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Current topic

The role of bicarbonate and base precursors in treatment of acute gastroenteritis

E J ELLIOTT, J A WALKER-SMITH, AND M J G FARTHING

Departments of Child Health and Gastroenterology, St Bartholomew's Hospital, London

Widespread use of oral glucose-electrolyte rehydration solutions (ORS) has resulted in a dramatic decrease in the morbidity and mortality associated with childhood gastroenteritis, regardless of its aetiology. Nevertheless, diarrhoeal disease remains the most common cause of death of children in developing countries, and current research efforts are directed towards optimising the efficacy of ORS, aiming for both simplicity and economy. Controversy regarding the 'ideal' sodium and glucose concentration continues to the extent that different formulations are now recommended in the developing and industrialised world. The inclusion of bicarbonate or a base precursor (citrate, acetate, or lactate) in ORS is generally assumed to be necessary, both for promotion of water and sodium absorption and correction of acidosis. This issue, however, has received little critical attention since the formal introduction of oral rehydration therapy. We have reviewed the available evidence from animal and human studies and conclude that there is little evidence to support the inclusion of bicarbonate or a base precursor in ORS.

Historical considerations

Intravenous treatment. As early as 1832 Latta recommended intravenous saline containing 'two scruples of subcarbonate of soda' for the treatment of cholera and its associated acidosis.[1] A similar regimen with intravenous sodium acetate or bicarbonate was used by 1910 by Sellards.[2] This treatment decreased the mortality from renal failure associated with cholera. Acidosis in infantile diarrhoea of other causes was also shown to improve after administration of bicarbonate.[3] Powers recommended bicarbonate in his plan of treatment for the 'intestinal intoxication of infants' in 1926,[4] and Hartmann used sodium lactate to relieve acidosis in diarrhoeal disease in 1938.[5] None of these studies, however, attempted to answer the important question as to whether rehydration with base was superior to rehydration with saline alone.

The use of parenteral bicarbonate was not without its problems. In the 1940s Rapoport *et al* recommended vigorous rehydration with saline containing sodium bicarbonate but without potassium and reported a 'post-acidotic state' in children whose diarrhoea had improved and in whom recovery seemed imminent.[6] The clinical syndrome he described of lethargy, irritability, abnormal cardiac function, intracranial haemorrhage, generalised oedema, and tetany can be attributed to the alkalosis and electrolyte disturbance (hypokalaemia, hypocalcaemia, hypophosphataemia, and hypernatraemia) after excessive rapid administration of sodium and alkali.

Oral treatment. Darrow was the first to recommend oral rehydration with a glucose-electrolyte solution as an alternative to intravenous fluids. Although all the children in his original study had low serum bicarbonate concentrations, these returned to normal after treatment with solutions containing lactate (53 mmol/l), even in the most severe cases. Although this often took more than 24 hours, acidosis did not recur after rehydration began, and alkalosis and the 'post-acidotic state' were never observed. Further studies confirmed these findings, leading Darrow and colleagues to conclude that additional bases such as sodium bicarbonate were seldom if ever required for the treatment of acidosis in diarrhoeal disease of infancy.[7] Furthermore, these investigators recognised that if bicarbonate was given rapidly or in large amounts the condition described by Rapoport could occur.

Since those early days, the use of oral rehydration solutions has rapidly increased. Bicarbonate or a base precursor is included in the World Health Organisation (WHO) ORS and in commercially manufactured ORSs in the United Kingdom (Table 1) and throughout the world, on the premises that

Table 1 *Composition of WHO and commercial ORSs (mmol/l)*

	WHO	*WHO citrate*	*BNF**	*Dioralyte†*	*Rehidrat‡*	*Dextrolyte§*
Bicarbonate	30		18	18	20	
Citrate		10			9	
Lactate						18
Sodium	90	90	35	35	50	35
Chloride	80	80	37	37	50	30
Potassium	20	20	20	20	20	13
Glucose	111	111	200	202	91	200
Sucrose					94	
Fructose					2	

**British National Formulary*, Sodium Chloride and Glucose Oral Powder Compound.
†Armour Pharmaceutical Co Ltd.
‡Searle Pharmaceuticals.
§Cow and Gate Ltd.

(a) bicarbonate enhances sodium and water absorption and (b) the metabolic acidosis of acute diarrhoea requires correction with exogenous base. Justification for the continued use of bicarbonate or base precursor in ORS must be supported by evidence for at least one or preferably both of these statements.

Effect of base on intestinal sodium and water transport

Bicarbonate stimulates water and sodium absorption in the normal human jejunum and ileum.[8] The magnitude of this effect on sodium absorption in the human jejunum is comparable with that of glucose and independent of luminal pH.[9] Short chain fatty acids, such as the base precursor acetate, share the ability of bicarbonate to stimulate sodium and water absorption in the human small intestine.[10]

Although bicarbonate has similar effects on water and sodium absorption in the normal rat small intestine,[11] we have shown that bicarbonate and the base precursors acetate and citrate are unable (unlike glucose) to reverse water and sodium secretion induced by cholera toxin (Unpublished observations). These findings suggest that bicarbonate may not be beneficial with respect to the promotion of water absorption in the enterotoxin mediated diarrhoeas.

Role of base in the correction of metabolic acidosis

It is now generally accepted that in metabolic acidosis of childhood administration of bicarbonate should be reserved for conditions in which endogenous production or conservation of bicarbonate is inadequate to restore normal pH. Examples of such specific disorders include salicylism, prolonged diarrhoea, disorders of organic and amino acid metabolism, and renal tubular acidosis. In acute hypoxia and prerenal or circulatory failure bicarbonate is only recommended when pH fails to correct after restoration of adequate intravascular volume. Similarly, children with diabetes with ketoacidosis do not require bicarbonate providing adequate insulin and fluids are given and cardiovascular and renal function is normal, unless blood pH falls below 7·2.[12]

Metabolic acidosis during acute diarrhoea is generally attributed to bicarbonate loss in the stool, which results in loss of total blood buffering capacity. In addition, when dehydration is severe and renal plasma flow falls excretion of hydrogen ions and regeneration of bicarbonate is impaired. Also poor perfusion of peripheral tissue may contribute to a lactic acidosis. Acidosis is more likely to complicate cholera than other acute diarrhoea, as the stool concentration of bicarbonate is higher than in rotavirus or enterotoxigenic *Escherichia coli* diarrhoea and dehydration more pronounced (Table 2).[13 14] Despite these theoretical considerations and the common finding of a reduced serum bicarbonate concentration in acute diarrhoea, mean arterial pH is often normal.

Thus, providing perfusion is maintained, renal compensation ensures that acid base state will normalise with rehydration *without* additional base in the vast majority of cases of acute gastroenteritis.

In severely dehydrated or acidotic patients

Table 2 *Electrolyte composition of stool in childhood gastroenteritis*

Aetiology	*Stool electrolytes (mmol/l)*			
	Sodium	*Potassium*	*Chloride*	*Bicarbonate*
Cholera	101*	27	92	32
	88†	30	86	32
Rotavirus	37†	38	22	6
Enterotoxigenic *Escherichia coli*	53†	37	24	18
Non-cholera diarrhoea	56*	25	55	14

*Reference 13.
†Reference 14.

(pH<7·2), in those with persistent high volume diarrhoea, and in those with impaired renal function and worsening metabolic acidosis the administration of intravenous base such as sodium bicarbonate is indicated and may be life saving. Correction of acidosis with parenteral sodium bicarbonate must be performed with caution to avoid its detrimental effects.[12]

Clinical observations

There is little clinical evidence to support the inclusion of base in the treatment of acidosis and dehydration in acute diarrhoea. Indeed, most regimens for intravenous rehydration are effective despite the omission of bicarbonate.[15] In a controlled trial in Capetown Heese compared a mildly alkalinising intravenous solution (26 mEq/l lactate) with or without additional sodium bicarbonate for treating children with acute gastroenteritis who were acidotic and 5–10% dehydrated. Those who received additional base regained normal pH, carbon dioxide tension, and serum bicarbonate more quickly than those who did not, but no ill effects were suffered by the latter group, and both groups were biochemically identical by 24 hours.[16]

Early uncontrolled studies based in hospitals have shown equal effectiveness in rehydration but slower correction of acidosis when comparing a labon-gur (common salt and brown sugar) ORS without bicarbonate with the WHO solution.[17] An uncontrolled study based in the community in the Punjab has shown successful treatment of acute diarrhoea in children and a substantial reduction in mortality even when both sodium bicarbonate and potassium chloride were omitted from the ORS.[18] Similarly, rice water without electrolyte additives has been used successfully in the treatment of infantile gastroenteritis.[19] In Cardiff 90 children admitted with gastroenteritis and reduced serum bicarbonate concentrations were adequately treated with intravenous or oral rehydration solutions without bicarbonate.[15]

Controlled trials examining the value of base in ORS are few and are outlined in Table 3. In a recent clinical trial in Bangladesh Islam compared the efficacy of ORS with and without bicarbonate.[20] He showed that while correction of serum bicarbonate was slower in the children receiving the solution free of bicarbonate compared with the control group (WHO-ORS) during the first 24 hours, there was no difference at 48 hours. The delayed return of plasma bicarbonate to normal almost certainly has no clinical relevance as the patients were rehydrated, with good urine output and no clinical evidence of acidosis. A double blind controlled trial in the

Table 3 *Recent controlled trials of bicarbonate and base precursors in ORSs*

Study	*Location*	*Age range*	*(n)*	*ORS tested*	*Result*		
					Rehydration	*Correction of acidosis*	*Stool volume*
Islam[20]	Bangladesh	<5 years	(98)	WHO-ORS *v* WHO-ORS without bicarbonate	Similar	Slower (serum bicarbonate) with WHO-ORS without bicarbonate at 24h, same at 48h	NS*
Clements[21]	Honduras	3–18 months	(61)	WHO-ORS *v* simple sugar salt solution	Similar	Slower (total carbon dioxide) with sugar salt solution, but similar at 48h	
Patra[23]	Calcutta	2·5–72 months	(40)	WHO-ORS *v* ORS acetate	Similar	Similar	NS*
Islam[27]	Bangladesh	2–10 years	(26)	WHO-ORS *v* ORS citrate	Similar	Similar (total carbon dioxide) at 4, 24, and 48h	NS*
		>10 years	(14)				
Hoffman[28]	Jakarta	3–82 years	(130)	WHO-ORS *v* ORS citrate	ORS citrate superior	Faster (total carbon dioxide) with ORS citrate	Less with ORS citrate
Islam[30]	Bangladesh	<5 years	(94)	WHO-ORS *v* ORS citrate	Similar	Slower (serum bicarbonate) with ORS citrate at 24h, same at 48h	NS*

*Trend to higher stool volume with ORS containing bicarbonate.

Honduras showed that a simple oral sugar/salt solution without bicarbonate will correct even pronounced acidosis (total carbon dioxide <10 mmol/l) as effectively, though slightly more slowly, than the WHO solution.[21] We have recently completed a double blind controlled trial comparing British National Formulary ORS (Table 1) with an identical solution in which bicarbonate was replaced by chloride. In 40 children with gastroenteritis inclusion of bicarbonate offered no clinical or biochemical advantage (Unpublished observations).

Practical problems with bicarbonate

Although intravenous solutions containing bicarbonate have been widely used, they must be autoclaved under a high carbon dioxide pressure, making production of sterile solutions difficult.[22] Regarding ORS, bicarbonate is often unavailable in developing countries and adds to the bulk and expense of ORS sachets. On exposure to high humidity or heat bicarbonate in ORS powders may form furfural compounds with glucose, causing decomposition of these substances, colouring the reconstituted solution brown, and making it less palatable.[23] Although this problem can be overcome by using chemically treated (encapsulated) sodium bicarbonate, this increases the cost of production.[24] In aqueous solution bicarbonate may decompose to form carbonate. Additionally, flavouring agents, such as citric acid, used in some commercial formulations react with bicarbonate to form carbon dioxide and water with a resultant sharp fall in bicarbonate concentration in the solution.[25] These difficulties associated with the use of bicarbonate have prompted the search for an alternative base.

The use of base precursors

The base precursors acetate, citrate, and lactate have been incorporated in intravenous and oral rehydrating fluids,[22] although a possible drawback is that their metabolism may be seriously impaired in severe dehydration with circulatory compromise.

Controlled clinical trials of base precursors in ORS are outlined in Table 3. Patra, in a double blind controlled trial of infants with diarrhoeal dehydration and reduced plasma carbon dioxide concentrations (mean 14–15 mmol/l) found that ORSs containing acetate or bicarbonate were equally effective in correcting dehydration and acidosis but that patients were less willing to take solutions containing bicarbonate, which had discoloured brown.[23] Acetate salts, however, being highly hygroscopic, have a shorter shelf life than those containing sodium bicarbonate[26] and turn to a jelly or gum like material by 12 hours at 37°C and more quickly if a small amount of water is added. Their use in powdered ORS, therefore, is not recommended.

In contrast, citrate is stable in tropical countries; no discoloration occurs during storage at up to 60°C for up to 3 years.[24] Islam showed that an ORS containing tribasic sodium citrate compared favourably with the WHO ORS containing sodium bicarbonate, with respect to both its ability to rehydrate and to correct acidosis.[27] A similar study in Jakarta concluded that the trisodium citrate based ORS resulted in less vomiting and stool output than the bicarbonate based ORS. Correction of serum carbon dioxide was more rapid with the citrate based ORS, despite a significantly lower serum carbon dioxide concentration on admission in the patients receiving this solution.[28] Several other unpublished clinical trials conducted by the WHO diarrhoeal diseases control programme have compared citrate ORS and bicarbonate ORS. Although stool volume was higher when bicarbonate ORS was used in cholera, there was no difference in non-cholera diarrhoeas.[29] Islam has recently investigated the use of tripotassium citrate monohydrate as a substitute for both sodium bicarbonate and potassium chloride in the WHO solution.[30] The solution containing citrate resulted in slower correction of serum bicarbonate, but there was no difference between the groups at 48 hours.

Although several clinical studies suggest that citrate containing ORS may result in slightly lower stool volumes than equivalent bicarbonate containing ORS, the advantage of citrate over a solution without base has not been investigated.

It has been argued that the greater stability of lactate over citrate salts makes the former preferable for use in powdered ORS, but lactate containing solutions support mould growth, which may cause deterioration of glasswear and alter shelf life of the solution.[21]

Conclusions

When considering ORSs, particularly for use in developing countries, our prime concerns must be simplicity, effectiveness, and economy. Bicarbonate and base precursors (acetate and citrate) pose problems with respect to availability, cost, packaging, and stability. Further, they are of dubious benefit therapeutically, both for correction of acidosis and rehydration. Exclusion of these substances would decrease the production cost of prepackaged ORS, make preparation in the home easier, and possibly result in earlier beginning of oral rehydra-

tion therapy, leading ultimately to the prevention of serious dehydration.

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Correspondence to Dr M J G Farthing, Department of Gastroenterology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.