Respiratory effects of Tris (THAM) in acidosis and alkalosis

Tris is an effective, safe, rapidly acting amine buffer for the treatment of metabolic and mixed acidosis. It is useful in diminishing cardiac irritability associated with acidosis and in treating acidosis of cardiopulmonary bypass. This study reports the quantitative effects of Tris in 14 normal patients and 13 others with varying degrees of acidosis and alkalosis, primarily metabolic. In patients with a normal resting pH and in those with acidosis, the expected changes of hypoxia, hypoventilation, and hypocapnia appeared. In patients with initial alkalosis, hyperventilation and a tendency to increased pO_2 were common. In the majority of patients, particularly those with stable initial ventilation, controlled, mild alkalosis could be produced and maintained within narrow limits. Control of shifts in pH may be of value in the therapy of cardiac irritability associated with acidosis.

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2-Amino-2-hydroxymethyl-1,3-propanediol (known as Tris buffer or THAM) is an effective, safe, rapidly acting alkaline amine buffer for the treatment of metabolic and mixed acidosis. As described by Moore and Bernhard,[4] it has been used to treat the metabolic acidosis incident to cardiopulmonary bypass. It has also been used to diminish cardiac irritability by Sierra and associates[7] and to treat acute respiratory illnesses in children by Kaplan and colleagues.[3] The absence of the sodium ion makes this buffer a valuable agent in cardiovascular therapy. With the latter in mind, it was thought important to examine the quantitative effects of the intravenous administration of Tris buffer on pH and ventilation.

Material and methods

Subjects selected for this study were male, free from significant cardiovascular disease, but convalescent from peptic ulcer, pneumonia, fractures, pulmonary coin lesions, or acute alcoholism. Peptic ulcer patients on an alkaline regimen tended to have a slightly alkaline resting pH. Patients with coin lesions, or convalescent from pneumonia, had a mildly acid resting pH. Preliminary lung volume studies and blood urea nitrogen determinations were performed, and patients who had grossly abnormal pulmonary and renal function were rejected from the study. Each patient was

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studied 1.5 hours after a light breakfast; a Riley needle (Becton-Dickinson) with a special blood sampling sidearm was inserted in the brachial artery under local anesthesia, and an intravenous drip of 5 per cent glucose in water was inserted in the antecubital vein of the opposite arm. Following heparinization of the patient (100 units per kilogram body weight), an oxygen microelectrode (Beckman) was placed in the Riley needle. The following determinations were performed as control observations and at 5 minute intervals during and after the administration of Tris:arterial pO_2, arterial pCO_2, minute ventilation, and pH. Each liter of ventilation, measured by a dry-gas test meter, was electrically signaled onto a multichannel recorder (Electronics for Medicine, model DR 8). Alveolar air, obtained through a Rahn sampler, was continuously analyzed for pCO_2 by a Godard capnograph. Arterial pO_2 was continuously recorded by means of a Beckman microelectrode and amplifier (Beckman model 160). Samples for pH and arterial pCO_2 were drawn every 3 to 5 minutes from the special sidearm of the Riley needle and analyzed by the micropH method of Andersen.[1] All pH measurements were checked in duplicate.

Actual and standard bicarbonate, buffer base and base excess, and arterial pCO_2 were calculated from pH measurements after equilibration of blood with 4 and 8 per cent carbon dioxide, according to the nomogram of Andersen.[1] The standard errors of the above methods as calculated by Cosby and co-workers[2] were: for minute ventilation ± 100 ml.; for pH ± 0.006 pH units; for arterial pO_2 by means of the oxygen microelectrode ± 1 mm. Hg; and for arterial pCO_2 ± 1 mm. Hg. The coefficient of variation of calculated values taken from the nomogram of Andersen[1] was 1 per cent in each case.

Three hundred milliliters of 0.3M Tris in 0.1M acetic acid* was administered to each of the 25 patients at a rate of 40 ml. per minute. In 7 patients an attempt was also made to maintain the new pH level by continuing the infusion of Tris at a slower rate, 5 ml. per minute, for a period of about 30 minutes.

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Results

Table I illustrates the acute effects of the intravenous injection of Tris in 27 patients. They were divided into 3 groups, depending on resting pH. Those with normal pH control comprised group A; those with resting pH above 7.45 comprised group B; and those with resting pH below 7.35 comprised group C. In the normal group, 14 patients, resting pH ranged from 7.37 to 7.44. The maximum pH shift after Tris varied from 0.027 to 0.140. The expected hypoventilation and arterial hypoxia occurred in every case. Resting arterial pCO_2 was normal in all but one subject. Arterial pCO_2 determinations following the injection of Tris varied, showing a slight decrease in 9 patients and a slight rise in 5. The resting standard bicarbonate was slightly elevated in 2 patients in spite of a normal resting pH, suggesting a mild state of compensated metabolic alkalosis. Increases of standard bicarbonate and buffer base after the Tris injection roughly paralleled changes in pH.

In Table I, group B, 6 of 9 patients whose resting pH was 7.45 or higher had increased ventilation after the injection of Tris. One other patient showed no change in ventilation. In 4 of the 6 patients whose ventilation rose, there was a comparable rise of arterial pO_2. The changes in pH in 2 patients were minimal. Base excess and standard bicarbonate changes were comparable to changes in the normal group. Arterial pCO_2 fell in 7 out of 9 cases, a higher percentage than in the normal group.

Only 4 patients showed arterial pH below 7.35. In general these patients reacted as did the normal group, although there was a greater decrease in ventilation. All had a decrease in arterial pCO_2. Two had

Table IA. *Effect of 300 ml. 0.3M Tris on 14 patients initially having normal pH (control values, maximum change, and per cent change)*

Patient	Resting pH	pH unit change	Arterial pO_2 (mm.)		Arterial pCO_2 (mm.)		Ventilation (L./minute)		Buffer base (mEq./L.)		Buffer excess (mEq./L.)		Standard HCO_3 (mEq./L.)		Actual HCO_3 (mEq./L.)	
			Control	Δ*	Control	Δ	Control	Δ	Control	Δ	Control	Δ	Control	Δ	Control	Δ
		+.060		−18		+ 7		− 2								+ 9.3
C. H.	7.423	(+14%)	84	(−21%)	42.0	(+17%)	3.0	(−67%)							25.7	(+36%)
		+.069		−25		+0.6		− 1.8		+ 7.3	+2.8	+6.4		+ 4.2		+ 3.9
L. P.	7.437	(+16%)	84	(−30%)	36.8	(+ 2%)	4.0	(−45%)	52.9	(+14%)			24.8	(+17%)	23.8	(+16%)
		+.087		− 6		− 1.1		− 1.5		+ 7.0	−0.8	+5.9		+ 4.5		+ 3.9
R. R.	7.408	(+21%)	76	(− 8%)	35.3	(− 3%)	6.0	(−25%)	44.8	(+16%)			22.2	(+20%)	21.4	(+18%)
		+.087		−24		− 2.7		− 1.5		+ 6.3	+3.7	+5.9		+ 4.5		+ 4.2
O. S.	7.398	(+22%)	96	(−25%)	44.9	(− 6%)	4.5	(−33%)	51.4	(+12%)			25.6	(+18%)	26.2	(16%)
		+.027		−36		− 1.1		− 1.5		+ 3.5	+3.7	+1.5		+ 1.2		+ 1.1
R. V.	7.407	(+ 7%)	96	(−38%)	43.3	(− 3%)	4.0	(−38%)	49.8	(+ 7%)			25.6	(+ 5%)	26.2	(+ 4%)
		+.035		−13		+ 0.3		− 3.0		+ 4.2	+2.8	+2.9		+ 2.2		+ 2.3
J. W.	7.418	(+ 8%)	92	(−14%)	39.7	(+ 1%)	5.0	(−60%)	51.0	(+ 8%)			24.8	(+ 9%)	24.7	(+ 9%)
		+.140		−10		− 7.6		0		+ 1.8	−1.0	+7.0		+ 4.9		+ 2.8
L. Mc	7.375	(+37%)	105	(−10%)	39.2	(−19%)	5.0	(0%)	54.9	(+ 3%)			22.3	(+22%)	22.0	(+13%)
		+.031		−18		− 2.0		− 2.0								+ 1.3
C. J.	7.407	(+ 8%)	78	(−23%)	42.0	(− 5%)	5.0	(−40%)							25.2	(+ 5%)
		+.131		− 4		− 6.0		0								+ 4.2
W. M.	7.388	(+34%)	80	(− 5%)	42.0	(−14%)	3.5	(0%)							24.8	(+17%)
		+.035		−23		− 2.7		− 3.0		+ 0.3	−1.8	+1.3		+ 0.9		+ 0.5
B. H.	7.373	(+ 9%)	93	(−25%)	38.9	(− 7%)	7.5	(−40%)	44.2	(+ 1%)			21.6	(+ 4%)	21.3	(+ 2%)
		+.029		−17		+ 3.0		− 2.0		+ 7.3	+0.1	+5.5		+ 4.7		+ 5.6
F. L.	7.379	(+ 8%)	67	(−25%)	40.5	(+ 7%)	5.0	(−40%)	48.0	+15%)			23.0	(+20%)	23.1	(+24%)
		+.072		−13		− 5.8		− 2.5		+ 0.2	+2.0	+3.4		+ 1.6		+ 0.4
L. V.	7.371	(+19%)	75	(−17%)	46.8	(−12%)	5.0	(−30%)	54.8	(+ 4%)			24.2	(+ 7%)	26.3	(+ 2%)
		+.088		− 4		+ 5.0		− 1.3								+ 7.2
S. K.	7.407	(+22%)	76	(− 6%)	37.0	(+14%)	3.0	(−43%)							22.8	(+32%)
		+.062		−17		+ 5.0		− 0.7								+ 3.0
E. N.	7.435	(+14%)	91	(−19%)	43.0	(+12%)	5.0	(−14%)							25.2	(+12%)
Mean	7.402	+.068	85.2	−16.3	40.8	− 0.6	4.7	− 1.6	50.2	+ 4.2	+1.3	+4.4	23.8	+ 3.2	24.2	+ 3.6
S. D.	±.022	±.036	±10.6	± 9.0	±3.2	± 4.4	±1.2	± 0.9	±9.5	± 3.0	±2.2	±2.2	±1.5	± 1.7	±1.6	± 2.5

*Δ = Change.

Table IB. *Effect of 300 ml. 0.3M Tris on 9 patients initially in alkalosis (control values, maximum change, and per cent change)*

Patient	Resting pH	pH unit change	Arterial pO_2 (mm.)		Arterial pCO_2 (mm.)		Ventilation (L./minute)		Buffer base (mEq./L.)		Buffer excess (mEq./L.)		Standard HCO_3 (mEq./L.)		Actual HCO_3 (mEq./L.)	
			Control	Δ*	Control	Δ	Control	Δ	Control	Δ	Control	Δ	Control	Δ	Control	Δ
		+.145		+ 2		−13		+ 0.5								+ 1.0
L. S.	7.513	(+28%)	74	(+ 3%)	46.0	(−28%)	3.0	(+17%)							36.0	(+ 3%)
		.+097		−13		− 1.6		+ 1.0		+ 3.0				+ 3.6		+ 3.7
G. B.	7.494	(+20%)	104	(−13%)	25.8	(− 6%)	3.0	(+33%)	50.4	(+ 6%)	+2.7	+4.6	23.3	(+16%)	19.2	(+19%)
		+.104		+ 4		− 1.4		+ 0.8		+ 3.2				+ 4.5		+ 4.6
A. A.	7.508	(+17%)	76	(+ 5%)	29.8	(− 8%)	5.5	(15%)	51.8	(+ 6%)	+3.1	+5.7	25.1	(+18%)	22.0	(+21%)
		+.015		+ 7		− 4.5		+ 0.5								+ 3.0
F. S.	7.445	(+ 3%)	55	(+13%)	52.0	(− 9%)	7.5	(+ 7%)							36.0	(+ 8%)
		+.018		−19		−10										+ 6.0
F. B.	7.462	(+ 4%)	92	(−21%)	51.0	(−29%)	3.0								35.0	(+17%)
		+.072		−22		+ 2.9		− 3.2		+ 5.5				+ 2.8		+ 3.0
L. W.	7.450	(+15%)	92	(−24%)	27.0	(+11%)	6.5	(−49%)	43.3	(+12%)	+3.0	+3.0	22.2	(+13%)	22.0	(+15%)
		+.035		+ 5		+ 2.1		+ 1.0		+ 6.0				+ 2.4		+ 2.9
H. S.	7.440	(+ 8%)	76	(+ 7%)	35.7	(+ 6%)	5.5	(+18%)	45.0	(+18%)	+2.4	+2.8	23.1	(+10%)	22.3	(+11%)
		+.126		−17		− 5.0		− 1.0								+ 3.5
W. B.	7.523	(+24%)	92	(−19%)	46.0	(−11%)	5.0	(−20%)							37.0	(+ 8%)
		+.107		−16		− 6.2		+ 0.5		+ 4.0				+ 3.0		+ 1.0
A. K.	7.445	(+24%)	100	(−16%)	34.0	(−18%)	9.5	(+ 5%)	49.0	(+ 8%)	+2.8	+2.8	23.6	(+13%)	22.3	(+ 4%)
Mean	7.476	+.080	84.6	− 7.7	38.6	− 4.1	5.4	− 0.1	47.9	+ 4.3	+2.8	+3.8	23.5	+ 3.3	28.0	+ 3.2
S. D.	±.034	±.048	±15.5	±11.8	±10.3	± 5.0	±2.2	± 1.3	±3.6	± 1.4	±0.9	±1.3	±1.1	± 0.8	±7.7	± 1.6

*Δ = Change.

Table IC. *Effect of 300 ml. 0.3M Tris on 4 patients initially in acidosis (control values, maximum change, and per cent change)*

Patient	Resting pH	pH unit change	Arterial pO_2 (mm.)		Arterial pCO_2 (mm.)		Ventilation (L./minute)		Buffer base (mEq./L.)		Buffer excess (mEq./L.)		Standard HCO_3 (mEq./L.)		Actual HCO_3 (mEq./L.)	
			Control	Δ*	Control	Δ	Control	Δ	Control	Δ	Control	Δ	Control	Δ	Control	Δ
		+.008		− 4		− 2.7		− 4.5		+ 0.2				−0.3		− 1.0
C. W.	7.318	(+ 2%)	88	(− 5%)	40.7	(− 7%)	9.0	(−50%)	43.8	(+ 1%)	−4.1	−0.7	20.0	(− 2%)	20.2	(− 5%)
		+.087		−54		− 5.0		− 1.5		+ 2.8				+2.1		+ 0.8
L. G.	7.340	(+23%)	101	(−54%)	39.3	(−13%)	4.0	(−38%)	46.4	(+6%)	−3.3	+3.3	20.7	(+10%)	20.5	(+ 4%)
		+.012		+5		− 7.2		+ 2.5		− 6.9				−2.2		− 3.3
W. W.	7.339	(+ 4%)	96	(+ 5%)	37.9	(−24%)	7.5	(+33%)	46.0	(−15%)	−3.8	−2.9	20.3	(−11%)	19.8	(−17%)
		+.095		−17		− 6.7		− 3.5		+ 5.8				+ 0.8		+ 0.5
O. T.	7.333	(+29%)	62	(−28%)	34.7	(−19%)	5.0	(−70%)	40.3	(+14%)	−5.8	+2.5	19.8	(+ 4%)	17.8	(+ 3%)
Mean	7.333	+.051	86.8	−17.5	38.2	− 5.4	6.4	− 1.8	44.1	+ 0.5	−4.3	+0.6	20.2	+ 0.1	19.6	− 0.8
S. D.	±.010	±.047	±17.4	±25.9	±2.6	±2.0	±2.3	±3.1	±2.8	± 5.5	±1.1	±2.9	±0.4	±1.8	±1.2	±1.9

*Δ = Change.

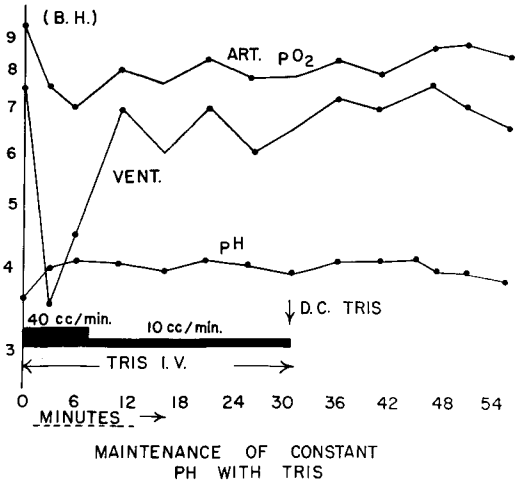

Fig. 1. Maintenance of constant pH with Tris in patient B. H. The three parameters are arterial pO_2 *(ART. pO_2)* measured in millimeters of Hg (initial fall from 92 to 75 mm.), ventilation *(VENT.)* in liters per minute (initial fall from 7.5 to 3.5 L. per minute), and pH expressed by last three digits of actual value (0.360 to 0.400 initial rise).

a decrease in actual and standard bicarbonate, and 2 had minimal pH changes.

The usefulness of Tris in maintaining pH at a given level was examined in 7 patients. Table II, A and Fig. 1 contain all the data collected from a single patient. Table II, B lists the pH data over a 30 to 40 minute period in all these patients. "Zero" time in Table II, B represents the termination of the original 300 ml. injection of Tris, at a flow rate of 40 ml. per minute, and the beginning of the period when Tris injection is slowed to a flow rate of 10 ml. per minute in order to maintain the new pH level. In general, good control of the new pH level was achieved by slowing the injection of Tris. In 3 patients, pH was controlled within ± 0.01.

Discussion

Nahas[6] has recently reviewed the pharmacology of Tris, emphasizing its role as a proton acceptor and its low toxicity. He considered 8.8M per kilogram per hour as being close to a toxic dose. Doses of approximately one-eighth this amount were employed by Moore and Bernhard[4] in cardiopulmonary bypass and were effective in increasing pH from 7.24 to 7.35. No reactions to the intravenous buffer were noted, even though a highly concentrated solution (1.5M) was employed. Kaplan and co-workers[3] found that a similar dose (approximately 350 ml. of 0.3M Tris) relieved acidosis in children with respiratory and mixed acidosis. The maximum dose was approximately 1M of Tris given over a 3 day period (0.5 ml. per kilogram per hour of 0.3M Tris). No toxic side effects were noted. No untoward reactions were noted in our study except for the apnea occasionally observed during injections at the rate of 40 ml. per minute.

Nahas[5, 6] has suggested the possible importance of achieving a frankly alkaline pH in the correction of acidosis. In dogs, during hypercapneic acidosis induced by apneic oxygenation, Nahas[6] found increase in plasma catecholamines in the presence of a constant O_2 uptake, but also found that when blood pH was rapidly changed from 6.44 to 7.52, oxygen uptake increased by 39 per cent and plasma catacholamines returned to normal levels. By the same mechanism, apparently, an infusion of epinephrine increased O_2 uptake when the pH was kept normal or alkaline with Tris. Nahas[6] suggests that a changed physiologic status may be present in the alkalotic patient, i.e., normal blood catecholamines and increased oxygen utilization. Our patients with initial alkalosis appeared to respond to Tris somewhat differently than the normal or acidotic person, particularly in that they maintained or increased ventilation, a finding not previously reported. Whether this phenomenon is related to the changed sympathicoadrenal response suggested by Nahas[6] or simply to a diminished buffering action of Tris in the more alkalotic patient, or whether there is some other explanation, is unclear.

The development of rapid and accurate micromethods of measuring pH and pCO_2[1] has allowed an additional measure of safety during the administration of Tris buffer;

Table II. *Maintenance of constantly elevated pH with Tris*

	Time (minutes)	*pH*	*pO_2 (mm.)*	*pCO_2 (mm.)*	*Ventilation (L./ minute)*	*Buffer base (mEq.)*	*Buffer excess (mEq.)*	*Standard HCO_3 (mEq.)*	*Actual HCO_3 (mEq.)*
				A. Illustrative case					
Control		7.365	93	38.9	7.5	44.2	−1.8	21.6	21.3
Tris (40 ml./ minutes)	3	7.402	76		3.5				
	6	7.408	70		4.5				
	11	7.404	80	36.2	7.0	44.5	−0.5	22.5	21.8
Tris (10 ml./ minutes)	16	7.395	76		6.0				
	21	7.409	83		7.0				
	26	7.403	78		6.0				
	31	7.393	78		6.5				
Tris off	36	7.409	83		7.3				
	41	7.393	79		7.3				
	47	7.394	87		7.5				
	51	7.390	88		7.5				
	56	7.382	84		7.5				
	61	7.381	80	34.7	6.0	43.6	−1.8	21.5	20.4

B. pH values—total group

Before minutes	*L. G.*	*H. S.*	*L. W.*	*L. V.*	*C. W.*	*F. L.*	*B. H.*
0	7.418	7.475	7.539	7.443	7.371	7.442	7.402
5	7.389	7.470	7.529	7.416	7.341	7.454	7.408
10	7.422		7.537	7.401	7.355	7.452	7.404
15		7.465	7.537	7.417		7.438	7.395
20	7.393	7.459	7.525	7.430	7.362		7.409
25	7.411	7.463	7.525				7.403
30		7.463					7.393
35							7.409

Thompson and associates,[8] administering doses of as much as 30 Gm. of Tris in 12 hours (close to a toxic amount), emphasized the value of frequent pH, pCO_2, and buffer-base determinations in dose regulation. By repeating pH determination every 5 minutes it was possible to limit pH shifts within ±0.01 in this series without difficulty in cooperative patients with stable ventilation at rest (Table II, A and B).

Summary and conclusions

1. Tris is an effective, safe, rapidly acting alkaline buffer for the treatment of metabolic and mixed acidosis and is particularly effective when respiration can be controlled to avoid hypoventilation.

2. In the normal group and in patients with an acid pH at rest, Tris usually produces hypoventilation, hypoxia, and often hypocapnia. In patients with an initially alkaline pH, Tris usually produces an increase in ventilation and a rise in arterial pO_2.

3. Dosage of Tris buffer may be adjusted to limit pH changes to within 0.01 to 0.02 in patients who are able to maintain a stable and even ventilation. The ability to produce and maintain controlled mild alkalosis is a valuable technique in the treatment of cardiac irritability.

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