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Intracranial Hemorrhage Following Intravenous Administration of Sodium Bicarbonate or Saline Solution in the Newborn Lamb Asphyxiated in Utero

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The effects of intravenously administered sodium bicarbonate were studied in near-term neonatal lambs asphyxiated *in utero* by maternal hypotension. Following tracheal intubation and manual ventilation with 100 per cent oxygen, the extracellular base deficits of ten neonates were corrected with sodium bicarbonate, 4.2 per cent, in 5 per cent dextrose (964 mOsm/l). Nine neonates alternatively received an isovolumic infusion of physiologic saline solution, 0.5 per cent, in 2.5 per cent dextrose (314 mOsm/l). Following sodium bicarbonate infusion (mean dose 6.7 mEq/kg), serum sodium and osmolality immediately increased to 160 mEq/l and 335 mOsm/l, respectively. However, sodium values were similar in the two groups by 15 min after infusion. Although significant differences in Pa_{O_2} values were not found between groups after infusion, sodium bicarbonate therapy was associated with a significantly higher Pa_{O_2} value (175 ± 60 torr) than was treatment with saline solution (51 ± 8 torr) in neonates with $pH_a < 7.00$ before resuscitation. Significant disparities in pH_a and base excess values occurred between bicarbonate- and saline-treated groups after infusion; two saline-treated lambs died, while all bicarbonate-treated lambs survived the study period. Intracranial subarachnoid hemorrhage occurred in three bicarbonate- and in two saline-treated lambs and was apparently related to severe asphyxia and not to the tonicity of the solutions. It is concluded that treatment of neonatal metabolic acidosis with appropriate doses of sodium bicarbonate is not associated with intracranial hemorrhage or sustained hypernatremia in the term neonatal lamb. (Key words: Acid–base equilibrium: acidosis; base excess; bicarbonate, sodium. Complications: intracranial hemorrhage. Hemorrhage: neonatal, intracranial.)

AT PARTURITION, neonatal depression is frequently associated with metabolic acidosis. Intravenous administration of sodium bicarbonate has been recommended to reverse acidosis and its cardiorespiratory effects.[1,2] The use of sodium bicarbonate has remained controversial,[3] for it may cause hypernatremia and hyperosmolality,[4] and it has produced intracranial hemorrhage in animal studies.[5,6] However, in these studies massive doses of sodium bicarbonate were used. Smaller therapeutic doses have not been investigated in the laboratory, while clinical reports relating intracranial hemorrhage to sodium bicarbonate therapy have been retrospective or uncontrolled.[7–9] As a result, sodium bicarbonate has been used conservatively, and opinions vary widely regarding proper indication and dose.

A controlled study in this laboratory did not reveal intracranial hemorrhage in acutely asphyxiated neonatal lambs given enough sodium bicarbonate to correct metabolic acidosis completely.¶ Since acute, total asphyxia may not correlate well with human fetal–neonatal asphyxia, we designed this study to resemble more closely the clinical situation. The effects of sodium bicarbonate were studied in neonatal lambs subjected to prolonged partial asphyxia *in utero*.

Methods

Spinal anesthesia was induced in 19 ewes at 135 days' gestation (term 144 days). Midthoracic sensory levels were produced by subarachnoid injection of bupivacain, 6.0 ml of 0.75 per cent, at L3–4 or L4–5. The ewes were placed in the left semilateral position and a femoral artery and vein were cannulated. Maternal mean blood pressure was continuously monitored with a pressure transducer and polygraph, while physiologic saline solution, 20 to 30 ml/hr, was infused through the intravenous line. A fetal hind limb was exposed through a midline hysterotomy incision. A purse-string suture prevented loss of amniotic fluid. A 19-gauge catheter was placed through a fetal femoral artery into the abdominal aorta, and 0.5 ml of fetal blood was collected anaerobically in a heparinized syringe. Pa_{CO_2} and pH_a were measured at 38.5 C with a Instrumentation Laboratories Ultra-Micro® blood-gas analyzer. Base excess was calculated from the Siggaard-Anderson nomogram.

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TABLE 1. Fetal Acid–Base Data (Mean ± SE)

	Before Hypotension		End of Hypotension	
	Bicarbonate (n = 10)	Saline Solution (n = 9)	Bicarbonate (n = 10)	Saline Solution (n = 9)
pH_a	7.32 ± 0.02	7.29 ± 0.05	7.03 ± 0.02	7.02 ± 0.02
Pa_{CO_2} (torr)	51 ± 3	52 ± 5	65 ± 6	64 ± 3
Base excess (mEq/l)	−2 ± 1	−4 ± 2	−16 ± 2	−17 ± 2

Utilizing a continuous infusion of trimethaphan camsylate, 0.4 per cent, in physiologic saline solution, the maternal mean blood pressure was decreased by 10 per cent every 20 min. Fetal blood Pa_{CO_2}, pH_a, and base excess were measured every 15 min until base excess decreased to −12 mEq/l or less. Five milliliters of fetal arterial blood were drawn to measure baseline blood-gas, hematocrit, serum sodium, osmolality, potassium, and glucose values. The total amount of fetal blood withdrawn was 7–9 ml, an insignificant fraction of the fetal blood volume. The fetus was then delivered through an extended hysterotomy, the umbilical cord was tied and severed, and the neonate was weighed and placed under a radiant warmer.

Following tracheal intubation, neonatal resuscitation was initiated with 100 per cent oxygen delivered by manual ventilation with a Mapleson D system (oxygen inflow 8 l/min). A rectal temperature probe was inserted while an umbilical vein and artery were cannulated. Physiologic saline solution was infused through the intravenous line, and mean umbilical-artery pressure was monitored continuously. The extracellular fluid base deficit prior to resuscitation was calculated with the formula:

Base deficit = weight (kg) × 0.4 × (−base excess)

In ten randomly selected neonates (bicarbonate-treated group), the calculated base deficit was completely corrected with an infusion of sodium bicarbonate, 4.2 per cent, in 5 per cent dextrose. The infusion volume in ml of this solution, containing 0.5 mEq sodium bicarbonate/ml and having an osmolality of 964 mOsm/l, was equal to two times the calculated extracellular base deficit. Nine lambs serving as controls (saline-treated group) received instead a nearly isotonic infusion of sodium chloride, 0.45 per cent, in 2.5 per cent dextrose (314 mOsm/l). The volume of this solution was equal to the volume given to the bicarbonate-treated group. Infusions were given through umbilical venous catheters over 1 min. Evans blue dye, a protein-bound dye (2.5 per cent, 5 ml/kg) was given intravenously to delineate intracranial hemorrhage. Five-milliliter samples of arterial blood were obtained 1, 5, 15, and 30 min after infusion for determination of blood-gas, serum sodium, osmolality, potassium, glucose, and hematocrit values.

Thirty minutes after infusion, heparin (500 units) was given intravenously, and the lambs were killed with an overdose of thiopental. The superior vena cava was transected and the descending aorta was cross-clamped through a left parasternal thoracotomy. To fix the brain *in situ*, buffered formalin (1,200 ml) was infused from a container positioned 2 feet above the neonate through a catheter placed in the left cardiac ventricle. The heads were severed and stored in formalin. At a later date, the brains were examined by a pathologist who was unaware of the therapy utilized. Following removal of the cranial vault, the brains were removed *in toto*. The surfaces of the calvarium and brain were examined under incident light for evidence of intracranial hemorrhage and extravasation of Evans blue dye. Then, standardized, serial coronal sections were made for examination of the interior.

Data were analyzed with the Student *t* test for un-

TABLE 2. Serum Biochemical and Hematocrit Values (Mean ± SE) before Resuscitation and after Infusion of Sodium Bicarbonate (Bic.) or Saline Solution (Sal.)

	Before Resuscitation		After Infusion							
			1 Min		5 Min		15 Min		30 Min	
	Bic. (n = 10)	Sal. (n = 9)	Bic. (n = 10)	Sal. (n = 9)	Bic. (n = 10)	Sal. (n = 9)	Bic. (n = 10)	Sal. (n = 7)	Bic. (n = 10)	Sal. (n = 7)
Sodium (mEq/l)	140 ± 3	145 ± 2	160 ± 1	146 ± 4*	154 ± 2	145 ± 3*	148 ± 3	147 ± 3	147 ± 3	146 ± 3
Osmolality (mOsm/l)	299 ± 4	300 ± 4	335 ± 3	291 ± 6*	323 ± 6	289 ± 7*	315 ± 5	294 ± 9*	312 ± 5	301 ± 7
Potassium (mEq/l)	4.4 ± 0.3	4.3 ± 0.2	3.5 ± 0.2	3.9 ± 0.2	3.1 ± 0.1	3.8 ± 0.2*	3.0 ± 0.1	3.7 ± 0.4*	2.9 ± 0.1	3.6 ± 0.2*
Glucose (mg/100 ml)	35 ± 8	34 ± 4	245 ± 26	153 ± 24*	182 ± 17	113 ± 17*	151 ± 17	84 ± 12*	143 ± 17	80 ± 12*
Hematocrit (per cent)	34 ± 1	31 ± 2	22 ± 1	24 ± 2	24 ± 1	23 ± 2	27 ± 1	23 ± 3	30 ± 1	24 ± 3*

* $P < 0.05$, bicarbonate versus saline solution after infusion.

TABLE 3. Neonatal Arterial Blood-gas Values (Mean ± SE) before Resuscitation and after Infusion of Sodium Bicarbonate (Bic.) or Saline Solution (Sal.)

	Before Resuscitation		After Infusion							
			1 Min		5 Min		15 Min		30 Min	
	Bic. (n = 10)	Sal. (n = 9)	Bic. (n = 10)	Sal. (n = 9)	Bic. (n = 10)	Sal. (n = 9)	Bic. (n = 10)	Sal. (n = 7)	Bic. (n = 10)	Sal. (n = 7)
Pa_{O_2} (torr)	19 ± 2	21 ± 2	268 ± 37	226 ± 62	253 ± 52	147 ± 41	229 ± 51	198 ± 48	213 ± 55	125 ± 34
pH_a (units)	7.03 ± 0.02	7.02 ± 0.02	7.49 ± 0.04	7.05 ± 0.05*	7.48 ± 0.06	7.04 ± 0.05*	7.49 ± 0.06	7.12 ± 0.05*	7.42 ± 0.06	7.08 ± 0.04*
Pa_{CO_2} (torr)	65 ± 6	64 ± 3	44 ± 3	33 ± 4*	41 ± 4	37 ± 5	33 ± 4	31 ± 4	31 ± 4	32 ± 4
Base excess (mEq/l)	−16 ± 2	−17 ± 1	8 ± 3	−21 ± 2*	5 ± 3	−21 ± 2*	3 ± 3	−19 ± 2*	−3 ± 3	−20 ± 2*

* $P < 0.05$, bicarbonate versus saline solution after infusion.

paired samples; significance was assumed when $P < 0.05$. Values are reported as mean ± standard error of the mean.

Results

The mean durations of maternal hypotension were 66 min in the bicarbonate-treated group and 65 min in the saline-treated group. In both groups, maternal blood pressure was decreased by 37 per cent. Fetal acid–base data for the bicarbonate- and saline-treated groups were similar before and at the end of hypotension (table 1). Neonatal weights were 4.1 ± 0.2 kg for the bicarbonate-treated group and 3.7 ± 0.4 kg for the saline-treated group; this difference was not significant. The bicarbonate-treated group received an infusion volume of 55 ± 6 ml of 4.2 per cent sodium bicarbonate in 5 per cent dextrose, for a mean sodium dose of 27.5 mEq, or 6.7 mEq/kg. The saline-treated group received 50 ± 5 ml of 0.45 per cent sodium chloride in 2.5 per cent dextrose.

Sodium bicarbonate infusion was associated with an increase in serum sodium from 140 mEq/l before resuscitation to 160 mEq/l 1 min after infusion. This increase was transient, as the sodium value decreased to 148 mEq/l 15 min after infusion, at which time the values for the two groups were again similar (table 2). Serum osmolality increased from 299 mOsm/l to 335 mOsm/l (1 min after infusion), which was due in part to a serum glucose of 245 mg/100 ml. By 30 min after infusion, osmolality had decreased to 312 mOsm/l. Serum potassium decreased in both groups after infusion; values in the bicarbonate-treated group were significantly lower than those in the saline-treated group 5 min after infusion.

Values of Pa_{O_2} were higher in the bicarbonate-treated group after infusion, but the difference between groups was not significant (table 3). However, lambs with $pH_a < 7.00$ before resuscitation had significantly higher Pa_{O_2} values 5 min after infusion of sodium bicarbonate (table 4). This analysis was not continued beyond 5 min because two of the severely acidotic saline-treated lambs died before the 15-min sample. Although significant disparities in pH_a and base excess values occurred between groups after infusion, Pa_{CO_2} values were similar except at 1 min, when they were 44 and 33 torr in the bicarbonate- and saline-treated groups, respectively ($P < 0.025$).

Decreases in hematocrit occurred in both groups immediately after infusion (table 2). For the remainder of the study period, a progressive increase in hematocrit occurred in the bicarbonate-treated group, while hematocrit remained essentially unchanged in the saline-treated group. Fetal rectal temperature and blood pressure values were unchanged during the study period.

Examination of the neonatal brains revealed single, large subarachnoid hemorrhages in three of the bicarbonate-treated and in two of the saline-treated lambs. All hemorrhages were located over the parietal

TABLE 4. Arterial Blood-gas Values from Eight Severely Acidotic Lambs ($pH_a < 7.00$)

	Prior to Resuscitation		5 Min after Infusion	
	Bicarbonate-treated Group (n = 4)	Saline-treated Group (n = 4)	Bicarbonate-treated Group (n = 4)	Saline-treated Group (n = 4)
Pa_{O_2} (torr)	20 ± 2	20 ± 3	175 ± 60	51 ± 8*
pH_a (units)	6.98 ± 0.02	6.96 ± 0.02	7.48 ± 0.12	6.94 ± 0.07*
Pa_{CO_2} (torr)	66 ± 14	67 ± 8	42 ± 8	40 ± 8
Base excess (mEq/l)	−19 ± 2	−20 ± 2	6 ± 6	−25 ± 1*

* $P < 0.05$, bicarbonate versus saline solution, 5 min after infusion.

and occipital lobes in proximity to the parieto-occipital fissure. Hemorrhage into cortical, midbrain, cerebellar, or brain stem tissue did not occur. In two bicarbonate- and in two saline-treated lambs with subarachnoid hemorrhage, extravasation of Evans blue dye was seen in gray matter in the periventricular area. Congestion of blood in meningeal veins was observed in the five neonates with subarachnoid hemorrhages, as well as in three bicarbonate- and three saline-treated lambs without hemorrhage. These small, multiple lesions, which suggest the presence of cerebral venous stasis, were primarily located in the parieto-occipital region.

The incidences of intracranial hemorrhage in the bicarbonate- and saline-treated groups was subjected to chi-square analysis; the difference between groups was not significant ($P > 0.9$). It was of note that the five neonates with intracranial hemorrhages had been severely acidotic, with $pH_a < 7.00$ before resuscitation. Grossly normal brains were found in four neonates in both groups, all of which had pH_a values above 7.00 before resuscitation.

Discussion

The normalization of neonatal pH may improve pulmonary perfusion by decreasing pulmonary vascular resistance.[10] Infusions of alkaline and dextrose solutions prolong respiratory movements, enhance cardiovascular stability, facilitate resuscitation,[11,12] and decrease the incidence of permanent brain damage[13] in acutely asphyxiated neonatal animals. At parturition, we have routinely observed improved respiratory activity, muscle tone, reflex response, and skin color in severely depressed term newborns given sodium bicarbonate, 5 mEq, in 10 ml of 5 per cent dextrose.

The relationship between neonatal sodium bicarbonate administration and intracranial hemorrhage was demonstrated by Finberg *et al.*[5] They found intracranial subdural hemorrhage in 23 of 27 non-asphyxiated kittens, 6 to 8 weeks old, given sodium bicarbonate, 175 mEq/kg, intraperitoneally. Resultant mean serum sodium and osmolality values were 196 mEq/l and 389 mOsm/l, respectively. Subdural hemorrhage was attributed to the simultaneous development of brain dehydration and venous engorgement causing disruption of superficial bridging veins.

The effect of sodium bicarbonate on the neonatal cerebrovasculature depends upon dose and rate of infusion, and it may be influenced by gestational age. It would be inappropriate to correlate the effects of massive doses of sodium bicarbonate as used by Finberg[5] with those of therapeutic doses. Moreover, the effect seen at one gestational age could not be easily extrapolated to an earlier stage of development. For example, hemorrhage resulting from cerebral ischemia occurs in the area of the periventricular germinal matrix in premature infants, while in term infants it occurs in superficial cerebral or subarachnoid veins.[14] It is possible that should sodium bicarbonate cause intracranial hemorrhage, the site and extent of hemorrhage may vary with gestation. Furthermore, correlating the effect of sodium bicarbonate from one species to another is difficult due to differences in cerebrovascular development that exist between species at comparable gestations.

While realizing these methodologic limitations, we were concerned about the reluctance of many clinicians to use sodium bicarbonate in any dose, regardless of neonatal status or gestational age. Our primary objective was to study the safety of a therapeutic dose of sodium bicarbonate in a clinically relevant model. Most laboratory reports of the effects of sodium bicarbonate have utilized acutely asphyxiated or non-asphyxiated neonates. Neither may represent the asphyxiated human neonate, which usually experiences prolonged, partial asphyxia secondary to uteroplacental insufficiency or umbilical cord compression.[15] With a controlled decrease in maternal blood pressure, an effort was made to produce a model of asphyxia better simulating that cause by uteroplacental insufficiency. Furthermore, we attempted to maximize the production of intracranial hemorrhage while keeping the dose of sodium bicarbonate within clinically indicated limits. The mean bicarbonate dose of 6.7 mEq/kg, which completely corrected the extracellular base deficit, greatly exceeds the 2 mEq/kg dose recommended for initial use in the delivery room.[2] Our experimental infusion rate was 6.7 mEq/kg/min, compared with the recommended rate of 2 mEq/kg/min.[2] This dose and rate of infusion appeared to be well tolerated, as sustained hypernatremia and hyperosmolality did not occur (table 2).

Saline solution and sodium bicarbonate were given in dextrose, as in common clinical practice, because fetal glycogen stores are easily depleted during prolonged periods of distress. Sodium bicarbonate was given in 5 per cent dextrose to increase the osmolality of that solution. Half-normal saline solution was given in 2.5 per cent dextrose to provide a control solution that was nearly isotonic. An infusion of hypertonic sodium bicarbonate–dextrose appeared to be more beneficial than isotonic volume alone for improving arterial oxygenation (tables 3 and 4). In addition, two of the saline-treated lambs died during the study period, while all of the bicarbonate-treated lambs survived.

Since sodium bicarbonate is rapidly converted to carbon dioxide, it has been suggested that neonatal

hypercarbia can result from bicarbonate therapy.[16] While Pa_{CO_2} values were initially higher in the bicarbonate-treated group (table 3), hypercarbia did not occur after bicarbonate infusion given in the presence of adequate ventilation.

The intracranial hemorrhages seen in both bicarbonate- and saline-treated lambs were subarachnoid, whereas those experimentally produced previously by hypertonic sodium solutions were subdural.[5] The very high serum sodium and osmolality values that have been associated with subdural hemorrhage were not observed in this study. In term neonates, subdural hemorrhage is usually produced by mechanical trauma, whereas subarachnoid hemorrhage is most often caused by severe fetal–neonatal hypoxia and acidosis.[14] In addition, the cerebral venous congestion found in both groups is a prehemorrhagic lesion, which has been attributed to hypoxemia and acidosis.[14] Since subarachnoid hemorrhages occurred only in neonates with preresuscitation pH_a values below 7.00, they were probably related to severe intrauterine asphyxia. The extravasation of Evans blue dye into the periventricular area in two neonates in both groups suggests that blood–brain barrier breakdown occurred following the transcapillary passage of serum proteins. This finding could also have been a result of asphyxia.[17]

While it is difficult to extrapolate data from animal studies to the human newborn, we believe that the following conclusions are valid. When subjected to prolonged partial asphyxia, neonatal lambs near term gestation may develop intracranial subarachnoid hemorrhages, which differ markedly from subdural hemorrhages that are caused by nonphysiologic doses of hypertonic sodium solutions.[5] In our study, infusion of hypertonic bicarbonate–dextrose solution given in a quantity to correct metabolic acidosis completely was not associated with evidence of intracranial subdural hemorrhage or prolonged hypernatremia and hyperosmolality. It was associated with better arterial oxygenation and survival of the asphyxiated neonatal lambs when compared with other lambs given equal volumes of a nearly isotonic sodium chloride–dextrose solution. Due to adequate ventilation of the lambs during bicarbonate administration, the hypercarbia accompanying bicarbonate treatment of metabolic acidosis was minimal. Our total dose of hyperosmolar bicarbonate solution, which represents two or three times the recommended dose for use in the delivery room, appeared to be well tolerated by asphyxiated lambs that were near term. Their gestational age corresponds to 37 weeks in man. Whether a less mature newborn lamb would tolerate an equivalent dose of hypertonic sodium bicarbonate requires further investigation.

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