CARBICARB, AN ALKALINIZING ION-GENERATING AGENT OF POSSIBLE CLINICAL USEFULNESS*,**

GILES F. FILLEY† and (*by invitation*) NEAL B. KINDIG

DENVER

"Both intracellular and extracellular aqueous solutions of the organism ... acting selectively as reservoirs of supply and as vehicles of escape ... surpass the efficiency of any possible closed aqueous solutions of like concentration in preserving hydrogen ion concentration."

L.J. Henderson (1908)

This paper will outline certain aspects of the medical history of sodium bicarbonate, $NaHCO_3$, and sodium carbonate, Na_2CO_3, analyze their acid-base chemistry using new methods (1), and present the results of experiments which indicate that a particular mixture of these salts, which we have named "Carbicarb", may be more useful clinically than traditional 1 M $NaHCO_3$ especially when pulmonary ventilation and tissue perfusion are inadequate.

Table 1 shows the composition of Carbicarb. Because its P_{co_2} is lower than in $NaHCO_3$, solution, it is more stable since it loses CO_2 more slowly when exposed to room air. Because of the CO_3^{2-} ion, it has unusual properties: it does not raise P_{co_2} when injected into blood (and under some conditions may lower P_{co_2}) and it has the capacity to generate HCO_3^- ions not only from the carbonate ion added to blood but from CO_2 either in the blood or in "reservoirs of supply" of CO_2 accessible to blood, for example, the CO_2 stores in poorly perfused tissues. To explain these properties we will use both historical and chemical information.

MEDICAL HISTORY

Over 150 years ago Latta (2) successfully treated cholera patients with intravenous "alkaline salt water" which probably contained the carbonate ion in unknown concentration (3). Since then, because of its caustic effects, use of pure Na_2CO_3 in solution for affecting acid-base states has been restricted to the laboratory (4, 5).

In 1908, Henderson recognized (6) that for the HCO_3^- ion to maintain the hydrogen ion concentration in the blood at physiological levels by the reaction

$$H^+ + HCO_3^- \rightarrow H_2O + CO_2 \qquad [1]$$

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* From the Webb-Waring Lung Institute and the Department of Anesthesiology, University of Colorado Health Sciences Center, Denver, Colorado.

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† Requests for reprints: Giles F. Filley, Webb-Waring Lung Institute, Box C-321, 4200 East Ninth Avenue, Denver, Colorado 80262.

TABLE 1
Sodium Bicarbonate for Intravenous Injection Compared with Carbicarb

	$NaHCO_3$	Carbicarb
$[Na^+]$ millimoles/L (mM)	1000	1000
$[HCO_3^-]$ millimoles/L (mM)	1000	333
$[CO_3^{2-}]$ millimoles/L (mM)	0	333
P_{co_2} mm Hg 37°C	>200	3
pH 25°C	8	9.6
Osmolality per kg (Osm) (approx.)	2000	1667

Note: Osmolality per kg of solvent as measured by freezing point depression is a close estimate of osmolarity (per liter of solution). The P_{co_2} of modern $NaHCO_3$ solutions prepared for intravenous use can be calculated to be in excess of 400 mm Hg at 37°C. At the time they are transferred to a "blood gas machine" (which reads low at high CO_2 tensions) CO_2 bubbles frequently escape.

it was necessary that the animal organism have "vehicles of escape" (i.e., alveoli) so that the reaction could proceed sufficiently far to the right to neutralize an acid load. This concept is frequently forgotten in the emergency treatment of acidotic patients with inadequate ventilation (7, 8) in whom the arterial P_{co_2} can be driven to over 100 mm Hg with $NaHCO_3$ injections (9). This fact was one of the motivations for developing an improved alkalinizing agent.

Henderson also recognized that non-bicarbonate buffers are "reservoirs of supply". These buffers enable the lungs to convert, at rest, ⅛th of the plasma bicarbonate (venous $[HCO_3^-] = 27$, arterial $[HCO_3^-] = 24$ mM) to CO_2 with very little pH change by the reactions

$$\begin{array}{l} H^+ + Pr^- \leftarrow HPr \qquad [2] \\ \downarrow \\ H^+ + HCO_3^- \rightarrow H_2O + CO_2 \qquad [1] \end{array}$$

because the blood proteins supply enough H^+ ions (vertical arrow) so that reaction [1] can proceed without a large fall in $[H^+]$.

In 1916 Howland and Marriott (10), after heat-sterilizing $NaHCO_3$ solutions for the parenteral treatment of the acidosis of infantile diarrhea, found that the solution became so alkaline that necrosis of subcutaneous tissues could result from its injection. Heating $NaHCO_3$ in an unbuffered solution drives off CO_2 and extracts protons from HCO_3^- (a Bronsted acid as well as a base) by reaction [3]:

$$\begin{array}{l} H^+ + CO_3^{2-} \leftarrow HCO_3^- \qquad [3] \\ \downarrow \\ H^+ + HCO_3^- \rightarrow H_2O + CO_2 \qquad [1] \end{array}$$

Howland and Marriott avoided this difficulty by bubbling CO_2 into the sterilized solution to reverse these reactions.

For 50 years following World War I infusion of $NaHCO_3$ solution,

often dilute by today's standards, was widely used for the treatment of severe metabolic acidosis. Most of the patients so treated were hyperventilating (as a diabetic ketoacidosis) or at least had adquate ventilation. But since the advent of vigorous methods of resuscitation and pre-loaded syringes, very rapid injections of concentrated $NaHCO_3$ are common practice in ambulances and emergency rooms even when pulmonary ventilation is inadequate. Despite warnings in resuscitation manuals (11) and elsewhere (12–20) about the dangers (raised P_{co_2}, sudden hyperosmolality, delayed alkalosis) of $NaHCO_3$ therapy, patients are being overdosed because the drug is so often ineffective in raising blood pH in shock, trauma, cardiopulmonary arrest, lactic acidosis (21, 22) etc.

As recently as 1972, Ostrea and Odell (23) found it necessary to quantitate how ineffective $NaHCO_3$ can be. They injected the equivalent of 25 ml of 1 M $NaHCO_3$ into 1 liter of blood in a closed system and found that the P_{co_2} nearly doubled and the pH rose only about 0.1 units. They urged that the salt be used cautiously if at all because of its dangers and inefficacy.

We have formulated and tested an alkalinizing agent containing a bicarbonate precursor which may avoid these objections.

METHODS

1. *Charge neutrality and its graphic representation.*

The Carbicarb concept emerged during theoretical studies of $NaHCO_3$ infusion using the Log C – pH diagram (24–27) recently introduced into biology (28). The concentration and charge of all species in blood which contribute to acid-base equilibria can be displayed on this diagram. For clarity, only the data of this paper are plotted in Figure 1 in which the trajectories between the points (stars) represent the paths between experimentally changed states of equilibrium.

The ionized constituents of true plasma which mainly determine these equilibria are Na^+, Cl^-, HCO_3^- and the non-bicarbonate buffers (mostly protein) symbolized by Pr^-, where Pr^- includes the effect of shared buffering by red cell hemoglobin. Charge neutrality requires that

$$[HCO_3^-] = [Na^+] - [Cl^-] - [Pr^-] \qquad [4]$$

This form of the equation is convenient because it separates bicarbonate buffers from strong ions and protein buffers. The term $[Na^+] - [Cl^-]$ is equivalent to the buffer base of Singer and Hastings (29) and its value referred to a standard value, the base excess of Siggaard-Anderson (30). Stewart has recently called this term the "strong ion difference" or SID (31). Equation [4] can be written

$$[HCO_3^-] = [SID^+] - [Pr^-] \qquad [4.1]$$

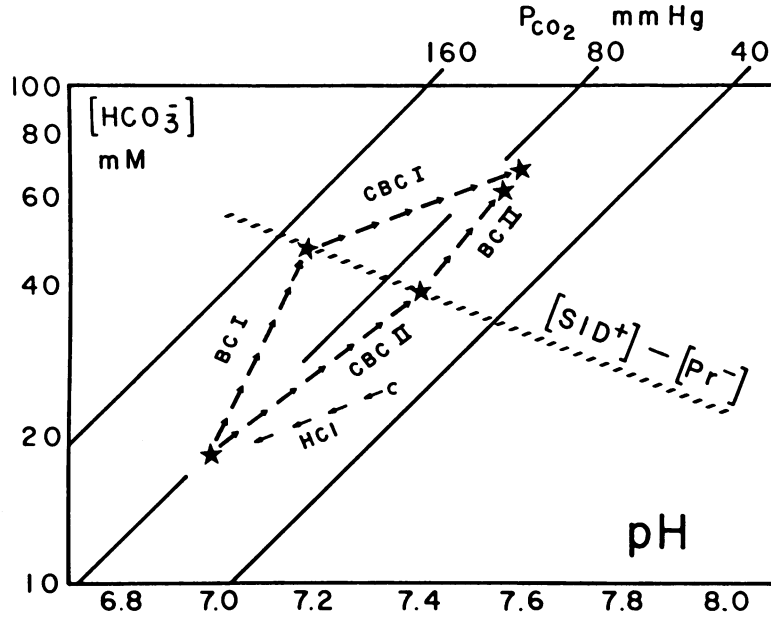

FIG. 1. The stars show the experimental acid-base data (Table 2) at equilibrium on the Log $[HCO_3^-]$ – pH diagram. C is the control. The arrows show the trajectories that result from successive injections into syringe I—HCl, BC_I, CBC_I—and syringe II—HCl, CBC_{II}, BC_{II}. The diagonal P_{co_2} isopleths show the pH dependence of log $[HCO_3^-]$ according to the Henderson-Hasselbalch equation. The $[SID^+] - [Pr^-]$ curve is one of a family of buffer curves and has 4 properties. (i) It shifts vertically up and down strictly as $[SID^+]$ shifts. (ii) Any point on it measures the charge of HCO_3^- needed to balance the net charge of SID^+ and Pr^-. (iii) Its negative slope reflects the fact that Pr^- increases as pH increases and is a measure of the non-bicarbonate buffer strength of blood, equation [5]. (iv) It is the "CO_2 equilibrium curve" of Siggaard-Anderson (30) as seen by the fact that the same amount of Na^+ was added to acidified blood with CBC_{II} as with BC_I but 2/3 as much total CO_2, i.e. the curve connects 2 points (stars) at different pH's since the blood was titrated with different amounts of CO_2 at these points. The intersection of the buffer curve with a $[HCO_3^-]$ dissociation curve establishes equilibrium, graphically solving equation [4.1].

How this coordinate system suggested an alternative to $NaHCO_3$ (32) can be seen by following the steps of the cross-over experiment. Starting at C, HCl injection lowered the buffer curve (by the $[Cl^-]$ rise) and also the charge $[Pr^-]$. Traditional $NaHCO_3$ treatment, BC_I, caused a significant P_{co_2} rise but little pH change. By contrast CBC_{II} caused a significant pH rise, the desired effect, while P_{co_2} actually fell without the intervention of respiration. That P_{co_2} falls even more when the initial $[HCO_3^-]$ is high is illustrated by the injection of CBC_I into blood which was still acidic after BC_I. (Equation [7] is solved graphically by a right triangle with its hypotenuse connecting initial and final injection points because its base represents the log $[H^+]$ ratio, its height the log $[HCO_3^-]$ ratio, and their difference, the log P_{co_2} ratio.) Finally, the cross-over injection of BC_{II} shows that the end equilibrium points are virtually independent of the injection order.

in which the plus sign indicates the excess of strong cations over strong anions in plasma. The solution of this equation determines equilibrium and appears as a single point on the Log C − pH diagram, i.e., at the intersection of the HCO_3^- and $SID^+ - Pr^-$ dissociation curves (Figure 1). Either the P_{co_2} (open system) or the total CO_2 concentration (closed system) determines the shape of the HCO_3^- dissociation curve (1).

2. *Quantitative predictions.*

The calculations that follow were suggested by graphical analysis on the Log C − pH diagram. Values were chosen to allow comparison with the results of the experimental procedures.

When 25 ml of 1 M $NaHCO_3$ (BC_I) are added to a liter of blood containing 600 ml of plasma, the positive charge of Na^+ from BC_I rises by $25 \times 1000/600 = 41.7$ mEq, just equal to the transient rise in negative charge from HCO_3^-. If the reaction starts near pH = 7, approximately 1/9 of the negatively charged HCO_3^- will be converted to neutral CO_2, the reaction

$$H^+ + HCO_3^- \rightarrow H_2O + CO_2 \qquad [1]$$

reducing the negative charge by $41.7/9 = 4.7$ mEq. The balance of charge necessary to maintain neutrality with added Na^+ comes mainly from protein in the reaction

$$H^+ + Pr^- \leftarrow HPr \qquad [2]$$

in which the H^+ supplied is consumed in reaction [1]. As Pr^- is produced (4.7 mEq), the pH rises. How much it rises, ΔpH, depends on the nonbicarbonate buffer strength ($\beta = 28$ slykes in true plasma)

$$\beta = \Delta Pr^-/\Delta pH$$

from which the estimated rise of pH is

$$\Delta pH = \Delta Pr^-/\beta = 4.7/28 = 0.17 \text{pH units} \qquad [5]$$

From the Henderson equation

$$[H^+][HCO_3^-] = K_1' S P_{co_2} \qquad [6]$$

we may predict the final $P_{co_{2f}}$ from the initial $P_{co_{2i}}$ as

$$P_{co_{2f}} = P_{co_{2i}} \times \frac{[H^+]_f}{[H^+]_i} \times \frac{[HCO_3^-]_f}{[HCO_3^-]_i} \qquad [7]$$

in which $[H^+]f/[H^+]i = 10^{-\Delta pH}$. With $[HCO_3^-]_i = 19$ mEq and $P_{co_{2i}} = 82$ mm Hg, equation (7) predicts $P_{co_{2f}} = 82 \times 10^{-0.17} \times (19 + 37)/19 = 163$ mm Hg.

When 25 ml of Carbicarb (CBC_{II}) is added to a liter of another sample of the same blood, the positive charge of Na^+ from Na_2CO_3 rises by $25 \times 666/600 = 28$ mEq. All of the CO_3^{2-} changes to HCO_3^- in the reaction

$$H^+ + CO_3^{2-} \leftarrow HCO_3^-$$

reducing the negative charge from this source to 14 mEq. The positive charge of Na^+ and the negative charge of HCO_3^- from the sodium bicarbonate in Carbicarb each rise by 14 mEq. (The change of negative charge because of reaction [1] is ignored because it moves to the left for existing P_{co_2} and the right for added HCO_3^-.) Charge neutrality with added Na^+ is maintained as the H^+ and negative charge consumed in reaction [3] are produced by reaction [2]. According to equation [5] the rise in pH is $\Delta pH = 14/28 = 0.5$ pH units. From equation [7] the final P_{co_2} is $P_{co_{2f}} = 82 \times 10^{-0.5} \times (19 + 14 + 14)/19 = 64$ mm Hg.

3. *Experimental procedure.*

Using the same drug to blood volume ratios as in the above predictions, crossover experiments were carried out to compare Carbicarb with $NaHCO_3$ treatment of acidosis *in vitro*. Into 2 syringes labelled I and II, each containing 20 ml of heparinized venous blood, 2 ml of 0.1 M HCl were injected to produce metabolic acidosis. After ejecting 2 ml of the mixed blood from both syringes for analysis, syringe I was treated with 2 ml of 0.25 M $NaHCO_3$ (BC_I) and syringe II with 0.25 M Carbicarb (CBC_{II}). After again returning the volume of each syringe to 20 ml, syringe I was further treated with 0.25 M Carbicarb (CBC_I) and syringe II with 0.25 M $NaHCO_3$ (BC_{II}).

RESULTS

Table 2 and Figure 1 show that HCl acidification of blood in a closedsystem raised P_{co_2} as well as lowering $[HCO_3^-]$, so that a combined "respiratory" and "metabolic" acidosis was produced, similar to that in asphyxia. When BC treatment was given first (BC_I), the P_{co_2} rose to 133 mm Hg and the pH by 0.19 units, whereas when CBC was given first (CBC_{II}), it lowered P_{co_2} and raised pH by 0.43 units. The second (crossover) treatments were administered to blood with higher $[HCO_3^-]$ levels and lower hematocrits and caused somewhat different effects: BC_{II} raised P_{co_2} less and CBC_I lowered it more than before. Again the pH rise was much less with BC than CBC.

The hematocrit did not change significantly with acidification. With the alkalinizing agents, it decreased more than would be expected from dilution alone.

The rise in osmolality was about the same with CBC as with BC.

TABLE 2

Diluted $NaHCO_3$ (BC) and Carbicarb (CBC) injected into Acidified Blood in Vitro in a Cross-over Experiment

Syringe	Injectate*	pH	$[HCO_3^-]$	P_{CO_2}	Hct	Osm	Vc'/Vc**	
			mM	mm Hg			Hct	Osm
1	Control C	7.36	26	47	45.8	.278		
	.1 M HCl	6.98	19	82	45.3	.258	1.09	1.08
	.25 M BC_I	7.17	47	133	36.8	.289	0.89	0.89
	.25 M CBC_I	7.59	67	73	30.0	.311	0.90	0.93
II	Control C	7.36	26	47	45.8	.278		
	.1 M HCl	6.97	19	82	45.8	.261	1.10	1.07
	.25 M CBC_{II}	7.40	39	64	36.0	.286	0.86	0.91
	.25 M BC_{II}	7.57	64	72	30.5	.312	0.93	0.92

* Two ml of each agent were injected in the orders shown into separate syringes (I and II) each containing exactly 20 ml of heparinized venous blood. After each injection, the blood volume (Vb) was returned to 20 ml, ejecting red cells in the process. Each injection diluted the blood by 9%.

** The calculated fractional change in red cell volume for hematocrit changes is Vc'/Vc = Hct 'Vb'/HctVb. For osmolal changes, it is Vc'/Vc = Osm/Osm', assuming that the cells are perfect osmometers.

Table 3 compares measured values of ΔpH, ΔHCO_3^- and $P_{co_{2f}}$ with the values predicted from the simplified model in "Methods" during the first alkalinization with BC_I or CBC_{II} starting with virtually the same lowered HCO_3^- levels.

DISCUSSION

Quantitative acid-base considerations.

Table 2 shows that Carbicarb not only does not raise P_{co_2} (as with $NaHCO_3$ injection) but can lower it under certain conditions. One of these conditions is that the drug be injected into blood with a relatively high bicarbonate level. The explanation for this is as follows. For identical injectates the ΔpH and ΔHCO_3^- are nearly independent of the initial pH and bicarbonate levels (*cf.* BC_I with BC_{II} or CBC_I with CBC_{II}). In contrast, the increase or decrease of P_{co_2} and the $P_{co_{2f}}/P_{co_{2i}}$ ratio depend on the initial bicarbonate, but not on the initial pH, since the final to initial bicarbonate ratio in equation [7] is smaller for the same $\Delta[HCO_3^-]$ when the initial bicarbonate is high.

As an example, consider crossover injection of CBC_I into blood with the initial experimental values pH = 7.17, $[HCO_3^-]$ = 47 mM and $P_{co_{2i}}$ = 133 mm Hg. Following the computations in "Methods", ΔHCO_3^- = 28 and ΔpH = 0.5 if β and Hct are unchanged. The predicted final P_{co_2} from equation [7] is

$$P_{co_{2f}} = 133 \times 10^{-0.5} \times (47 + 28)/47 = 67 \text{ mm Hg}$$

TABLE 3

Comparison of Measured with Predicted Changes after First Treatment of Acidified Blood with BC_I and CBC_{II} and after Cross-over Treatment CBC_I

		Δ pH		Δ [HCO_3^-]		Final P_{CO_2}	
				mM		mMHg	
Syringe	Injectate	Meas	Pred	Meas	Pred	Meas	Pred
I*	BC_I	0.19	0.17	28	37	133	163
II*	CBC_{II}	0.43	0.5	20	28	64	64
I**	CBC_I	0.42	0.5	20	28	73	67

* Initial [HCO_3^-] = 19, initial P_{CO_2} = 82

** Initial [HCO_3^-] = 47, initial P_{CO_2} = 133

a reduction to 50% of the initial P_{CO_2} of 133. During CBC_{II} the predicted reduction was to 78%. These results are summarized in Table 3. For similar reasons, the percentage rise in P_{CO_2} after BC_{II} is less than for BC_I because of the high initial bicarbonate level.

The results are affected by variation of buffer strength with pH and dilution. For example, if in CBC_{II}, "Methods", the buffer strength is reduced from 28 to 20 slykes, one finds $\Delta pH = 14/20 = 0.7$ pH units and $P_{CO_{2f}} = 82 \times 10^{-0.7}\ (19 + 28)/19 = 40$ mm Hg, compared with the previous values of 0.5 pH units and 64 mm Hg.

Other factors which contribute to the difference between measured and predicted results include dilution by finite injectate volume, water transport across the red-cell membrane because of osmotic forces, and anion shifts that maintain Donnan equilibrium.

Volume considerations.

The effects of dilution were ignored in "Methods". Except for dilution, 25 ml of 1M (in Na^+) injectate into one liter of blood in the theory is equivalent to 100 ml of 0.25M (in Na^+) injectate into one liter (2 ml into 20 ml) of blood as in the experiment. The 2 ml injectate dilutes the blood by 9% and creates a 9% fall in hematocrit if cell volume remains constant. Estimated fractional cell volume changes calculated from hematocrit or osmotic pressure are shown in Table 2.

When the injectate is HCl, the reduction of plasma [Na^+] causes water to enter the cells. The acid shift causes Cl^- and HCO_3^- to enter the cells as Donnan's r increases. Both of these factors cause the cells to swell as indicated by the 7–10% increase in cell volume in Table 2.

When $NaHCO_3$ is injected, the extra plasma sodium draws water into the plasma and the cells shrink. A small outward movement of anions may also contribute as Donnan's r decreases because of the slightly increased pH. Experimentally, the cells shrank 7–11% in both cases of $NaHCO_3$ injection, more for low initial bicarbonate levels.

When Carbicarb is injected, the volume of water drawn into plasma because of increased sodium is the same as before. The large increase in pH contributes more to cell shrinkage than before. Experimentally, the cells shrank 7–14% in both cases of Carbicarb injection, more for low initial bicarbonate levels. For similar initial bicarbonate levels the shrinkage calculated from hematocrit was greater for CBC than for BC, but the shrinkage calculated from osmotic pressure was inconsistent.

Qualitative physiological consideration.

The P_{co_2}-lowering ability of Carbicarb is great when it is added to blood with a relatively high bicarbonate level and a low hematocrit, conditions seen in asphyxia and shock. The reason for the effect of HCO_3^- levels has been explained above. The low Hct effect, associated with a low buffering capacity, can be visualized as follows. The carbonate ion, as a strong base added to plasma, abstracts protons from 2 reservoirs: from buffer acids [HPr] and from dissolved [CO_2], the effective proton-donating concentration of carbonic acid. These 2 reservoirs of proton supply are, respectively, in blood itself and in tissues to which the blood has access, i.e., tissues perfused by capillaries. The protein reservoir is shown in reaction [2]; the CO_2 reservoir by reaction [1]. When reaction [3] is considered in relation to these

$$\begin{array}{ll} H^+ + Pr^- \leftarrow HPr & [2] \\ \downarrow & \\ H^+ + CO_3^{2-} \rightarrow HCO_3^- & [3] \\ \uparrow & \\ H^+ + HCO_3^- \leftarrow H_2O + CO_2 & [1] \end{array}$$

it may be seen that with high buffer concentration, most of the protons may be supplied from protein (upper vertical arrow) so that few come from the CO_2 system, in which case P_{co_2} may change but slightly. On the other hand in a poorly buffered medium (e.g., plasma with few or no red cells), the P_{co_2} fall with Carbicarb would be more pronounced (the lower vertical arrow would be more important).

Clinical implications.

Our results and preliminary work in dogs (32) show that Carbicarb raises blood pH more than 1 M $NaHCO_3$ in the same dose, probably regardless of the presence or absence of adequate ventilation. The dosage of Carbicarb needed for treating metabolic acidosis would be lower and therefore the dangers of bicarbonate overdosing reduced.

There may be other advantages. Although Carbicarb contains fewer osmols than 1 M $NaHCO_3$, the osmolality of blood increases equally after

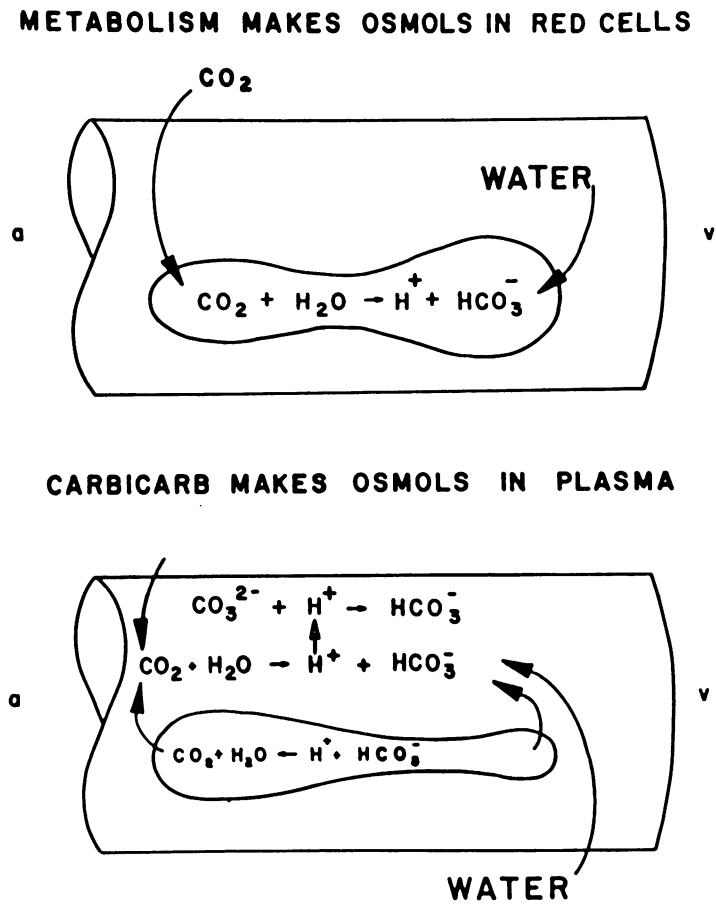

FIG. 2. Blood traversing a systemic capillary. Above: The normal swelling (34) of a red cell (exaggerated) as it moves from the arterial to the venous end caused by the increase in the Donnan ratio, r, of osmotically active anions, more bicarbonate being normally generated inside than outside the cell because of intracellular buffering. Below: The probable red cell shrinkage caused by Carbicarb's ability to generate HCO_3^- ions outside the cell from CO_2 and the consequent alkalinizations. "When pH_i [inside the cell] increases, the negative charge on Hb and organic phosphate increases, there are fewer permeable anions inside, r decreases, cell water decreases and thus the cell shrinks" (36).

equal doses of these drugs. Part of this increase probably results from HCO_3^- being generated in the plasma, not from CO_3^{2-} directly (which would not increase osmolality), but from CO_2 dissolved in the blood and elsewhere. Some of this CO_2 must come from red cells which therefore would lose HCO_3^- ions by reaction [1].

Figure 2 shows the probable effect of Carbicarb on red cell volume. It is known that red cells swell when exposed to CO_2 (33) and when they traverse normal systemic capillaries (34); how much they swell with

tissue ischemia with its attendant lactic acidosis and local hypercarbia, is not clear, but Shires et al. (35) have obtained evidence that the increase in red cell water in shock is significant. If Carbicarb can increase plasma osmolality by generating HCO_3^- *in situ*, it might act as a cell shrinker and plasma expander and be useful not only in treating metabolic acidosis, but also its commonest cause, reduced tissue perfusion.

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DISCUSSION

Rochester (Charlottesville): I think that was an extremely interesting and provocative paper. In some experiments in our own laboratory where we gave bicarbonate alone in an attempt to offset the acidosis consequent to high CO_2 levels, the dogs were hypotensive and had poor contraction of the diaphragm. So, I think that the notion of using a mixture of sodium carbonate and bicarbonate to avoid the CO_2 increasing effects is a terribly important advantage. Did I understand correctly that you think that the improvement in the oxygen delivery is really operating at the microcirculatory level and, if so, do you have any single organ perfusion studies to test for a given mean arterial pressure, what might happen in the microvasculature?

Filley: Thank you very much Dr. Rochester. No, we have no specific organ studies going. But to answer your question about oxygenation, there is another factor that we didn't have time to get to: that the improved oxygenation is partly due to the fact that this agent, because it is such a strong alkalinizer, moves O_2 dissociation curve to the left. Now when you move the curve to the left for the given alveolar PO_2 there is more oxygen in every cell so that you are loading the cells more. This is a notion I'd like to have more comments on because it is taught in all the textbooks that the most important thing is to

move the curve to the right and this is an objection to sodium bicarbonate. I think it is quite possible that in shock the curve should be moved to the left just as it should be moved to the left on Mt. Everest. Furthermore, in shocked rats from Holland (Kreuzer et al.) it was recently shown that survival was much better when you increase the saturation even at the expense of the PO_2. With carbicarb there is another factor beside increase in plasma volume; probably increase in O_2 saturation is a help.

Hellums (Jackson): Dr. Filley do you have any survival data on these dogs to show if this agent improves the mortality in the shock model? It is well known 75% will not survive regardless of the various therapies that have been used in this type of experimental shock.

Filley: Yes, that is a most important experiment and it must be done. It's going to require careful planning because shock is so complex that we must have comparable dogs. We have attempted to use each dog for his own control. We may have to go to having dogs treated only with bicarb versus dogs treated only with carbicarb.