THAM *v.* sodium bicarbonate in idiopathic respiratory distress syndrome*

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van Vliet, P. K. J., and Gupta, J. M. (1973). *Archives of Disease in Childhood*, 48, 249. **THAM *v.* sodium bicarbonate in idiopathic respiratory distress syndrome.** Two buffers (sodium bicarbonate and THAM) were used in a controlled trial for treatment of severe idiopathic respiratory distress syndrome. The results indicate that THAM is marginally superior to sodium bicarbonate. 1 infant died as a result of direct toxic effect of THAM because of inadvertent administration of a hyperosmolar solution of THAM. Blood gas analysis indicated that THAM caused a rise in PO_2 in a number of cases (7 out of 18), and a fall in PCO_2 in 13 out of 21 cases where blood gas determinations had been done before and after treatment. In contrast, bicarbonate caused no change in PO_2 and a rise in PCO_2 in 5 of 16 cases where blood gas determinations had been carried out before and after treatment. Apnoea due to THAM administration was not encountered. The incidence of intraventricular haemorrhage was not different in the 2 groups.

In spite of intensive research over the past 20 years, the aetiology of the idiopathic respiratory distress syndrome (RDS) still remains unknown. However, the pathophysiological disturbances are now well understood. As the condition is self limiting, treatment is aimed at correction of these pathophysiological disturbances (hypoxaemia and acidosis) by the administration of oxygen and buffers. The two commonly used buffers are tris-hydroxymethyl-amino-methane (THAM) and sodium bicarbonate. Theoretically, THAM appears to be superior as it is effective equally in a 'closed' or 'open' system, though it has the disadvantages of causing respiratory depression, hypoglycaemia, and hyperkalaemia (Nahas, 1963; Strauss, 1968). A comparative trial to determine the efficiency of these two buffers in the treatment of severe idiopathic RDS has not been reported. The present study was undertaken to determine which of these two buffers was safer and more valuable in the management of these patients.

Materials and methods

The subjects of this study were treated at the Royal Hospital for Women or the Prince of Wales Hospital. The infants treated at the Royal Hospital for Women were born at that hospital, whereas the infants at the

Prince of Wales Hospital were referred from other centres. The diagnosis of idiopathic RDS was made on clinical signs and symptoms (Gupta, Dahlenburg, and Davis, 1967), and was confirmed by chest x-ray (Donald and Steiner, 1953). Babies who failed to achieve an arterial oxygen tension of more than 100 mmHg in an environmental oxygen of 90 to 100% within the first 12 hours of life were considered to have severe RDS, and were randomly treated with either molar sodium bicarbonate solution or 0.3 molar THAM (3.6% solution). The pH of the THAM solution had been adjusted to approximately 8.7 at 37 °C by admixture with its hydrochloride. The dosages used are shown in Table I. Base therapy was discontinued if the pH was above 7.40.

The average age of entry to the trial of infants born at the Royal Hospital for Women who were treated with sodium bicarbonate and THAM was 7.9 hours (range 4 to 11½ hours) and 6.1 hours (range 4 to 10 hours),

TABLE I
Dosage of $NaHCO_3$ (molar solution) and THAM (0.3 molar solution)

<i>Initial dose (ml)</i>	
$0.3 \times \text{birthweight (kg)} \times 0.5 \text{ base deficit}$	
<i>Followed by</i>	
5 ml/100 ml in i.v. infusion*	if pH 7.31-7.40
10 ml/100 ml in i.v. infusion	if pH 7.21-7.30
15 ml/100 ml in i.v. infusion	if pH 7.11-7.20
20 ml/100 ml in i.v. infusion	if pH 7.01-7.10

*60 ml/kg of 10% dextrose daily.

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TABLE
Complete details of 50 infants treated

Case no.	Apgar score	Sustained spontaneous respiration (min)	Intubated at birth	Birthweight (g)	Gestational age (wk)	Sex	Antenatal factors
<i>Infants treated with THAM</i>							
1	5	2	Yes	1050	28	F	Twin I
2	4	2	Yes	1175	28	F	Twin II
3	7	$\frac{1}{2}$	No	1130	30	M	PRM
4	7	$\frac{1}{2}$	No	1230	29	F	
5	4	4	Yes	1310	29	M	
6	8	$\frac{1}{2}$	No	1500	32	M	Twin I
7	3	stat	No	1575	31	M	Twin I
8	2	10	Yes	1600	35	F	
9	9	15	No	1680	35	F	Twin I; LSCS
10	9	$\frac{1}{2}$	No	1720	35	F	PET
11	8	stat	No	1750	32	M	PRM
12	4	stat	No	1760	32	M	PRM
13	1	6	Yes	1770	32	M	
14	1	7	Yes	1930	31	M	APH
15	9	stat	No	2015	34	M	
16	9	stat	No	2090	33	F	Twin II
17	5	2	No	2275	33	M	APH
18	9	stat	No	2500	38	M	LSCS
19	7	stat	No	2600	37	F	APH
20	9	stat	No	2700	37	M	APH
21	4	10	Yes	2950	34	M	APH
22	1	3	Yes	3160	37	F	APH
23	6	$\frac{1}{2}$	No	3400	39	M	
24	9	stat	No	3640	39	M	APH
25	9	stat	No	2830	37	M	
<i>Infants treated with NaHCO₃</i>							
26	3	7	Yes	1030	29	M	APH; LSCS
27	7	$\frac{1}{2}$	No	1100	32	M	Twin II; breech
28	8	stat	No	1185	30	M	Twin I; breech
29	1	8	Yes	1225	28	M	Prolapsed cord; breech
30	1	10	Yes	1262	28	M	Placenta praevia
31	7	stat	No	1295	32	F	
32	4	2	No	1300	32	M	
33	8	1	No	1410	30	F	PRM
34	4	3	No	1550	31	M	Twin II; breech
35	3	2	No	1715	31	F	Twin II; LSCS; prolapsed cord
36	7	2	No	1720	34	F	
37	10	stat	No	1820	32	F	APH; toxæmia; forceps
38	8	$\frac{1}{2}$	No	1890	31	M	
39	4	5	No	1940	33	F	Twin I
40	5	4	No	2041	34	M	
41	9	5	No	2200	32	M	
42	2	10	No	2200	36	F	
43	8	stat	No	2270	38	F	LSCS
44	5	2	No	2400	36	M	
45	8	stat	No	2440	35	M	
46	6	1	No	2550	36	M	Forceps
47	8	$\frac{1}{2}$	No	2570	35	M	Twin II
48	6	2	No	2560	36	M	
49	7	stat	No	2730	37	M	
50	8	stat	No	3005	38	M	LSCS

*See text.

Note: Blood gases and pH estimations were done in 100% O₂ before the age of 12 hours.

PRM, premature rupture of membranes; LSCS, lower segment caesarian section; PET, pre-eclamptic toxæmia; APH, antepartum haemorrhage; HMD, hyaline membrane disease; IVH, intraventricular haemorrhage; PDA, persistent ductus arteriosus; stat, immediate.

respectively. The corresponding age of entry into the trial of infants admitted to the Prince of Wales Hospital was 8.5 hours (range 7 to 12 hours) and 9.2 hours (range 5 to 12 hours), respectively. No infant had received any base therapy (other than for resuscitation at birth) before admission to the trial.

Blood gases were monitored every 4 to 6 hours for the first 24 to 48 hours, and less frequently thereafter. The arterial blood was either obtained by an indwelling umbilical artery catheter or frequent radial artery punctures. The environmental oxygen was regulated to achieve an arterial Po₂ of 60 to 90 mmHg. In both

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with THAM (25) and NaHCO₃ (25)

PO ₂ (mmHg)	Pco ₂ (mmHg)	pH	Respirator therapy	Outcome	Necropsy findings
89	49	7.09	No	Died (dy 7)	Septicaemia;* lung abscesses
30	62	7.11	Yes	Died (dy 4)	HMD
92	46	7.26		Lived	
53	47	7.24		Died (dy 5)	Haemorrhagic colitis*
59	66	7.13	Yes	Died (dy 16)	IVH organizing*
78	49	7.23	Yes	Died (dy 7)	HMD
52	37	7.31	No	Lived	
87	47	7.22	No	Died (dy 11)	Septicaemia*
48	42	7.28	No	Lived	
59	76	7.03	No	Died (dy 2)	HMD
87	66	7.14	Yes	Died (dy 3)	HMD; pneumothorax
42	80	7.02	No	Lived	
41	86	7.10	Yes	Died (dy 3)	IVH; HMD; pneumothorax
80	68	7.09	No	Lived	
80	40	7.19	No	Lived	
74	43	7.18	No	Lived	
90	63	7.13	Yes	Died (dy 2)	HMD; necrosis of liver, brain, and kidney
43	64	7.05	Yes	Died (dy 3)	HMD
83	46	7.16	No	Lived	
52	43	7.37	Yes	Lived	
20	86	7.02	Yes	Lived	
71	62	7.13	No	Lived	
73	72	7.24	No	Lived	
90	67	7.17	No	Lived	
16	59	7.12	Yes	Lived	
100	41	7.29	Yes	Died (dy 2)	IVH; pulmonary atelectasis; PDA
31	26	7.36	Yes	Died (dy 2)	HMD
54	40	7.15	Yes	Died (dy 2)	HMD; IVH
41	48	7.23	No	Died (dy 2)	HMD
44	73	7.18	No	Died (dy 2)	HMD
60	77	7.24	Yes	Died (dy 3)	HMD
59	80	7.14	Yes	Died (dy 5)	Not done
72	110	6.85	Yes	Lived	
54	54	7.25	Yes	Died (dy 3)	HMD
44	37	7.24	No	Lived	
26	82	6.95	Yes	Lived	
86	24	7.34	No	Died (dy 3)	IVH
51	36	7.25	Yes	Died (dy 3)	HMD; left pneumothorax
86	39	7.27	No	Died (dy 7)	Septicaemia* with multiple abscesses
42	45	7.22	No	Lived	
63	34	7.22	Yes	Lived	
94	—	7.07	Yes	Died (dy 4)	HMD; IVH; PDA
98	52	7.17	No	Died (dy 3)	HMD; left pneumothorax
33	45	7.09	No	Lived	
35	44	7.20	No	Died (dy 2)	HMD
41	52	7.24	No	Lived	
87	35	7.30	No	Lived	
95	46	7.16	Yes	Died (dy 3)	HMD bilateral pneumothorax
46	52	7.14	Yes	Died (dy 3)	HMD; IVH
72	43	7.23	No	Lived	

groups of infants respirator therapy was instituted if the infant failed to maintain adequate ventilation (apnoeic spells not responding to stimulation, arterial Po₂ less than 30 mmHg). All infants were given 10% dextrose intravenously at the rate of 60 ml/kg per 24 hr until oral feeding was started which was usually within

24 to 48 hours of birth. Necropsy was carried out in all but one of the infants who died.

Results

Over a period of 3 years 50 newborn infants

with severe idiopathic respiratory distress were studied. 25 of these infants were treated with sodium bicarbonate and 25 with THAM. The number of infants born at the Royal Hospital for Women, who were treated with sodium bicarbonate and THAM, were 14 and 11, respectively. Table II shows details of the clinical features (Apgar score, onset of spontaneous respiration, resuscitation, birthweight, gestational period, sex, and antenatal factors, blood gas analysis in the first 12 hours in 90 to 100% environmental oxygen, the need for respirator therapy, outcome, and necropsy findings). It will be observed that the 2 groups of infants are similar, i.e. there was no bias regarding clinical features, blood gas analysis, or the institution of respirator therapy. These parameters are summarized in Tables III, IV, V, VI, and VII.

TABLE III
Distribution of birthweight of two groups

Birthweight (g)	1001-1500	1501-2000	2001-2500	>2500	Total
THAM treated	6	8	4	7	25
NaHCO ₃ treated	8	6	6	5	25

$\chi^2 = 0.653$ for 3 degrees of freedom, $0.9 > P > 0.7$.

TABLE IV
Distribution of gestational age of two groups

Gestational age (wk)	<30	30-31	32-33	34-35	36-37	>37	Total
THAM treated	4	3	6	5	4	3	25
NaHCO ₃ treated	3	5	6	4	5	2	25

$\chi^2 = 1.256$ for 3 degrees of freedom, $0.9 > P > 0.7$.

TABLE V
Distribution by sex in two groups

	Females	Males
THAM treated	9	16
NaHCO ₃ treated	8	17

$\chi^2 = 0.089$ for one degree of freedom, $0.9 > P > 0.7$.

TABLE VI
Initial blood gases and pH in two groups

Group	Pao ₂ (mmHg)	Paco ₂ (mmHg)	pH
THAM treated	64	59	7.16
NaHCO ₃ treated	61	49	7.17

TABLE VII
Outcome of respirator therapy in two groups

Group	Lived	Died
THAM treated	4*	6
NaHCO ₃ treated	3	10

$\chi^2 = 1.53$ for one degree of freedom, $0.3 > P > 0.1$.

*One of these infants died later from an unrelated cause (see Table II and text).

Of the babies treated with THAM, 14 survived. Of the 11 infants who died, death was due to respiratory insufficiency in 7. The other 4 had recovered from their respiratory problems (as determined by clinical features and blood gas analysis), and in 2 of those death was due to septicaemia. In the third, death occurred after an exchange transfusion and necropsy revealed haemorrhagic colitis, and the fourth who died (aged 2 weeks) was found at necropsy to have an organizing intraventricular haemorrhage. It therefore appears that 18 infants in the THAM-treated group recovered from their respiratory problems. In the infants treated with sodium bicarbonate, 15 died from respiratory insufficiency: death occurred in 1 as a result of septicaemia. These results are presented in Tables VIII and IX which show

TABLE VIII
Primary cause of death found at necropsy

Cause of death	THAM treated	NaHCO ₃ treated
Intraventricular haemorrhage	2*	5†
Respiratory insufficiency due to pneumothorax and HMD*	2	3
Respiratory insufficiency due to HMD*	4	6
Septicaemia	2	1
Bowel perforation	1	—

*Includes 1 infant who also had respiratory insufficiency due to HMD.

†These infants also had respiratory insufficiency due to HMD. HMD, hyaline membrane disease.

TABLE IX
Outcome of treatment in the two groups

Group	Recovered from respiratory distress	Died from respiratory distress
THAM treated	18*	7
NaHCO ₃ treated	10†	15

$\chi^2 = 5.2$ for one degree of freedom, $0.05 > P > 0.02$.

*Includes 4 infants who died from other causes.

†Includes 1 infant who died from another cause.

that recovery from severe RDS was significantly better in the THAM-treated group. However, if one considers mortality irrespective of the cause of death in both groups, there is no significant difference in survival rate.

We analysed our results in relation to birthweight categories, namely 1001 to 1500 g, 1501 to 2000 g, 2001 to 2500 g, and more than 2500 g. The recovery rate of each of these weight groups is shown in Table X. It will be noted that more of the babies

TABLE X
Birthweight of infants who recovered

Birthweight	1001–1500	1501–2000	2001–2500	> 2500	Total
THAM treated	4	5	2	7	18
NaHCO ₃ treated	1	3	3	3	10

under 2000 g treated with THAM (9 out of 14) recovered than of those treated with sodium bicarbonate (4 out of 14 recovered). However, the difference was statistically not significant ($\chi^2 = 3.59$). There were 33 male and 17 female infants in this trial. There was no difference in distribution and survival rate of the two sexes in the various weight groups. As indicated earlier, some of the babies were offered ventilatory assistance. Table VII shows the number of infants who received ventilatory assistance in each group and the outcome. Once more there was no bias, and the survival rate in the 2 groups that received ventilatory assistance is not different.

Discussion

The severity of idiopathic respiratory distress is variable. The condition may be transitory (Sundell *et al.*, 1971), the infant in such cases recovering within 24 to 36 hours; or mild, where the infant requires small amounts of added oxygen for 3 to 4 days; or severe, in which case the infant progressively requires increasing amounts of oxygen and, in spite of intensive alkali therapy, may continue to develop progressive respiratory failure. It is, therefore, not surprising that in a disease of such variability, various treatments have been instituted (Usher, 1963; Troelstra *et al.*, 1964; *Lancet*, 1964; Hutchison *et al.*, 1962) and success has been reported with each form of treatment. Treatment with oxygen and alkalis (Usher, 1963; Troelstra, *et al.*, 1964) appears to be rational because it corrects the basic pathophysiological disturbances. Boston, Geller, and Smith (1966) have shown that infants

who fail to achieve arterial oxygen tension of more than 100 mmHg in an environmental oxygen of 90 to 100% have a mortality rate of 81%. The mortality rate in the group treated with sodium bicarbonate in our trial was 64% and compares favourably with the report of Boston *et al.* (1966). However, this favourable comparison is not surprising as we were using respirators in addition to oxygen and bicarbonate in the management of these patients. In contrast, the mortality rate from the disease in the THAM-treated group was 28% though, as emphasized earlier, 4 of these infants died subsequently due to unrelated conditions. Troelstra *et al.* (1964) reported a mortality rate of 43% in babies with severe idiopathic RDS who were treated with THAM (but their criteria for the diagnosis of severe RDS are not clear). It appears that the use of THAM in the management of severe idiopathic RDS is to be preferred to sodium bicarbonate.

Ventilatory assistance was given to 13 of the 25 babies who were treated with sodium bicarbonate and 10 of the 25 THAM-treated babies. Of these there were 3 survivors in the group treated with sodium bicarbonate as compared to 4 treated with THAM. There was no bias in regard to ventilatory assistance offered in each group of babies. It is interesting to note that if the respiratory assistance had been withheld in both groups, and assuming that all of the survivors would have died, the mortality in the 2 groups of patients approaches that of Boston *et al.* (1966) and Troelstra *et al.* (1964), respectively.

Detailed analysis of the trial reported in this paper and a critical appraisal of the data presented in Table II suggest that the 2 groups are not comparable in regard to PCO_2 (13 infants in the bicarbonate-treated group had a PCO_2 of less than 45 mmHg compared to 5 in the THAM-treated group), pH (11 infants had a pH of less than 7.20 in the bicarbonate-treated group compared to 17 infants in the THAM-treated group), and the amount of base given (molar bicarbonate compared to 0.3 molar THAM). It is obvious that the THAM-treated group was heavily weighted against in terms of severity of the illness (if one accepts PCO_2 and pH as criteria of severity of illness), yet the amount of base given was less than bicarbonate. We have purposely not taken these factors into account in the final assessment of our results because we regard pH and PCO_2 as poor indicators of the final outcome. Ostrea and Odell (1972) have drawn attention to the deleterious effects of molar bicarbonate in a 'closed system', and it might be argued that the better results obtained

in the THAM-treated group may be due to the deleterious effects of molar bicarbonate rather than the benefit of THAM.

THAM is known to cause respiratory depression in experimental animals. Robertson (1970) reported the occurrence of apnoeic spells within 2 minutes of administering THAM to newborn infants. On the other hand, Gupta *et al.* (1967) encountered this problem in only 1 case. As Robertson has indicated, the explanation may lie in the fact that, whereas Gupta *et al.* (1967) used 0.3 molar THAM, some of his patients received a solution that was of much higher concentration. In our series of 25 patients we did not encounter this problem, and this is mainly related to the method of administration and concentration of solution of THAM (see above). We would also like to emphasize that we did not observe any changes in respiratory rate or respiratory excursion soon after administering the initial dose of THAM.

Robertson (1970) has suggested that THAM might have caused an increase in death rate in his series by causing apnoea either directly or by increasing the intraventricular haemorrhage rate. Table VIII shows the necropsy findings in the 22 out of 23 infants who died. Our results strongly suggest that there is no increase in the incidence of intraventricular haemorrhage in babies treated with THAM. Death was directly attributed to the administration of THAM in 1 infant who was inadvertently given a solution of 1.5 molar (18%) THAM. The cause of death in this infant was haemorrhagic necrosis in the left lobe of the liver, extensive cortical haemorrhages in the kidney, and extensive neuronal damage in the brain. There is little doubt that some of the pathological changes in this infant were related to hypoxia. However, necrosis of the liver has been observed by Goldenberg, Wiegenstein, and Hopkins (1968) and Brinkman *et al.* (1961) with the use of hyperosmolar solution of THAM. As similar lesions have been described after the use of hyperosmolar solutions of sodium bicarbonate (Adamsons *et al.*, 1963), it appears that the liver and renal damage may be related to the hyperosmolality of the solution rather than to a direct toxic effect of THAM.

Hypoglycaemia and hyperkalaemia have been reported with the use of THAM in experimental animals (Bennett and Tarail, 1961). Hypoglycaemia is a recognized biochemical disturbance in newborn babies with idiopathic RDS (Usher, 1961). In our series all babies were routinely monitored with Dextrostix and there were no babies who had either clinical or biochemical evidence of hypoglycaemia. We did not routinely perform estima-

tions of serum electrolytes, but in those babies who had serum potassium estimations we did not find any values above 6 mEq/l.

Gupta (1965) and Gupta *et al.* (1967) have reported a rise in P_{aO_2} after administration of THAM in infants with idiopathic RDS. Similar results have been reported by Russell and Cotton (1968) with the use of sodium bicarbonate. In our trial, of the 16 cases where blood gas analysis had been done within 30 to 60 minutes before and after the initial dose of sodium bicarbonate, no appreciable change was noticeable in P_{O_2} . On the other hand, in the 18 infants of the THAM-treated group in whom pre- and post-treatment blood gas measurement had been carried out, there was a rise in P_{O_2} in 7 cases, a fall in P_{O_2} in 1, and no appreciable change in the other 10 (Table XI).

TABLE XI

Effect on blood gas tensions of buffer administration

	Effect on P_{O_2} (no. of cases)		Effect on P_{CO_2} (no. of cases)	
	THAM treated	NaHCO ₃ treated	THAM treated	NaHCO ₃ treated
Rise	7	—	—	5
Fall	1	—	13	—
No change	10	16	8	10
Not done	7	9	4	10

THAM is supposed to be theoretically superior to sodium bicarbonate in the treatment of acidosis in idiopathic RDS because of its ability to act in a closed system. We therefore looked at our blood gas results in relation to changes in P_{CO_2} after the administration of the initial dose of the two buffers. It was found that of the 16 cases treated with sodium bicarbonate in which blood gas analysis had been done before and after treatment (within 30 to 60 minutes), P_{CO_2} rose in 5 cases and remained unchanged in 10. On the other hand, of the 21 cases treated with THAM in which P_{CO_2} had been determined before and after treatment, P_{CO_2} fell in 13 cases and remained unchanged in 8 cases (Table XI). Similar results have been reported by Gupta *et al.* (1967).

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