Use of THAM and Sodium Bicarbonate in Correcting Acidosis in Asphyxiated Newborns

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Treatment of asphyxia of the newborn requires correction of the attendant acidosis, in addition to any necessary artificial ventilation. Currently, two buffer substances are used for this purpose, sodium bicarbonate and THAM (tris-hydroxymethylaminomethane). The effect of these buffers on the respiration of rabbits is the subject of this paper.

Material and Methods

Further details of material and methods are published elsewhere (Berg *et al.*, 1968).

12 rabbits weighing 2400 g. were anaesthetized with chloral hydrate. Polyvinyl catheters were placed in the femoral vein and artery of one leg. The arterial blood passed through the electrode described below, allowing arterial pH to be measured continuously. Tracheostomy was performed and a tube inserted into the trachea. Assessment of tidal volume was carried out in a closed system using a small Krogh spirometer, movements of the lid being converted into electrical impulses and registered graphically.

Fig. 1 shows schematically the pH-electrode assembly. Samples of arterial blood were equilibrated at short intervals with an O₂-CO₂ gas mixture with a CO₂ tension of 40 mm.Hg, and the pH was measured to give the 'pH (qu 40) value' (Saling, 1966). Knowing the Hb concentration, the other parameters of the acid-base status, including the actual PCO₂, could be extrapolated from the nomogram of Siggaard Andersen (1962).

Results

Results are set out in Tables I and II. Further details are published elsewhere (Berg *et al.*, 1968).

The influence of THAM administration on respiration and pH was studied in seven experiments. 0.5–1.0 mmole/kg. was injected in 15–25 sec.

After about 20 sec., a significant decrease of PCO₂ occurred ($p < 0.01$) amounting to about 20 mm.Hg, i.e. to about half its initial value. At the same time, ventilation decreased significantly by an average of 78% ($p < 0.0025$). The respiratory rate fell only slightly, provided that apnoea

was absent. The decrease of ventilation was thus caused mainly by a fall in tidal volume. On 4 occasions apnoea lasted between 5 and 60 seconds. Respiratory depression lasted between 30 and 120 seconds. Initially, pH increased by an average of 0.43; subsequent to the depression of ventilation, pH fell almost invariably, due to the increased PCO₂, caused by respiratory depression.

Fig. 2 shows a simultaneous record of pH and respiration and illustrates a typical experiment.

In seven experiments the influence of sodium bicarbonate on respiration was studied. 1–2 mmole/kg. was given within 15–20 seconds. After about 15 seconds, hyperventilation began and continued for more than 3 minutes. The minute volume increased by more than 100%. This increase was statistically significant ($p < 0.0025$). The actual pH values increased by an average of 0.18, and PCO₂ by about 23 mm.Hg (or 62%) ($p < 0.0125$).

Fig. 3 shows a simultaneous record of pH and respiration in a typical experiment.

Discussion

These studies were made on adult rabbits. How far are the results of such animal experiments transferable to man, and especially to human newborns? There is little to suggest they are

FIG. 1.—Capillary electrode for continuous measurement of pH.

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FIG. 2.—Spirogram (lower trace) and arterial pH (upper trace) before, during, and after injection of 4.3 mmole THAM. Note apnoeic phase. Values for pHqu40 (see 'Methods') and arterial PCO₂ are shown. $\dot{V}_E$: minute volume of respiration in ml./min. BTPS. (The pH swing recorded at the end of injection was an artefact.) The low pre-treatment pH in this case was caused by a lactic acid acidosis; this case is therefore not included in Table I.

not, having regard to the fact that the chemical regulation of respiration and buffering of blood are fundamental processes which take place qualitatively in the same way in mammalia. It must also be pointed out that the rabbits at the start of an experiment had a near normal pH, which after alkali treatment rose to levels as high as 7.65–8.0. Are the physiological effects the same under these conditions as in cases of asphyxia where the pH is raised from a very low value to normal? Studies published elsewhere (Berg *et al.*, 1968) have shown that there is no qualitative difference between these two situations (see also Fig. 2).

An important side-effect of THAM is the depression of respiration, due mainly to reduction in tidal volume rather than in frequency (Brown *et al.*, 1959, 1961; Jarre, Ketterle, and Reinwein,

1965; Müller-Plathe, 1965; Ngai *et al.*, 1961; Nahas and Lumpkin, 1959; Nahas *et al.*, 1963; O'Connor *et al.*, 1959). Theoretically, the respiratory depression might be caused by one of the following mechanisms.

- (1) A pharmacological effect of THAM on the respiratory centre or the chemoreceptors.
- (2) An increase of pH due to the properties of THAM as a base.
- (3) A decrease in PCO₂.

Observations made by Ngai *et al.* (1961) and by Nahas *et al.* (1963) did not favour the first of these hypotheses, since there was little depression of respiration when a THAM solution buffered to pH 7.4 was administered.

The decrease of H⁺ ion concentration and the consequent abolition of an important respiratory

TABLE
Effect of THAM on Ventilation

Experiment No.	THAM (mmole/kg.)	Resp. Rate/min.		V _T (ml.)		V _E (ml./min.)	
		Control	Max.	Control	Max.	Control	Max.
1	1.0	46	42	34	28	1576	1177
2	1.0	42	36	51	15	2152	571
3	1.0	60	0	29	0	1630	0
4	0.5	63	0	36	0	2289	0
5	0.5	46	0	35	0	1588	0
6	0.5	52	54	29	12	1470	572
7	0.5	62	0	26	0	1608	0

V_T, tidal volume (ml.) BPTS; V_E, ventilation (ml./min.) BTPS; pH (act.), actual arterial pH; pH(qu40); pH equilibrated at Pco₂ 40 mm.Hg; day.
* Blood samples not taken at time of maximum change in pH.

TABLE
Effect of Sodium Bicarbonate on

Experiment No.	NaHCO ₃ (mmole/kg.)	Resp. Rate/min.		V _T (ml.)		V _E (ml./min.)	
		Control	Max.	Control	Max.	Control	Max.
1	1	44	48	30	52	1370	2512
2	1	44	41	24	45	1039	2302
3	1	51	54	36	48	1853	2590
4	2	58	58	25	44	1446	3667
5	2	44	51	40	79	1799	4077
6	1	42	62	27	34	1138	2119
7	1	44	52	17	40	777	2083

FIG. 3.—Spirogram (lower trace) and arterial pH (upper trace) before, during, and after injection of 3 mmole sodium bicarbonate.

I

Arterial pH, and PCO₂

pH (act.)		pH(qu40)		PCO ₂ (mm.Hg)		Duration of Apnoea (sec.)	Duration of Depr. (sec.)	Delay (sec.)
Control	Max.	Control	Max.	Control	Max.			
7.43	7.63	7.40	7.59	38	28	Nil	60	15
7.39	7.64	7.43	7.68	38	21	Nil	65	10
7.50	7.88	7.36	7.52	26	12	50	105	35
7.35	8.00	7.35	7.56	42	18	60	115	40
7.35	8.00	7.35	7.62	42	13	5	30	65
7.35*	7.36*	7.38*	8.40*	46*	47*	Nil	90	12
7.41*	7.55*	7.36*	7.49*	36*	33*	5	80	8

time elapsing until response to drug; max., maximum of alteration of the value.

II

Ventilation, Arterial pH, and PCO₂

pH (act.)		pH(qu40)		PCO ₂ (mm.Hg)		Delay (sec.)
Control	Max.	Control	Max.	Control	Max.	
7.43	7.42	7.41	7.62	39	94	15
7.39	7.58	7.35	7.62	37	58	10
7.37	7.51	7.36	7.61	41	59	5
7.38	7.60	7.40	7.73	45	65	25
7.35	7.60	7.36	—	30	—	15
7.41	7.65	7.35	7.77	35	58	20
7.44	7.64	7.44	7.69	42	49	15

stimulus seem to be of more importance. It is well known that a decrease in pH and an increase of PCO₂ have additive effects (within physiological range) as respiratory stimulants. There is agreement that pH increases, after the administration of THAM, but there is no accepted opinion about the effect on PCO₂ (Cosby *et al.*, 1964; Henschler, 1963; Nahas and Lumpkin, 1959; Nahas *et al.*, 1963). The results of our experiments are in agreement with those of Nahas *et al.* (1963); they show a brief but significant decrease of PCO₂ followed by a secondary normo- or hypercapnic phase caused by the hypoventilation (Fig. 2). The duration of each of these two phases is between 20 and 30 seconds, so that if only random tests are made, the results will depend on the time of sampling.

In asphyxiated and acidotic newborn infants, hypercapnia is always present. Therefore, the hypocapnic effect of THAM is probably advantageous. Moreover, the effect of THAM does not depend on adequate ventilation, as is the case in bicarbonate buffering. For these reasons the use of THAM seems logical for the rapid correction of the acidosis of this situation.

But an important disadvantage of THAM is the danger of respiratory depression. Nahas and

Holmdahl (1961) pointed out that THAM should be used only when artificial ventilation can be applied. Its use in the newborn infant has been associated with respiratory depression on various occasions (Cosby *et al.*, 1964; Jarre *et al.*, 1965).

The buffering system bicarbonate/carbonic acid has the advantage of a rapid elimination of the acid component by the lung, the CO₂ formed by the buffering process being eliminated quickly so long as breathing is adequate. But if pulmonary function is inadequate, CO₂ will be retained, and the alkalinizing effect of the buffer will be partially offset by the increased PCO₂. The gradual ascent of the pH curve shown in Fig. 3 is caused by an increase in both bicarbonate and PCO₂. If the rabbit had not been able to exhale CO₂, the increase of pH would probably have started even more gradually. Holmdahl *et al.* (1961) obtained similar results.

Transferred to the conditions of the depressed and/or apnoeic newborn, this means that the second phase of the bicarbonate buffering, the elimination of the acid component of the system, is absent. On these grounds, the value of buffering the apnoeic newborn with sodium bicarbonate should be questioned.

A high PCO₂ may have two undesirable conse-

quences. First, a markedly raised PCO_2 (above 80 mm.Hg) depresses the respiratory centre (Asmussen and Nielsen, 1957; Graham, Hill, and Nunn, 1960). Secondly, CO_2 as an easy diffusible gas may invade the intracellular space more rapidly than the bicarbonate ion (Adler, Roy, and Relman, 1965a, b). It is therefore possible that the intracellular acidosis may be increased, and Adler *et al.* (1965a, b) found that the intracellular pH decreased if PCO_2 in the extracellular fluid exceeded 70 mm.Hg. Thus the administration of sodium bicarbonate for the treatment of the asphyxiated newborn seems to be appropriate only if adequate ventilation has been established to ensure elimination of CO_2 .

The above considerations lead us to suggest a sequential therapy for asphyxia of the newborn.

Initially, i.e. immediately after the delivery of an apnoeic child, THAM should be administered because its alkalinizing effect is more reliable than that of bicarbonate.

Saling (1966) has recommended that in all cases where pH_{qu40} values below 7.15 have been found by fetal blood sampling, a maximum dose of 7 mmole THAM should be given to the baby on delivery. 2 ml. 40% THAM solution (3.3 molar) in 10 ml. 10% glucose is made up, and of this solution up to 4 ml./kg. body weight is injected via the umbilical vein.

If spontaneous respiration has started or if artificial ventilation has been established, sodium bicarbonate is given. This has the advantage of avoiding respiratory depression, hypoglycaemia, and disturbance of potassium level, which are all possible effects of THAM.

Dosage may either be based on the scheme of Hutchison *et al.* (1962): volume of 8.4% NaHCO_3 required (ml.) = base deficit (mEq/l.) $\times$ kg. body weight $\times$ 0.35, or that of Saling (1966) who suggests a gradual correction of acidosis (4 ml. of 8.4% NaHCO_3 per kg. body weight) depending on pH values.

Summary

In experiments on rabbits, the influence of buffering substances in acid-base balance and respiration was measured using spirometry and continuous measurement of arterial pH.

A sequential therapy of the acidosis of the asphyxiated newborn is suggested. An initial injection via the umbilical vein of THAM in a maximum dose of 7 mmole is given. As soon as spontaneous or artificial respiration is established, treatment of the acidosis is continued with sodium bicarbonate.

Such sequential therapy aims to correct the acidosis rapidly, without increasing the hypercapnia and intracellular acidosis, while avoiding the side-effects caused by THAM.

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