ROLE OF CHLORIDE IN METABOLIC ACIDOSIS

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One of the main causes of misunderstanding about the role of chloride in the acid-base balance is vagueness of the so called "reciprocal way" with which chloride and bicarbonate seem to vary.1 There are two well-known terms which would imply such a way—hypochloremic alkalosis and hyperchloremic acidosis. Besides, there are two experimental facts, which seem to favor them, that chloride deficiency accelerates the bicarbonate reabsorption2 and that chloride excess inhibits it in the renal tubules.3 Therefore, it might be quite natural for us to believe that excessive chloride would push bicarbonate out of the blood through the kidney4 and that it would induce hyperchloremic acidosis.5 Hence many specialists of body fluids say that in cases of acidosis saline must not be administered, as it is, because of its high chloride content relative to that of the extracellular fluid.5,6 On the other hand, however, some say that isotonic saline does not intensify acidosis, and even that it tends to correct acidosis.8 Because of the considerable clinical importance of this subject the author studied the behavior of the excessive chloride administered. A part of these studies was already published as a preliminary report elsewhere.9

METHODS

The experiments consist of three parts as follows:

(1) Infusion of isotonic saline into two healthy men: Two healthy men weighing 58 and 62 kg were used. Five hundred ml isotonic saline was infused intravenously within 40 minutes to examine its acidifying effect and the effect on the electrolyte excretion of the kidney. The blood samples for pH, Paco2 and bicarbonate measurements were drawn from the brachial artery before and after the infusion, but those for plasma electrolytes and creatinine measure-
ments were obtained from the antecubital vein at the mid-point of each clearance period to avoid frequent arterial punctures. Urine was collected via a catheter in the bladder. Glomerular filtration rate (GFR) was estimated from endogenous creatinine clearance.

(2) Infusion of isotonic saline and glucose into dogs at various rates: The experiments were performed in 7 dogs, which received infusion of an isotonic saline or glucose solution at various rates (0.2-3.5 ml/kg/min).

(3) Infusion of three kinds of isotonic solutions into dogs at the same rate: Nine dogs were divided into three groups, each containing three. The dogs of each group were given intravenous infusion of isotonic saline, glucose and mannitol, respectively, at the same rate (3.5 ml/kg/min) in order to compare the effects of those three kinds of solutions. Two of the nine experimental data were those included in the second series above—the saline and the glucose infusion at the rate of 3.5 ml/kg/min.

All dogs (8-11 kg) used had been anesthetized with intravenous sodium pentobarbital (20-40 mg/kg). A femoral vein was opened for the administration of an isotonic fluid. A femoral artery was cannulated to obtain blood samples. A polyethylene air way was inserted into the larynx, and the animal breathed spontaneously throughout the experiment. Infusion was performed by a Sigma-motor constant infusion pump.

Measurements of pH, Paco₂ and plasma bicarbonate were done by Astrup's method. Sodium and potassium were measured by flame photometry, chloride by Schales & Schales method, creatinine by Jaffe method.

RESULTS

(1) Infusion of isotonic saline solutions into two healthy men: Isotonic saline is usually given to patients at a rate of 400 ml per hour. In these experiments it was infused more rapidly to exaggerate its effect on the acid-base balance and the electrolyte excretion through the kidney. No metabolic acidosis was brought about in the two men by the infusion of 500 ml isotonic saline in 40 minutes (Table 1). Since the two experiments showed a similar tendency, the details of only one of them are given in Table 2. Following the rise of GFR by 11.8 to 3.8 ml/min during the infusion, the quantity of the filtered sodium and chloride rose by 1.7 to 0.5 and 1.3 to 0.5 mEq/min respectively. At the same time the reabsorption of sodium and chloride also increased by 1.6 to 0.5 and 1.3 to 0.5 mEq/min respectively, but the fractional reabsorption of both decreased. Before the infusion the fractional reabsorption of sodium was not
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Table 1

<table>
<thead>
<tr>
<th></th>
<th>Subject 62 kg ♂</th>
<th>Subject 58 kg ♂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>pH</td>
<td>7.368</td>
<td>7.380</td>
</tr>
<tr>
<td>Paco₂ (mmHg)</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Actual Bicarbonate (mEq/l)</td>
<td>24.3</td>
<td>24.0</td>
</tr>
<tr>
<td>Standard Bicarbonate (mEq/l)</td>
<td>23.3</td>
<td>23.5</td>
</tr>
</tbody>
</table>

significantly different from that of chloride (Na: 99.16—99.20, Cl: 99.17—99.16%). However, during the infusion the latter tended to reduce more than the former, (Na: 99.03—98.75, Cl: 98.91—98.76%) and, especially, after the infusion the latter reduced exceeding the former significantly (Na: 98.76—98.98, Cl: 97.95—98.58). Hence the excretion rate of chloride surpassed that of sodium by 0.02 mEq/min at the last 20 minutes after the infusion (Table 2).

(2) Infusion of isotonic saline and glucose solutions into dogs at various rates: Figure 1 shows the change of standard bicarbonate, when saline or 5% glucose was infused more and more rapidly. When the infusion rate was almost the same as the above human experiments (0.2 ml/kg/min), no acidify-

Fig. 1. The effect of isotonic saline infused at various rates compared with isotonic glucose.
Table 2 Infusion of Isotonic Saline into a Healthy Man (Subject E.T.)

<table>
<thead>
<tr>
<th>TIME</th>
<th>Cretat</th>
<th>VENOUS PLASMA CONCENTRATION</th>
<th>URINE CONCENTRATION</th>
<th>SODIUM</th>
<th>CHLORIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Na</td>
<td>Cl</td>
<td>ml/min</td>
<td>mEq/liter</td>
</tr>
<tr>
<td>Min.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-20</td>
<td></td>
<td>75.6</td>
<td>142</td>
<td>111</td>
<td>0.85</td>
</tr>
<tr>
<td>20-40</td>
<td></td>
<td>75.2</td>
<td>142</td>
<td>111</td>
<td>0.80</td>
</tr>
<tr>
<td>40</td>
<td>Infusion started: 0.9% NaCl 500 ml</td>
<td>arterial blood: pH 7.365, Pco, 44 mmHg, bicarbonate 24.3 mEq/liter</td>
<td>venous plasma: Na 142, Cl 111, K 4.3 mEq/liter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-60</td>
<td>87.0</td>
<td>142</td>
<td>111</td>
<td>1.00</td>
<td>117.5</td>
</tr>
<tr>
<td>60-80</td>
<td>79.0</td>
<td>142</td>
<td>112</td>
<td>1.00</td>
<td>139.0</td>
</tr>
<tr>
<td>80</td>
<td>Infusion stopped</td>
<td>arterial blood: pH 7.330, Pco, 42 mmHg, bicarbonate 24.0 mEq/liter</td>
<td>venous plasma: Na 142, Cl 112, K 4.4 mEq/liter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-100</td>
<td>77.0</td>
<td>142</td>
<td>111</td>
<td>1.00</td>
<td>134.5</td>
</tr>
<tr>
<td>100-120</td>
<td>76.0</td>
<td>142</td>
<td>111</td>
<td>0.90</td>
<td>125.4</td>
</tr>
</tbody>
</table>
ing effects were seen. As the rate increased, standard bicarbonate tended to reduce. Namely, when they were infused for 20 minutes at the rate of 1.0 and 3.5 ml/kg/min, standard bicarbonate reduced by about 1.0 and 4.0 mEq/liter respectively. But there seemed to be no significant difference between the effects of isotonic glucose and saline.

(3) Infusion of three kinds of isotonic solutions into dogs at the same rate: The acidifying effect of isotonic saline was compared with that of other isotonic solutions. Especially an isotonic solution of mannitol was selected as a control because it is not metabolized and, therefore, inert in the body.

![Graph showing changes of standard bicarbonate during the infusion of isotonic solutions at the rate of 3.5 ml/kg/min.](image)

Fig. 2. Changes of standard bicarbonate during the infusion of isotonic solutions at the rate of 3.5 ml/kg/min.

![Graph showing three representative examples of infusion of isotonic solutions, showing the change of blood pH, PaCO₂ and standard bicarbonate.](image)

Fig. 3. Three representative examples of infusion of isotonic solutions, showing the change of blood pH, PaCO₂ and standard bicarbonate.

![Graph showing changes of the plasma electrolytes produced by the infusion of isotonic saline and glucose for 25 minutes at the rate of 3.5 ml/kg/min.](image)

Fig. 4. Changes of the plasma electrolytes produced by the infusion of isotonic saline and glucose for 25 minutes at the rate of 3.5 ml/kg/min.
2 shows the effects of three kinds of isotonic solutions, 0.9% saline, 5% glucose and 5% mannitol, when infused at the same rate (3.5 ml/kg/min). The regression lines are shown on the right of the Figure 2. All of them show the reduction of standard bicarbonate by 4 to 5 mEq/liter in 25 minutes. The whole data of three representative experiments are shown in Figure 3. Three groups, each including three experiments, were statistically compared in regard to the gradient of their regression lines, using the “analysis of variance” method (one way layout). As the variance within each group was larger than that among the three groups, the latter was regarded as insignificant. The plasma electrolyte changes at that time are summarized in Figure 4 and Table 3. After the saline infusion both the plasma sodium and chloride level rose, by 5 to 9 and 12 to 15

<table>
<thead>
<tr>
<th>mEq/liter</th>
<th>Dog 1</th>
<th>Dog 2</th>
<th>Dog 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>before after</td>
<td>143 152</td>
<td>+9</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>before after</td>
<td>115 127</td>
<td>+12</td>
</tr>
<tr>
<td>Na⁺−Cl⁻</td>
<td>before after</td>
<td>28 25</td>
<td>−3</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>before after</td>
<td>20.3 17.7</td>
<td>−2.6</td>
</tr>
<tr>
<td>K⁺</td>
<td>before after</td>
<td>3.9 3.0</td>
<td>−0.9</td>
</tr>
</tbody>
</table>

Table 3
The Acidosis with Hyperchloremia Produced by Infusion of Isotonic Saline for 25 Minutes at a Rate of 3.5 ml/kg/min

Fig. 5. The effect of respiratory acidosis on standard bicarbonate.
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mEq/liter respectively, accompanying decrease of the bicarbonate level by 2.6 to 5.9 mEq/liter. However, since the rise of the chloride level was more than that of the sodium level, the difference between them decreased (Table 3). It looks, therefore, as if bicarbonate had been pushed out of the blood by chloride (Figure 4, on the left). But, on the contrary, the glucose and the mannitol infusion reduced the bicarbonate level by the same degree (2.5 to 4.6 mEq/liter) without the rise of chloride level (Figure 4, on the right).

DISCUSSION

The extracellular water contains more sodium than chloride. (Na: 140 mEq/liter, Cl: 100 mEq/liter) Since isotonic saline, however, contains 154 milliequivalents of both per liter, chloride can be regarded as excessive. The ground on which this excessive chloride was considered to cause acidosis by reducing the bicarbonate content of the blood is the reciprocal way with which chloride and bicarbonate seem to vary. The reciprocal relationship between chloride and bicarbonate can be found in the reabsorption process of the renal tubules. In the state of chloride deficiency tubular fluid becomes depleted of reabsorbable anions to follow the reabsorbed sodium ions. Hence the inside of the tubular lumen becomes electrically more negative and the hydrogen ion secretion or the bicarbonate reabsorption is accelerated, as a result of which hypochloremic alkalosis ensues. Chloride excess, on the contrary, is said to inhibit the bicarbonate reabsorption, when administered extremely in large excess. This fact, erroneously, gives us an impression that chloride excess would cause hyperchloremic acidosis. Those two terms—hypochloremic alkalosis and hyperchloremic acidosis, are too well-known. It is certain that hypochloremic alkalosis can be brought about by chloride deficiency, but hyperchloremic acidosis which we often clinically encounter is caused not by chloride excess but by specific tubular defects of bicarbonate reabsorption. When the bicarbonate reabsorption is out of order, the other common reabsorbable anion, chloride, would be reabsorbed instead. Pitts and Lotspeich found that chloride reduces the capacity of the tubular bicarbonate reabsorption, when administered in very large excess. But the results of their extreme experiments cannot be applied to these clinical events in spite of their contribution in the physiological field. The results of the author show that excessive chloride is very apt to be removed through the kidney and that it is not retained in place of bicarbonate, though the bicarbonate reabsorption was not measured (Table 1 and Table 2). Gamble et al. showed similar data. They fed sodium chloride, which also contains chloride in excess,
to a child with tissue fluids depleted by fasting and found that more chloride was excreted than sodium, showing that the latter had been retained in greater quantities. Furthermore, the plasma bicarbonate level rose and the chloride level was approximately sustained. Hence they concluded that the body is able to retain, in order to maintain the acid-base balance, that ion of a neutral salt of which it is most in need. These facts do not favor the theory that excessive chloride, being reabsorbed in place of bicarbonate, becomes a cause of hyperchloremic acidosis.

The data presented here tell that the acidosis which would be produced by saline infusion is more closely related to the infusion rate rather than to chloride itself. Since rather rapid infusion did not produce metabolic acidosis in the above two persons, more rapid and much infusion had to be tried in dogs (Figure 1). But it must be noted that intravenous administration of any fluid can cause a respiratory change. Since the change of Paco2 influences not only on the blood pH but also on the plasma bicarbonate level, a more accurate index or parameter of metabolic (nonrespiratory) acidosis must be selected. We attempted to exclude the respiratory factor by measuring standard bicarbonate, for which the Paco2 is constant at 40 mmHg.

(Recently, standard bicarbonate is not considered to be an appropriate index of metabolic acid-base changes because of the difference between the carbon dioxide titration curves in vitro and in vivo. But the discrepancy between the two curves is large only when the change of Paco2 is severe. Our data say that the reduction of standard bicarbonate is only about 0.32±0.20 mEq/liter (mean ± standard deviation) when Paco2 rises by 10 mmHg (Figure 5), while even the standard deviation of the standard bicarbonate measurements, performed ten times on a same sample, was 0.19 mEq/liter. Standard bicarbonate, therefore, can be used as a convenient parameter of the changing process of metabolic acidosis, when the change of Paco2 is not so large.)

As the rate of infusion was increased, standard bicarbonate reduced progressively. Besides, no significant differences were found between the effects of isotonic saline and chloride-free solutions. But it is noteworthy that acidosis with hyperchloremia was brought about by rapid infusion of saline solution (Figure 4). What is the mechanism of that event at all? It is illustrated in Figure 6. For example, if one liter of plasma is diluted, anaerobically, with the same volume of isotonic saline, the bicarbonate concentration will reduce by a half. At that time the chloride concentration rises from 100 to 127 mEq/liter, and the sodium concentration from 140 to 147 mEq/liter. Since the rise of the former (27 mEq/liter) is larger than that of the latter (7 mEq/liter), it looks
as if the reduction of the bicarbonate level was caused by chloride. However, the fact is that the reduction of bicarbonate was caused by dilution (Figure 6, the left lower beaker). Hence, if the plasma is diluted with an isotonic glucose or mannitol solution, the bicarbonate and the chloride level will reduce, by a half, simultaneously (the right lower beaker). The “hyperchloremic” acidosis caused by saline infusion in vivo is just the same as the one seen in the left beaker, since not only the chloride but also the sodium concentration increased, though the latter rose less (Table 3). It is taken to indicate that this type of acidosis has nothing to do with the role of chloride in the renal tubules. Such a type of acidosis is the one Shires and Holmann named “dilution acidosis” which means dilution of plasma bicarbonate by an exogenous fluid. Furthermore, the fact that an isotonic solution of mannitol, which is not metabolized in the body, had the same effect as others may well be taken to verify that the cause of the acidosis was dilution by water, the medium, and not chloride. It may sound paradoxical that water causes acidosis, but it is not so. The infused solution, or its medium water, will dilute the extracellular bicarbonate—the numerator of the bicarbonate/carbonic acid buffer pair in Henderson-Hasselbach's equation—while the denominator remains at almost the same concentration, since the production of carbon dioxide in the body is constant (Note that the Paco2 changed little in comparison with the reduction of bicarbonate; Figure 3). Therefore, pH of the blood is lowered. There is no reason why saline must be feared on account of its high chloride content, because chloride-free solutions equally have an
acidifying effect when infused too rapidly. Nevertheless, there will be an opinion that chloride may be excessively reabsorbed when the kidneys are impaired. But it has never been reported that the sodium chloride, which also contains chloride in excess, induced hyperchloremic acidosis in renal insufficiency. The above mentioned explanation does not mean that isotonic saline is effective enough to correct severe acidosis. Hartmann tried to reduce the chloride concentration of isotonic saline by adding sodium lactate. It is, of course, useful in acidosis, because it enhances an alkalinizing effect when metabolized in the body, but not because it reduces the chloride concentration of saline.

SUMMARY AND CONCLUSION

So far the role of chloride in metabolic acidosis has not been established. Accordingly, many clinicians are afraid of isotonic saline considering that it will intensify metabolic acidosis because of its high chloride content. However, the data do not indicate that isotonic saline has an acidifying effect, unless it is infused enormously. The acidosis which has been thought to be caused by isotonic saline is simply the one due to dilution of plasma bicarbonate by the water when it is given in very large quantities. Excessive chloride contained in sodium chloride and saline is easily excreted through the kidney and, therefore, cannot be the cause of acidosis. Hyperchloremia which follows hyperchloremic acidosis is not a cause but a result of the lack of bicarbonate reabsorption in the renal tubules. The significance of sodium lactate in the Hartmann’s solution is in the alkalinizing effect of sodium lactate, but not in its ability to reduce the chloride concentration of saline.

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