to control acidaemia in a series of patients undergoing orthotopic liver transplantation at New York University Medical Center. Control of acidaemia, and bicarbonate and Na^+ concentrations, was achieved with no rebound alkalosis and diuresis was well maintained. THAM appears to be an effective and safe titrating agent in the course of liver transplantation.

THAM acetate 0.3 mol/L (pH = 8.6) may be administered to correct base deficit according to equation 6 (section 5.3.1). As THAM is excreted by the kidney, patients with a serum creatinine level of >2.0 mg/dl should be monitored. During the anhepatic phase, THAM is administered at a rate of 2 ml/kg/h when the base deficit is greater

than 3 mmol/kg, and at a rate of 4 ml/kg/h when the base deficit is greater than 6 mmol/kg. The infusion is discontinued after liver reperfusion. Acid-base balance, electrolytes (especially potassium), glucose, lactate concentration and renal function should be monitored.

6.5 Diabetic Ketoacidosis

Management of diabetic ketoacidosis with alkali therapy is controversial. In patients with severe metabolic acidosis (pH <7.10), it might seem appropriate to administer alkali therapy to help correct insulin resistance and prevent secondary complications such as cardiac and neurological dysfunction. However, sodium bicarbonate therapy does not improve recovery from severe ketoacidosis, and reported complications of its use include hypokalaemia, paradoxical cerebral acidosis and cerebral dysfunction.[233-236]

Since the observation[110] that 8.8 mmol/kg of THAM 0.3 mol/L given over 60 minutes could produce a 50% or greater reduction of glucose in healthy men, there has been interest in the use of THAM to treat both acidaemia and hyperglycaemia associated with diabetic ketoacidosis.[7,186,187,237]

Severe acidaemia of diabetic ketoacidosis was transiently corrected by administration of THAM 0.3 mol/L in 10 severely ill patients with severe cardiac and renal failure.[238] Subsequently,[186] THAM 0.3 mol/L (pH 10.2) was administered for the correction of severe ketoacidosis (pH 6.98) in 8 patients with insulin resistance. A dose of 150 mmol (approximately 2 mmol/kg) of THAM 0.3 mol/L was administered with insulin, glucose and saline. Correction of acidaemia was associated with enhanced efficacy of insulin and correction of hyperglycaemia.[239]

The effect of THAM acetate 0.3 mol/L (pH 8.6) in the treatment of diabetic acidosis was studied in 8 children administered an average of 5.6 mmol/kg of THAM. Diabetic acidosis was corrected faster with than without THAM and smaller doses of insulin were required.[7]

For the treatment of severe diabetic ketoacidosis (pH <7.15), in addition to routine measures, THAM acetate 0.3 mol/L (pH = 8.4) may be given at a rate of 0.5 to 1 mmol/kg/h to correct metabolic acidosis. The infusion of THAM should be stopped when the pH exceeds 7.20 and the daily dose of THAM should not exceed 15 mmol/kg. Monitoring of plasma glucose, potassium, calcium and phosphate levels is advisable, and the insulin dose should be titrated. When the plasma glucose falls below 250 to 300 mg/dl (13.8 to 16.5 mmol/L), a 5% dextrose solution is required to prevent hypoglycaemia and cerebral oedema.

6.6 Renal Acidosis

THAM 0.3 mol/L was first administered to 5 patients in the terminal stage of renal failure who presented with significant renal acidaemia.[240] THAM 0.3 mol/L (80 to 300 mmol in dextrose), given over 30 minutes to 24 hours, produced a correction of pH that persisted for 48 hours.

THAM has been used for the symptomatic relief of renal acidosis associated with cystic fibrosis and glomerulonephritis for an average period of 7 months.[188,239] Patients received oral THAM citrate syrup[83] in daily doses amounting to 2 to 7g of THAM equivalent (8 to 35 mmol/kg). This regimen was well tolerated and improved acid-base status while providing symptomatic relief.

THAM has been used to correct renal acidosis.[241] Poli et al.[242] compared intravenous THAM 5.4 g/day (44.6 mmol/day) with intravenous sodium bicarbonate 7.5 g/day (80 mmol/day) in patients with renal acidosis. THAM-treated patients had a more gradual and prolonged correction of acid-base balance. THAM did not alter $paCO_2$, or plasma K^+ and Na^+ concentrations, or significantly change muscle electrolyte concentrations.

THAM acetate (pH 8.6) was administered intravenously to 10 children with renal acidosis,[7] but without renal insufficiency. The daily dose administered varied from 1.5 to 9 mmol/kg. Symptomatic improvement and correction of acidaemia were recorded following THAM administration.

The use of THAM by the intravenous route in renal acidosis might be indicated for symptomatic relief in some patients. Studies on the use of oral THAM citrate syrup[83] for chronic renal tubular acidosis would be useful.

6.7 Severe Burns

In the treatment of patients with burns, the addition of THAM 0.3 mol/L to the fluids administered has restored acid-base balance promoted diuresis, and enhanced excretion of myoglobin.[243,244] The use of THAM might be reinvestigated in the treatment of severe burns requiring correction of acidaemia and maintenance of diuresis.

6.8 Gastroenteritis

70 infants and young children aged 7 days to 16 months, weighing 2 to 10kg who presented with acute gastroenteritis, and an initial arterial pH 7.0 to 7.2, were treated with THAM 0.3 mol/L, diluted in half with saline or 5% glucose.[187] The amount administered was 12 mmol/kg over a period of 1 hour, repeated on the same day and on the following one.

THAM was used to correct acidaemia in 200 children with gastroenteritis.[185] Similar observations[7,184] were reported in the treatment of gastroenteritis of infants and children aged from a few days to 7 years. The dose administered was 21 ml/kg or 6.3 mmol/kg, which resulted in rapid pH correction of arterial blood.

6.9 Brain Injury

6.9.1 Clinical Evidence

Administration of THAM to treat refractory elevations of ICP in patients with traumatic brain swelling produces an immediate decrease in ICP, without changing mean arterial pressure.[142,245] Thus, cerebral perfusion pressure (CPP) is increased.[137] There are, however, only a few prospective investigations comparing THAM with other drugs for the treatment of intracranial hypertension in human head trauma. THAM was at least as effective as mannitol 20% in lowering ICP and stabilising CPP,[245] with a longer-lasting effect. The improvement in the electroencephalogram (EEG), as measured by computerised evaluation, was also observed in animal experiments.[246] Gaab[245] therefore recommended THAM as the treatment of first choice in traumatic brain swelling (e.g. as an alternative to osmotherapy). When used in conjunction with mechanical hyperventilation, THAM limits wide fluctuations of ICP and reduces mannitol requirement, but mean ICP is not reduced.[247,248]

The effects of THAM in lowering increased ICP and its immediate improvement of EEG findings have been attributed to:

- correction of CSF and brain acid-base balance;[136,245,247-249]
- decreased cerebral oedema;[135,137,245,247,249]
- osmotic diuresis;[250]
- reduction in brain injury.[78,251,252]

6.9.2 Patient Selection

THAM may be used in the following indications.

1. Immediate management of head injury: THAM started early in conjunction with conventional therapies may decrease the level and fluctuation of ICP.[141,142,245]

2. Delayed therapy of head injury: in patients with brain oedema and persistently elevated ICP, THAM may be initiated after failure to control ICP despite conventional management with hyperventilation, mannitol and barbiturates.[137,249]

3. Prolonged hyperventilation: THAM has been used in conjunction with prolonged hyperventilation (>12 to 24 hours) to control extreme fluctuation of ICP.[248,253]

6.9.3 Clinical Guidelines

THAM reduces ICP within 20 minutes after initiating therapy.[137] Reduction and stabilisation of ICP is probably the most important therapeutic marker of THAM administration. The specific ICP-lowering effect of THAM is difficult to quantify, since the patient usually receives multiple therapy. Monitoring the transcranial Doppler flow velocity of the middle cerebral artery may be a marker of ICP, as increased flow velocity is asso-

ciated with the presence of intracranial ICP plateau waves, and THAM administration normalises middle cerebral artery flow velocity. In 2 clinical studies,[248,249] a therapeutic goal was to alkalinise the arterial blood to pH 7.60; although it was not achieved, a beneficial effect on ICP control was still observed.

Patients with intracranial pathology who receive THAM should be intubated and maintained on controlled ventilation. THAM acetate 0.3 mol/L solution (pH 8.4) may be infused via a peripheral vein, but THAM base (pH 10.5) should be given through a central line. Pfenninger[137] uses a more concentrated 0.6 mol/L THAM solution (pH 10.4) in 5% glucose via a central line to increase the osmotic effect of the drug and to decrease the volume administered.

Initially, THAM 0.5 to 1 mmol/kg is given over 30 minutes. Treatment may be continued with: (a) continuous infusion at a rate not to exceed 0.3 to 0.6 mmol/kg/h; or (b) intermittent short term infusions given when necessary to correct elevated ICP, at a dose equal to the initial administration. Plasma glucose levels must be monitored and 5% dextrose should be available for concurrent administration. The dosage of THAM should not exceed 15 mmol/kg/day. THAM therapy has been continued for over 5 days to control ICP, with a mixed outcome.

Fluid balance, blood glucose, sodium, potassium levels, and plasma osmolarity (P_{OSM}), should all be monitored. Use of hypertonic THAM solutions may cause transient hyponatraemia. Relative contraindications to the use of THAM include renal dysfunction [glomerular filtration rate (GFR) <40 ml/min], systemic alkalaemia (pH >7.50) and hyperosmolarity (P_{OSM} >340 mOsm/L).

It is best to maintain the plasma THAM concentration below 5 mmol/L, which necessitates monitoring. Plasma THAM concentration may be estimated from THAM infusion rate and CL_{CR}.

Additional experimental studies are required to document the mechanisms of action of THAM in reducing intracranial pressure in brain trauma. The respective contribution of the buffering, metabolic, osmolar and diuretic effects should be investigated in a dose-related fashion to define the most effective THAM solution and protocol for its administration. THAM administration might also be considered in conjunction with hypothermia.

6.10 Intoxications

6.10.1 Clinical Evidence

Alkalinisation of body fluids by sodium bicarbonate administration and, if indicated, hyperventilation is part of the routine treatment of intoxications resulting from the absorption of salicylates, barbiturates, tricyclic antidepressants, chlorpropamide and class IA antiarrhythmics, or ingestion of methyl alcohol (methanol) or ethylene glycol.[93,254] THAM administration is indicated because of its osmotic and diuretic properties, which increase urinary elimination of salts of weak acids, as they are excreted by the kidney after alkalinisation of body fluids.[254-256]

Intravenous THAM administration has been used to treat salicylate poisoning in children.[257,258] Diuresis, urine alkalinisation and marked salicylate elimination were observed. THAM 0.3 mol/L solution was also used to treat patients with phenobarbital (phenobarbitone) intoxication[255,259] and secobarbital overdose.[124,260]

THAM was added to peritoneal dialysates to increase the extraction of salts of weak acids, such as barbiturate,[261,262] salicylate[144] and urates,[263] and following methyl alcohol intoxication.[264] It was significantly more effective in removing pentobarbital, phenobarbital and salicylate than an equimolar concentration of bicarbonate added to the dialysate.[143]

Metabolic acidaemia following ingestion of methyl alcohol (through the formation of formic acid) or ethylene glycol (formic acid and oxalic acid) has been treated with THAM.[264] In methyl alcohol poisoning, THAM increased formic acid elimination and corrected acidaemia (table VIII).[254] THAM has been successfully used in the treatment of ethylene glycol and of diethylene glycol poisoning.[263,265]

Sodium bicarbonate (in hypertonic solution) is an effective antidote to tricyclic antidepressant

overdose and reverses arrhythmias.[30,266] THAM has also been used.

6.10.2 Therapeutic Guidelines

Overdose of salicylates or long-acting barbiturates may be treated with THAM acetate 0.3 mol/L in conjunction with conventional intensive treatment. A urinary pH close to 7.5 is desirable. THAM acetate may be administered over 30 minutes in an initial loading dose as determined by equation 6 (section 5.3.1). Additional THAM is administered at the rate of 1 to 1.7 mmol/kg/h; the daily dose should not exceed 12 mmol/kg. Arterial blood gases, plasma electrolyte levels (especially potassium) and blood glucose level should be monitored.

The use of THAM in the management of other common intoxications (methyl alcohol, ethylene glycol) that are associated with severe acidaemia, may also be considered, either in the form of intravenous administration or with peritoneal dialysis. The effectiveness of THAM in the management of the cardiac complications of quinidine and tricyclic antidepressants requires further investigation.

6.11 Chemolysis of Renal Calculi

6.11.1 Case Reports

The radiographic demonstration of disintegration of a pyeloureteric cystine calculus was first reported[267] in a patient treated with a combination of oral alkalinisation and pelviocaliceal lavage with an alkaline antiseptic solution. Subsequently, oral THAM acetate syrup[83] was used to dissolve uric acid and cystine calculi in patients with lithiasis of the pyeloureteric tract.[268] 40 to 80 mmol/day (6 to 12g/day) of THAM equivalent was administered orally in 4 divided doses over periods of 2 to 4 months, and intermittently over several years as a preventive measure.

The techniques of retrograde ureteric catheterisation or percutaneous nephrostomy were used for pyeloureteric irrigation of cystine stones.[269] THAM E (section 5.1) [pH 10.4] in combination with acetylcystine was the most effective agent for stone dissolution.[269,270] Others[271-276] have reported the use of THAM for the chemolysis of cystine calculi, using the same techniques used for dissolution of uric acid stones.[272,277]

6.11.2 Clinical Guidelines

The irrigation fluid for chemolysis of ureteric or caliceal calculi should contain THAM acetate 0.3 mol/L (pH 8.6) rather than THAM base 0.3 mol/L (pH 10.4), as the latter solution has caused injury to the bladder and ureteric epithelium of rabbits.[15] Perfusion fluid may also contain acetyl cystine and penicillamine, with irrigation pressure not exceeding 25cm H_2O.[273,277]

Table VIII. Laboratory values recorded during the management of a patient with methyl alcohol (methanol) intoxication usign peritoneal dialysis with THAM 60 mEq/L together with intravenous administration (675 mmol over 60h, from hour 1 to hour 60 in column 1) (from Gjessing et al.,[264] with permission)

Time (h)	pH	$paCO_2$ (mm Hg)	Standard bicarbonate (mmol/L)	Serum levels			Blood methyl alcohol level (g/L)	Protein (mg/dl)	Serum creatinine level (mg/dl)	Hct (%)	Urine volume (ml)
				Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)					
0	7.10	26	7	147	5.9	101	2.7	8.5	1.60	55	NR
1	7.20	18	8	NR	NR	NR	NR	NR	NR	NR	NR
4	7.31	22	11.5	NR	NR	NR	NR	NR	NR	NR	1200
12	7.56	26	23	134	3.3	93	2.5	7.2	1.50	50	NR
20	7.51	34	26	NR	NR	NR	2.1	NR	NR	NR	3100
36	7.52	32	25	139	3.9	91	1.0	6.8	2.50	50	NR
48	7.46	35	24	NR	NR	NR	0.8	NR	NR	NR	500
60	7.46	35	24	147	3.7	98	0.5	NR	2.75	NR	1200
84	7.42	34	21	139	3.4	97	0.4	5.9	1.20	44	NR

Abbreviations: Hct = haematocrit; NR = data not recorded at this time; $paCO_2$ = partial pressure of carbon dioxide in arterial blood.

Since renal lithiasis, with cystine or uric acid stones, results from a genetic, metabolic disease, it tends to recur. In this case, the periodic oral use of THAM citrate syrup[83] 5g twice daily to alkalinise the urine could provide a preventive therapy.

6.12 Malignant Hyperthermia

Malignant hyperthermia is triggered by specific drugs (e.g. succinylcholine and fluorinated hydrocarbon anaesthetics) in patients with an inherited myopathy. Its acute onset is marked by a hypermetabolic state, associated with elevated body temperature, metabolic acidosis (base deficit >10 mmol/L) and muscle contractures.[278] In 1973, Bull[279] recommended that the acidaemia be corrected by the administration of either THAM or sodium bicarbonate. It is recommended that after discontinuing trigger anaesthetic agents, therapy for malignant hyperthermia should include administration of dantrolene, 100% oxygen and sodium bicarbonate.[280]

Since large amounts of carbon dioxide are produced by accelerated metabolism, malignant hyperthermia is also associated with an elevated $paCO_2$. The addition of sodium bicarbonate may transiently exacerbate hypercapnia and thus intracellular acidosis. Administration of THAM in amounts required to correct the base deficit would be indicated. While correcting metabolic acidaemia, THAM will also titrate excess carbon dioxide and, because of its diuretic properties, promote excretion of potassium and myoglobin (each vial of dantrolene also contains mannitol to promote diuresis).

7. Conclusion

THAM ($R\text{-}NH_2$) is a weak base that provides a temporary surrogate buffer ($R\text{-}NH_2/R\text{-}NH_3^+$) 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 $R\text{-}NH_3^+$. When disturbance of vital functions results in severe acidaemia (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.

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