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EVALUATION OF A NUTRITIVE ORAL REHYDRATION SOLUTION FOR THE TREATMENT OF CALF DIARRHOEA

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SUMMARY

The essential constituents of a conventional oral rehydration solution (ORS) are sodium, glucose and a bicarbonate precursor. The glucose promotes sodium uptake but because these solutions are isotonic, it is insufficient to sustain calorie requirements. This paper examines the performance of a novel ORS with over three times the conventional glucose concentration, by comparing it with two leading commercial ORSs in calves with induced *Escherichia coli* diarrhoea. This solution showed greater ability than the current market-leading ORS to repair extracellular fluid and plasma volume and to correct both hyponatraemia and metabolic acidosis, especially in more severely affected calves. In acidotic calves it was more effective in correcting hyperkalaemia, probably by supplying glucose to promote cellular potassium uptake as well as by correcting the acidosis. It therefore appears possible to depart from the traditional isotonic formulations for calf ORSs and gain significant nutritional support while retaining effective rehydration and correction of acid–base and electrolyte disturbances. This seems especially important in young animals where energy deprivation imposes a particular penalty; the use of hypertonic ORSs should not, however, be extended to other species without further research.

KEYWORDS: Diarrhoea; oral rehydration; calf; fluid therapy; hypertonic.

INTRODUCTION

The central concept underlying the mainstream developments in oral rehydration therapy (ORT) has been the promotion of enteric uptake of sodium, and therefore water, by isotonic solutions with an appropriate molar ratio of glucose and sodium. Additional components of a typical oral rehydration solution (ORS) have

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included organic acid anions (e.g. acetate, citrate, propionate) to act as bicarbonate precursors for the correction of metabolic acidosis, and amino acids (e.g. glycine) as enhancers of sodium co-transport. The need for isotonicity, the optimum Na: glucose ratio and the effects of nutrient deprivation are the main issues awaiting clarification in the field of ORT for calf diarrhoea and they have recently been reviewed (Michell, 1994, 1995).

A conventional (2% glucose) ORS imposes severe energy deprivation in the interests of rehydration; having merely 10% of the energy density of milk, it should only be used as the sole intake for 48 h. A 50% increase in glucose content, as in Lectade Plus (SmithKline Beecham), still leaves energy content low and necessitates a reduction of sodium content if the ORS is to remain isotonic. Since sodium is the osmotic skeleton of extracellular fluid (ECF), this undermines the ability to repair ECF volume and correct hyponatraemia (Michell *et al.*, 1992). If a calf loses 10% of its ECF volume, there is a sodium deficit of some 170 mmol, which cannot be covered by the first dose of ORT (2 l), even assuming 100% absorption and no further losses, unless the sodium concentration of the ORS is at least 85 mmol l^{-1}.

The potential adverse effect of a hypertonic ORS is to draw water into the intestine, causing hypernatraemia and increased diarrhoea, especially if the additional solute is fermentable. This tendency towards hypernatraemia may be reinforced by dermal and respiratory water loss, influenced by both ambient and patient temperature and the humidity of the environment. The effect of diarrhoea on plasma sodium concentration, however, is usually a reduction because it depends not only on the faecal losses of sodium and water but also on the renal responses (Michell, 1988; Michell *et al.*, 1989). In calves, the outcome is almost invariably hyponatraemia rather than hypernatraemia largely because of water retention in response to hypovolaemia; in contrast, children may become hypernatraemic, probably because of their greater water losses in warm, dry surroundings (Michell *et al.*, 1992; Michell, 1995).

In human medicine, the conundrum of combining successful rehydration with minimal nutrient setback has been addressed in two main ways: (1) by continuing milk feeding alongside ORT; and (2) by formulating ORSs based on simple, locally available nutrients (e.g. rice in many Asian countries) or solutes which deliver more energy without immediate 'osmotic penalty' because their breakdown is gradual, e.g. polysaccharides. Both approaches depend on a substantial database of knowledge concerning the ability of the intestine, especially in young children, to digest and absorb the relevant solutes, even during diarrhoea.

In seeking more satisfactory nutritional support during ORT for calf diarrhoea we decided that the fastest progress would result from a formulation applying the following principles (Michell *et al.*, 1992; Grove-White & White, 1993; Michell, 1994):

(1) The paramount importance of a sufficient supply of sodium.
(2) The need for adequate repair of metabolic acidosis, which is often severe, and predisposes to hyperkalaemia despite underlying deficits of cell potassium.
(3) The likelihood that the concentration of the main co-transport substrate for sodium, i.e. glucose, could be greatly increased without harm.

The third of these principles is based on two foundations. First, in a milk-deprived diarrhoeic calf there is likely to be excess sodium in the gut as a result of the underlying problem, as well as the sodium delivered by the ORS; i.e. ratios derived from healthy calves may underestimate the optimal glucose:sodium ratio (Michell, 1995). Second, long-standing evidence from Phillips (1983) and collaborators, both in piglets and in calves, suggests that hypertonic ORSs with increased glucose concentration were efficacious. Normal calves can absorb large quantities of glucose and hypertonic solutions are well within the transport capacity of their small intestine (Phillips, 1982).

Our primary objective was to develop a calf ORS which combined effective rehydration and adequate repair of acidosis with significant nutritive support; such a product was not available in the United Kingdom. Following pilot studies with a number of formulations (starting from Groutides, 1988), we arrived at the composition in Table I and this nutrient ORS (N) was evaluated against two market-leading formulations, using principles previously discussed in this journal (Michell *et al.*, 1992; Brooks *et al.*, 1995). Our most important comparators were the effects on plasma and ECF volume, plasma pH, sodium, potassium and glucose concentrations.

MATERIALS AND METHODS

Our methods for formation of calf groups, husbandry, induction of diarrhoea (using enterotoxigenic *Escherichia coli*), scoring of faecal consistency and measurement of changes in fluid spaces and plasma composition (based upon Michell *et al.*, 1992) have recently been described (Brooks *et al.*, 1995).

In brief, calves (dairy or dairy-cross breeds) were admitted from their original farms within 24 h of birth, individually penned on wood chips, fed on 2 l warm milk substitute (Easimix, Volac) twice daily and observed during an initial 48 h period in which those with loose faeces (high faecal scores) were rejected. Baseline bodyweights and blood samples (C) were then taken and colostrally-derived immunity was assessed using the zinc sulphate turbidity test (ZST).

On the following 2 days, enterotoxigenic *E. coli* (09: K30: K99) was given and the response monitored as previously described (Brooks *et al.*, 1995); when at least three successive faecal consistency scores were high, the animal was classed as diarrhoeic and treatment with ORS began at the next afternoon feed. Before this, the calves were reweighed and a pre-treatment blood sample was taken (V). Further samples (W–Z) were taken during the next 4 days. Comparisons were thus possible between pre-treatment diarrhoeic values (V) and control values (C) or those obtained after 2 days when ORS was used as sole therapy (X). Values at Day Z followed 2 further days when ORS was mixed 50:50 with milk replacer in accordance with the manufacturer's instructions.

Calves were allocated to treatment groups initially by random ballot but, as the trial progressed, the three groups (each n=12) were kept evenly matched for body weight and ZST status (Michell *et al.*, 1992). The composition of the three solutions (L, LP, N) is shown in Table I; they were dissolved in lukewarm water (2 l) and given once on Day V (p.m.), twice on Day W and once on Day X (a.m.).

On Day X (p.m.) and Days Y and Z (a.m.) calves received 2 l of a 50:50 mixture with milk replacer.

On Days C, V, W, X and Z, samples were taken for haematocrit (PCV), plasma biochemistry and acid–base status. ECF and plasma volume were measured by the marker dilution technique, using thiocyanate and Evans Blue as previously described (Wagstaff *et al.*, 1992; Brooks *et al.*, 1995).

The initial comparability of plasma parameters and fluid space data between treatment groups (L, LP, N) was assessed by applying Student's *t* test to differences in mean absolute values. Effects of diarrhoea or responses to therapy were tested within individuals by examining means of individual changes from prediarrhoeic samples (C) and of individual changes from pre-treatment samples (V) using paired *t* tests.

RESULTS

Our main findings concern fluid spaces (ECF and plasma volume), correction of metabolic acidosis (pH, bicarbonate) and plasma electrolytes (Na and K concentration), as well as protection against hypoglycaemia. Other findings (e.g. PCV, albumin, urea, creatinine, divalent cations) are discussed under 'Subsidiary Findings'. Means are stated±SEM.

The groups did not differ significantly prior to diarrhoea (Day C) or prior to treatment of diarrhoea (Day V: Table II). ZST levels were comparable between groups on Day C; those in the eventual group N were lowest, but not significantly so (L, LP, N; 33.7±4.2, 29.7±2.5, 28.8±2.5 units respectively). Bodyweights were also similar (41.8±2.0 kg; 42.0±2.0; 42.5±1.8 respectively).

The decisive differences are those seen on Day X which reflect the use of ORS alone, whereas the reintroduction of milk replacer influenced subsequent changes (Michell *et al.*, 1992). All diarrhoeic calves completed the experiment

Table I
Composition of solutions
On reconstitution in 2 l of water the available concentrations are as follows

	L	*LP*	*N*
Sodium mmol l^{-1}	73	50	133
Potassium mmol l^{-1}	16	20	20
Chloride mmol l^{-1}	73	39	60
Propionate mmol l^{-1}	—	—	10
Acetate mmol l^{-1}	—	—	33
Citrate mmol l^{-1}	0.4	10	16.54
Dextrose mmol l^{-1}	114	160	378
Bicarbonate	1	29	93
Total*			

L, Lectade (SmithKline Beecham);
LP, Lectade Plus (SmithKline Beecham);
N, Nutrient ORS (Royal Veterinary College, subsequently marketed as 'Energaid' by Elanco Animal Health).
*Assuming 1 mmol citrate yields 3 mmol bicarbonate.

without becoming so dehydrated as to require parenteral therapy (hence withdrawal from their group) and all solutions were totally consumed. Some calves needed teats or oesophageal feeders but this did not differ between solutions.

The responses to treatment up to Day X are shown in Table III. No solution restored ECF or plasma volume within 48 h, nor were there significant differences between solutions. If, however, attention was focused on calves with the greatest fall of ECF and plasma volume (>10%) during diarrhoea, the responses were as follows: plasma +0.24±0.1, +0.16±0.1, +0.21±0.1 (L, LP, N; *n*=9, 9, 7); ECF +0.46± 1.0, −0.90±0.4, −0.64±0.3 l (*n*=7, 7, 10). Thus, while plasma volume was improving,

Table II
Comparability of the three treatment groups prior to therapy
(Day C—pre-diarrhoea, Day V—pre-treatment of diarrhoea)
(Mean±SEM)

Group	*L* (n=*12*)	*LP* (n=*12*)	*N* (n=*12*)
Day C			
Plasma Vol (l)	2.8±0.2	2.9±0.2	2.9±0.1
ECF Vol (l)	12.5±0.8	11.9±0.9	11.3±0.6
pH	7.38±0.02	7.39±0.01	7.39±0.02
HCO_3 (mmol l^{-1})	37.6±1.2	38.7±0.9	39.3±1.1
Na (mmol l^{-1})	140.8±0.8	139.4±0.6	140.0±0.9
Glucose (mmol l^{-1})	7.9±0.2	7.8±0.5	7.0±0.6
Day V (change from Day C)			
Plasma Vol (l)	−0.6±0.1	−0.5±0.1	−0.4±0.1
ECF Vol (l)	−2.3±0.4	−1.5±0.3	−1.6±0.3
pH*	−0.024±0.022	−0.023±0.025	−0.003±0.012
HCO_3 (mmol l^{-1})*	−8.7±2.0	−6.5±1.1	−6.2±1.4
Na (mmol l^{-1})	−3.8±0.9	−2.7±0.8	−3.1±0.9
Glucose (mmol l^{-1})	−2.2±0.2	−2.3±0.6	−2.0±0.5

*n=7, 10, 10: see Results.

Table III
Response to therapy with ORS after 48 h (day X)
Change from value at Day V
(Mean±SEM)

Group	*L* (n=*12*)	*LP* (n=*12*)	*N* (n=*12*)
Plasma Vol (l)	+0.20±0.1	+0.11±0.1	+0.08±0.1
ECF Vol (l)	−0.04±0.6	−0.94±0.3 (b)	−0.61±0.3
Na (mmol l^{-1})	+1.3±1.2	+1.3±0.7	+3.8±0.6 (a)
Glucose (mmol l^{-1})	+0.4±0.6	+2.1±0.6 (b)	+0.4±0.9 (a)
HCO_3 (mmol l^{-1})*	−0.9±2.3	+3.2±1.9	+4.9±1.6 (c)
Weight change (4 days: kg)	−2.0±0.6 (b)	−1.5±0.3 (a)	−0.6±0.3

*n=7, 10, 10: see Results;
(a), Significance $P<0.001$; (b), $P<0.01$, (c), $P<0.02$.

recovery of ECF volume had begun with L alone; these responses were least with LP and intermediate with N.

In all three groups, a few calves failed to develop metabolic acidosis during the first 48 h of diarrhoea. When they are excluded, the remainder (L, LP, N; n=7, 10, 10) show improvement in plasma bicarbonate during treatment with LP or N (+3.2±1.9, +4.9±1.6 mmol l^{-1}) but not L (−0.9±2.3 mmol l^{-1}). The superior performance of N compared with L is statistically significant (P<0.05), in fact N was the only solution to produce a statistically significant increase in plasma bicarbonate; the responses reflect the bicarbonate precursor content of the solutions (L< LP<N). The correction of hyponatraemia similarly reflects the sodium content of the solutions, with N performing significantly better than LP (P<0.02). This difference is heightened when consideration is restricted to calves whose plasma sodium fell by 4 mmol l^{-1}, or more, in response to diarrhoea (L, LP, N; n=8, 5, 5). The effect of treatment is then to raise plasma sodium concentration by 1.8± 1.7 mmol l^{-1} (L), 2.6±1.2 mmol l^{-1} (LP) and 5.4±1.2 mmol l^{-1} (N). Only the increase with N is statistically significant (P<0.01). The fall in plasma sodium in these groups prior to therapy was 5.6±0.6, 5.4±0.6, 6.4±0.8 mmol l^{-1}; N thus came closest to correcting the hyponatraemia. Both LP and N reduced plasma potassium in acidotic calves (by 0.3±0.2, 0.5±0.1 mmol l^{-1}; n=10, 10); the fall with N was statistically significant (P<0.001).

The improvement of blood glucose reflected the glucose concentration of the three solutions (L, LP, N; 0.4±0.6, 2.1±0.6, 4.0±0.9 mmol l^{-1}). In calves with the greatest hypoglycaemia (a fall of 1.5 mmol l^{-1} or more following induction of diarrhoea), the response was 0.9±0.7, 2.4±0.8, 4.9±1.5 mmol l^{-1} (n=9, 7, 6). The average fall in these three groups had been 2.6±0.2, 3.5±0.6, 3.5±0.6 mmol l^{-1}, thus N restored calves to pre-diarrhoeic levels or slightly (not significantly) above, whereas L-treated calves remained significantly below (1.7±0.7 mmol l^{-1}; P<0.05).

Subsidiary findings

We have previously noted the unreliability of changes in PCV, plasma albumin or total protein concentrations as indices of dehydration (Michell *et al.*, 1992). These conclusions were reinforced in this experiment with 16 calves having a fall of more than 10% in both plasma and ECF volume, of which five showed no rise in PCV, six showed no rise in albumin and the majority (10) showed no rise in total protein.

Calcium and magnesium were not included in the solutions tested and we saw a similar pattern to before (Michell *et al.*, 1992); plasma calcium fell during diarrhoea and continued to fall during therapy until milk replacer was introduced. With magnesium, the fall occurs only during treatment rather than the untreated period of diarrhoea; the fall ends when milk replacer is introduced. These trends are not explained by plasma albumin which tended to rise during the corresponding periods.

The initial values of both plasma urea and creatinine were very comparable between groups (L, LP, N; 3.6±0.5, 3.4±0.4, 3.5±0.4 mmol l^{-1}; 131±4, 123±5, 124±4 μmol l^{-1}). The concentration of both metabolites rose during diarrhoea (urea by 2.7±1.2, 1.5±0.5, 1.6±0.5 mmol l^{-1}, and creatinine by 20.3±5.2, 9.3±5.1, 14.4±4.0 μmol l^{-1}). During the first 48 h of ORT, the fall in plasma creatinine

reflected the greater improvement of plasma volume with L (20.3±5.2, 12.4±3.1, 6.5±4.4 μmol l^{-1}) whereas the fall in plasma urea did not (0.4±0.5, 1.2±0.3, 2.5±0.3 mmol l^{-1}). During the entire treatment period (4 days), calves treated with L and LP showed a significant weight loss (2.0±0.6, 1.5±0.3 kg), whereas those treated with N did not (0.6±0.3 kg). Three calves showed a deterioration of faecal consistency score during ORT, one in each treatment group.

In summary, most measurements showed a more favourable response to solution N than to solution L, except for plasma and ECF volume, for which L gave a better response. Calves tested with N showed more favourable changes than those treated with LP in their plasma and ECF volume, plasma sodium and bicarbonate concentration, blood glucose, and better correction of acidosis and hyperkalaemia. They also showed least weight loss.

DISCUSSION

Before addressing the main issues, two points merit discussion. First, the use of an experimental model rather than field cases. The problems with field cases are their variability and the limited range of feasible measurements; this is exacerbated by the fallibility of traditional clinical criteria (Michell *et al.*, 1992). Fortunately, it is well recognized in oral rehydration that the success of a solution depends mainly on its formulation rather than the type of diarrhoea (Carpenter, 1987). This is less surprising when one remembers that the main route of uptake is probably the majority of the enteric surface which remains unaffected, even in severe diarrhoea (Michell, 1995).

Second, consumer acceptance of an ORS is undermined if there is no readily apparent improvement of the diarrhoea, even though this is a poor guide to efficacy (Brooks *et al.*, 1995). The prime objective, however, is to treat the patient, not the diarrhoea and this is well recognized in human medicine, alongside the fact that rehydration of the patient may also be accompanied by a transient increase in faecal output (Carpenter, 1987; Ludan, 1988; Avery & Snyder, 1990; Ribeiro & Lifshitz, 1991). One might have expected such a tendency to be more obvious in an ORS with increased glucose content (due to fermentation or osmotic purging). It was therefore reassuring that no such trend emerged from the faecal score data; only one calf in each group showed an increased faecal consistency score within the first 48 h of ORT. While the scores reflect faecal consistency, rather than output, one would expect a deterioration in the event of malabsorption; moreover, a farmer's assessment of faecal response would probably reflect consistency rather than daily output. Certainly there was no evidence of the hypernatraemia which should result from such an osmotic diarrhoea.

In a separate study, for drug registration purposes, it was found that even when the solute concentration was doubled, healthy calves could still tolerate the solution with little adverse effect on faecal consistency (confirming the view of Phillips, 1982). Recent data in adult humans suggest that 6% glucose solutions, infused into the normal intestine, do not impede water absorption even when they contain little sodium (Gisolfi *et al.*, 1992).

Food deprivation is a cornerstone of the traditional management of diarrhoea.

The reasons include 'resting the intestine' or, more scientifically, to prevent further malabsorption, accumulation of abnormal substrates and development of an abnormal intestinal environment favourable to potential pathogens. Nutrient deprivation imposes a particular penalty on young animals, however, where a large surface area:body weight ratio dictates a relatively high energy requirement and where reserves, for example of fat, are not yet well developed. The inclusion of additional glucose inevitably creates a wider glucose: Na ratio than in a conventional ORS but it is likely that during diarrhoea the intestine contains additional sodium which could be absorbed by co-transport with the extra glucose.

The additional energy content of solution N (6.8% glucose) is clinically significant, not just numerically. The daily dose of anhydrous glucose (272 g) yields 4.3 mJ of energy, about 75% of the maintenance requirement of a 40 kg calf (ARC, 1980; NRC, 1988; Tomkins & Jaster, 1991), whereas a traditional ORS (2% glucose) provides only 20%. Diarrhoeic calves are not only predisposed to hypoglycaemia by nutrient deprivation but also by any associated endotoxaemia and an increased metabolic rate.

The rise in blood glucose following oral rehydration in the calves with the greatest hypoglycaemia caused by diarrhoea was in the ratio 1:2.7:5.4 mmol l^{-1} for solutions L, LP and N; this reflected their glucose content (1:1.5:3.4). The bicarbonate precursors (acetate, citrate, propionate) provide a further energy source, though this is small. Even with a conventional (2% glucose) ORS, acetate, citrate and propionate provide only 0.9×10^{-3}, 2.1×10^{-3} and 1.5×10^{-3} mJ $mmol^{-1}$. Thus, even if the bicarbonate yield is as high as 60 mmol l^{-1}, the calorie content from such precursors is 0.13 mJ l^{-1} at the most, whereas glucose yields 0.3 mJ l^{-1}.

In addition to its significantly greater energy content, reflected in less weight loss during diarrhoea, solution N showed greater ability than the market-leading product (LP) to repair ECF and plasma volume and to correct both hyponatraemia and metabolic acidosis, especially in more severely affected calves. In acidotic calves it also showed a greater tendency to correct hyperkalaemia (probably by supplying glucose which promotes cellular uptake of potassium, as well as correcting the acidosis; Michell *et al.*, 1989). The advantage of L in rehydration is outweighed by its ability to correct acidosis.

It is, therefore, possible to depart from the traditional isotonic formulations for calf ORSs and gain a clinically significant degree of nutritional support while retaining comparable or superior rehydration and correction of acid–base and electrolyte disturbances. This contrasts with current trends in human ORT where there is growing evidence in favour of the use of hypotonic solutions in developed countries, though not necessarily in severe diarrhoea (El Mougi *et al.*, 1994; Anon, 1995). The underlying objective of reducing the nutritional setback associated with traditional ORT is, however, consistent with the current trends in human ORT for severe diarrhoea (for example in Asia, Africa and South America). The problem of hypernatraemia with hypertonic ORT in humans has necessitated the use of alternative energy sources with less osmotic penalty (Michell, 1994, 1995). Fortunately, the simple approach, using glucose, works in calves.

Finally, we would caution against the extrapolation of our findings to companion animals because puppies and kittens particularly, being smaller and kept in much warmer, drier surroundings, are likely to have greater water losses and,

therefore, a greater susceptibility to hypernatraemia as a result of hypertonic ORT. In any species, the risk of hypernatraemia is reduced if water is available and the patient is able to drink it.

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