Personal Practice

Alkali Therapy for Neonates: Where Does it Stand Today?

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The first report of the therapeutic intravenous use of sodium bicarbonate has been attributed by Kaehny and Anderson(l) to Thomas Latta who reported the practice of intravenous injections of bicarbonate ($NaHCO_3$) and chloride into patients with cholera in 1832(2). Since the commercial availability of $NaHCO_3$ for medical use in the late 1950s, there have been continuing efforts to clarify aspects of the "bicarbonate controversy"(l).

Clinical Studies

In 1963, Usher reported use of an intravenous solution of 10% glucose in water to which 5-15 mEq/ml of $NaHCO_3$ was added (based on blood pH) infused at a rate starting at 65 ml/kg/day(3). He compared 35 premature infants with respiratory distress syndrome (RDS) and a mean age of 32 weeks treated with this regimen beginning the first three hours of life to 35 neonates in a control group who received "conventional" treatment (no intravenous or oral

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fluids for at least the first 24 hours of life). By seven days of age the study group mortality was 17% while the control group mortality was 37% (p=0.06). His reported five year experience using bicarbonate infusion demonstrated mortality of 24/118 (20%) versus 38/94 (42%) (p<0.01) in babies who did not receive this regimen(3). It remains unclear whether the benefits were due to volume infusion, provision of glucose, or bicarbonate administered by continuous intravenous infusion.

In the 1970s concern began to be expressed about the rapid infusion of $NaHCO_3$, to correct acidosis in premature babies. Wigglesworth demonstrated a relationship between use of alkali and intraventricular hemorrhage (IVH) on autopsy of babies with RDS(4). Comparing neonates having the same degree of acidosis and hypoxia, those with IVH received 10.21 ml/kg day of $NaHCO_3$ while those without IVH had received 6.34 ml/kg/day (p <0.001). In a retrospective study, Simmons expressed similar concern relating IVH to hypernatremia often from administration of intravenous $NaHCO_3$(5). When a more restrictive policy of use of $NaHCO_3$ was instituted, the incidence of hypernatremia was reduced from 8.8 to 0.6% and the incidence of IVH from 13.4 to 2.6%. Rather than using autopsy data, Papile used computer tomography to detect IVH in babies with birthweights <1500 g(6). She compared 44 babies with IVH to 56 babies without this diagnosis failing to show a significant relationship between the amount of intravenous $NaHCO_3$, administered, serum sodium concentrations and IVH. However, in analyzing the method of infusion of $NaHCO_3$, rapid infusion was

associated with an increased incidence of IVH(6).

In a controlled trial of bicarbonate therapy in premature newborn infants with birth weights <1500 g who had RDS, 30 infants assigned to liberal $NaHCO_3$ similar to the Usher regimen(3) were compared to 30 infants who did not receive $NaHCO_3$ except for delivery room resuscitation. The infants who received $NaHCO_3$ did not have better pH or less mortality (7). Deaths were increased in babies receiving >8 mEq/kg day compared to those who received <4 mEq/kg day $NaHCO_3$. There were significantly more deaths (11/13) and IVH (6/13) in babies who received $NaHCO_3$, at birth compared to those who did not (death - 12/49, IVH 7/49)(7). However, these infants were likely sicker at birth.

Finberg cautioned against the use of hyperosmolar $NaHCO_3$ in treatment of neonatal asphyxia(8). He indicated the danger of transient or unsteady state solute gradient of 5-6 mOsm/L for plasma over brain extracellular fluid. Water flows out of the brain to eliminate the gradient which may result in IVH. The shift of solute-free water to the interstitial and intravascular space following administration of hypertonic $NaHCO_3$ to acidotic neonates has been demonstrated by Rhodes(9). He indicated that these studies did not provide an answer to the clinical problem of whether the beneficial effects of prompt correction of metabolic acidosis outweighed the potentially harmful effects of the osmotic alterations that accompany rapid infusion of hypertonic $NaHCO_3$.

The paradoxical effect of bicarbonate on cytoplasmic pH has been described(l0). It has been suggested that carbonic anhydrase catalyzed dissociation of carbonic acid results in production of CO_2 with differential diffusibility of $NaHCO_3$ and CO_2 (CO_2 enters the cell more readily) resulting in a decrease in intracellular pH(11). In a "closed system" (with fixed ventilation), administration of hypertonic $NaHCO_3$ has been shown to increase $PaCO_2$(12).

$NaHCO_3$ is not recommended for the treatment of respiratory acidosis(13). Even in situations of cardiac arrest, it is suggested that bicarbonate may have no value and that greater attention should be paid to coronary perfusion pressure(14). Although administration of $NaHCO_3$ to acidotic patients may result in improved skin blood flow(15), this (like improvement in blood pH) may be deceiving. Using xenon clearance, Lou demonstrated that cerebral blood flow decreased by 50% in 6 of 7 newborn infants after infusion of 1-8 mEq of bicarbonate(16).

Animal Studies

Graf, in his experiments on dogs, showed that intravenous infusion of $NaHCO_3$ to hypoxic dogs with lactic acidosis resulted in a decrease in cardiac output and blood pressure compared to no treatment or an equivalent amount of normal saline(17). There was no improvement in arterial pH and serum lactate actually increased, suggesting impaired tissue oxygenation secondary to a decrease in cardiac output. Although acute lactate acidosis adversely effects left ventricular performance,(18,19), buffer agents do not reverse intramyocardial acidosis during cardiac resuscitation(20). Administration of hypertonic $NaHCO_3$ in animals studies results in a further reduction in left ventricular performance (21,22). While sodium bicarbonate may improve outcome in dogs subjected to ventricular fibrillation(23) and perhaps to hemorrhagic shock(24), the conclusion that bicarbonate improves survival and neurologic outcome has been questioned(25). Objective evidence fails to

securely establish that benefits of alkali, especially $NaHCO_3$, outweigh risks when utilized in treatment of cardiac arrest(26). Despite correction of arterial and venous acidemia, the use of $NaHCO_3$ does not improve resuscitation from prolonged cardiac arrest(27). Studies of the systemic effects of $NaHCO_3$ in experimental lactic acidosis in dogs indicate that bicarbonate infusion may actually be associated with an increase in production of lactate(28), possibly related to decreased cardiac output. Steichen showed in dogs with fixed ventilation rapid infusion of $NaHCO_3$, increased serum osmolality and a less than predicted elevation of arterial pH(29). $PaCO_2$ increased and PaO_2 decreased. She suggested the net effect may be a worsening rather than an improvement in the metabolic state.

In animal studies with hypercapnia, administration of $NaHCO_3$ has not been shown to improve hemodynamics, organ blood flow and survival(30,31). However, in these situations there was no lactic acidosis and endeavours to provide an increase in cardiac and organ blood through normalization of ventilation were not reported.

Tris-Buffer THAM-A Substitute to Bicarbonate

The use of a Tris-buffer THAM (trimethamine) in the treatment of both respiratory and metabolic acidosis has also been suggested as an effective buffering agent(32). THAM buffers CO_2 as well as generates bicarbonate. For this reason, it has been suggested that it may be superior to bicarbonate for the treatment of metabolic acidosis, especially as it may reduce the adverse intracellular pH changes (although it is cautioned that this has not been demonstrated to be beneficial)(32). It has been suggested that THAM may be preferable to $NaHCO_3$ in the presence of a hyperosmolar

state. As 3 ml of 3.6 g/ml THAM is required to have the equivalent buffering capacity to 1 mmol of $NaHCO_3$, the osmolar load is similar. In a study comparing the two agents in dogs', increases in plasma osmolality were greater following infusion of THAM than infusion of either $NaHCO_3$ or NaCI (33).

Although THAM is stated to penetrate the cerebrospinal fluid compartment very slowly(32), use in babies with respiratory distress was associated with a 17% incidence of apnea or significant respiratory depression within 2 minutes of injection(34). It requires excretion by the kidneys and its use may be also associated with hypoglycemia, hyperkalemia, oliguria and hydropic degeneration of hepatic and renal tubular cells(32,35). Although THAM was initially reported to be associated with improvement in the oxygen tension of arterial blood of individual neonates with RDS(36), the study by Baum demonstrated no significant improvement in PO_2 with a moderate fall in 1 of 6 infants treated(37). These infants received 5 or 10 ml of 7% THAM over 30 seconds or an equivalent volume of 8.4% $NaHCO_3$ over 30 seconds, 2 minutes or 5 minutes. The greatest increase in osmolality was seen with the more rapid infusion of either agent. Ten minutes after the base infusion there was significant increase in arterial pH in all groups. The fact that only 6 of 19 babies in this study (mean gestational age 31 weeks) survived was attributed to the severity of RDS without discussion of the potentially adverse effects of both these medications.

In another retrospective study, babies who survived had a greater increase in arterial PaO_2 following administration of 3.6% THAM than babies who died but the study did not assess whether THAM was beneficial(38). In a comparison of THAM and $NaHCO_3$ in resuscitation after ventri-

cular fibrillation in dogs, THAM initially produced a greater elevation of blood pH but this effect was not sustained and both THAM and NaHCO₃ were determined to be equally effective in correction of metabolic acidosis(39). With induced ventricular fibrillation, use of carbicarb (a carbon dioxide-consuming buffer) has been shown to be no more effective than NaHCO₃ or saline in improving arterial pH(20). However, 5 of 7 pigs treated with carbicarb and 6 of 9 pigs treated with saline were able to be resuscitated while only 3 of 13 bicarbonate treated pigs could be successfully resuscitated. In the study by Graf(17), acidotic dogs receiving normal saline had better cardiac output and blood pressure than those receiving an equivalent amount of NaHCO₃ or no therapy. The potentially beneficial effects of THAM may be due to its "volume" effects on cardiac output rather than its buffering capacity. There have been no controlled studies demonstrating a beneficial effect of THAM for neonates either with cardiorespiratory arrest or with continuing metabolic acidosis.

Guidelines for Bicarbonate Use

In Guidelines of the American Heart Association, NaHCO₃ is classified as definitely helpful (Class I) only if the patient has pre-existing hyperkalemia(40). It is a therapeutic option for which the weight of evidence is in favor of its usefulness and efficacy (Class II a) with pre-existing bicarbonate responsive acidosis, actual bicarbonate loss in urine, or need to alkalinize the urine in drug overdoses. It is a therapeutic option that is not well established by evidence but which may be helpful and is probably not harmful (Class II b) in intubation after long arrest interval. It is a therapeutic option that is inappropriate, without scientific supporting data and may be harmful (Class III) with hypoxic lactic acidosis. NaHCO₃ remains a consideration

in an arrest situation for adults(40,41), children(42) and neonates(43,44). It should be used with caution primarily for "prolonged arrest that does not respond to other therapy"(44). NaHCO₃ should be used only after ventilation is established in a dose of 2 mEq/kg slowly over 2 minutes. The rapid infusion of hyperosmolar NaHCO₃ in other situations is harmful(45,46).

Bicarbonate Therapy in Indian Setting

As the facilities for documenting blood gas analysis are not freely available at majority of places in India, most of neonatologists feel that bicarbonate therapy during neonatal resuscitation is indicated if the baby is still apneic or gasping following five minutes of effective bag and mask or bag and tube ventilation. One must ensure adequate ventilation before, during, and after administering NaHCO₃. Bicarbonate should be administered slowly, in a dose of 2 mEq/kg over two minutes. For other situations of metabolic acidosis, except for replacement for renal or gastrointestinal bicarbonate losses, alkali therapy may not have a positive effect. One should primarily endeavor to treat the primary cause of metabolic acidosis. Maintaining adequate tissue perfusion, ventilation and oxygenation is required in majority rather than alkali therapy.

Available Preparations

One should be aware that sodium bicarbonate marketted in India is 7.5% solution with an osmolality of 1590 mOsm/L (while in West 8.4% and 4.2% solutions are available). THAM solution is not manufactured in the country. Imported 7% solution of THAM has an osmolality of 708 mOsm/L and 3.5% solution an osmolality of 354 mOsm/L.

Complications of Bicarbonate Therapy

The possible complications of bicarbon-

ate therapy are enlisted in *Table I.*

TABLE I—*Complications of Bicarbonate Therapy.*

♦Decreased myocardial contractility

♦Increased intracellular calcium influx (and possible cell death)

♦Decreased blood pressure (and coronary perfusion)

♦Decreased cerebral blood flow

♦Decreased intracellular pH

♦Fluid shifts and other mechanisms leading to intracranial hemorrhage

♦Increased affinity of hemoglobin for oxygen may compromise tissue oxygen delivery

♦Compromised lactate metabolism

♦Other metabolic effects *(e.g.,* hypoglycemia with THAM)

It is often tempting to try to correct that which we can readily determine *(e.g.,* de creased arterial blood pH). It is more difficult to determine other, perhaps more important, effects such as cardiac output and perfusion to the brain. It may well be that slow iso-osmolar infusion of $NaHCO_3$, or THAM has benefit without many of the harmful effects associated with rapid infusions of hyperosmolar solutions, but this remains to be demonstrated. While the ethical issues may be difficult, a definite answer can only be provided by a controlled, blinded, randomized study of buffer versus normal saline in babies with RDS who have acidosis. Outcome measured should be intact (without significant neurologic abnormality) survival rather than improvement in arterial pH. We should be reminded that the preponderance of evidence does not support benefits of this treatment and remember "on primum nocere" (primarily do no harm).

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