Archives of Disease in Childhood 1997;**77**:F12–F15

Randomised controlled trial of acetate in preterm neonates receiving parenteral nutrition

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Abstract

***Aims*—To determine whether by partly replacing chloride with acetate in parenteral nutrition, hyperchloraemia, metabolic acidosis, and the subsequent use of interventions such as colloid infusion, alkali treatment, increased assisted ventilation, would be reduced.**

***Methods*—Fifty eight neonates of less than 32 weeks gestation, receiving parenteral nutrition from days 3 to 10, were given either standard parenteral nutrition or a novel formulation with replacement of any chloride dose > 3 mmol/kg/day as acetate.**

***Results* —Acetate (0 to 14.2 mmol/kg/day) reduced the incidence of hyperchloraemia from 77% to 25%, and caused an increase in base excess from day 5 onwards (mean intergroup difference 3.6 to 9.9 mmol/l), an increased pH (day 8, 7.34 *vs* 7.26), with an increased pCO_2 (1 kPa). The acetate group received less bicarbonate (median 0 mmol *vs* 4.8 mmol) and less colloid (41 ml/kg *vs* 204 ml/kg). There was no difference in any parameter of assisted ventilation.**

***Conclusion*—Acetate in neonatal parenteral nutrition reduces metabolic acidosis and hyperchloraemia.**

(*Arch Dis Child* 1997;**77**:F12–F15)

Keywords: parenteral nutrition; sodium acetate; metabolic acidosis; hyperchloraemia

Preterm neonates often start parenteral nutrition early. It is indicated when gut functional maturity, which is delayed in relation to structural maturity, is so poor that enteral feeding cannot be established. The degree of multisystem pathology, the need for nutrients for rapid growth, and the limited nutrient reserves of such infants also underpin the decision to start parenteral nutrition. Although the institution and duration of parenteral nutrition varies widely, some of this variation being dictated by case mix, a large number of preterm neonates receive parenteral nutrition for extended periods.

Preterm neonates are at increased risk of many of the complications of parenteral nutrition, such as cholestasis and infection, compounded by their immature physiology and immune system. The preterm kidney is functionally immature,[1] giving rise to two problems in particular: excessive sodium loss in urine[2] and failure of urinary acidification.[1 2] The consequence of the first is the requirement for additional sodium in the diet, usually provided by sodium chloride salt in parenteral nutrition. Intakes of up to 12 mmol/kg/day of sodium are required to maintain sodium balance. This results in concomitant excess chloride administration up to 12 mmol/kg/day. The recommended dietary intake of chloride is 3–6 mmol/kg/day.[3] The result of this excessive chloride intake is an increased incidence of hyperchloraemia (>115 mmol/l), which occurred in 88% of neonates fed parenteral nutrition on our neonatal unit (Cheng K, Ryan SW, abstact presented at the 67th Annual Meeting, British Paediatric Association, 1995). The high incidence of hyperchloraemia on this neonatal unit probably relates to the large number of very immature neonates being cared for. Typically, 80 to 90 babies <1.0 kg are cared for annually on this unit.

Hyperchloraemia is also associated with metabolic acidosis. In the same pilot study we showed a significant linear correlation between metabolic acidosis (increased base deficit) and blood chloride concentration (Cheng K, Ryan SW, abstract presented to the 67th Annual Meeting, British Paediatric Association, 1995). Acidosis is a major and important problem in preterm neonates. Trying to keep the pH within acceptable limits (>7.30) is an important part of neonatal intensive care, because acidosis is thought to be a causative factor in intraventricular haemorrhage and pulmonary hypertension.[4 5] Arterial pH is closely monitored during assisted ventilation and if acidosis occurs, tidal ventilation may be increased to overcome it. Quite frequently the acidosis is mixed in nature, with both respiratory and metabolic components, and we may end up using a respiratory intervention to overcome a metabolic problem. Given that lung damage could be increased using this approach, a better strategy might be to treat the metabolic component.

Metabolic acidosis has multiple causes in preterm parenterally fed neonates. Poor tissue and renal perfusion is common and plasma volume expansion and inotropic support have been advocated for its treatment.[6] From time to time sodium bicarbonate is administered to counteract the acidosis. Unfortunately, its effect is transitory and metabolic acidosis quickly returns.

A previous intervention study adopted a strategy to deal with metabolic acidosis in parenterally fed preterm neonates. That study showed an improvement in acid base status in neonates in whom some of the parenteral nutrition chloride had been replaced with acetate.[3] This intervention is effective in two

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Accepted 4 March 1997

ways: first, it replaces chloride which is associated with metabolic acidosis; and second, acetate is metabolised to base itself.[7]

Our aim was to conduct a randomised controlled trial to assess the effect of acetate not only on acid base status but also on ventilation, use of plasma volume expanders, inotropes and sodium bicarbonate therapy. No subgroup analysis was planned, but the relation between acetate dose and biochemical variables was analysed.

Methods

Preterm neonates under 32 weeks gestation were entered into the study if they were still receiving intravenous glucose/electrolyte solution on day 3 but not receiving enteral nutrition. On day 3, after parental consent had been obtained these babies started parenteral nutrition with amino acid solution. Intravenous lipid solution was added on day 5. Babies with major malformations were excluded from the study. Randomisation was sequential.

Parenteral nutrition was prescribed according to standard unit protocol except for acetate and chloride. Sodium was prescribed at a standard dose of 4 mmol/kg/day, but this quantity was varied according to clinical status. If hyponatraemia developed in the presence of excessive urinary sodium excretion, higher sodium intakes were prescribed. Potassium was prescribed in a similar way, with a basic intake of 2 mmol/kg/day. Large fluctuations in potassium requirement did not occur. Before the trial these two cations were prescribed and administered as chloride salts.

During the trial the neonates were individually randomly allocated to the standard (chloride based) parenteral nutrition regimen (standard group) or to a modified parenteral nutrition solution containing acetate (acetate group). In the latter group the maximum dose of chloride allowed was 3 mmol/kg/day and any anion requirement in excess of this was provided as acetate. In practice this could be achieved by using sodium acetate solution without having to consider changing the potassium salt. For example, a neonate in the acetate group requiring 4 mmol/kg/day of sodium and 2 mmol of potassium/kg/day would receive 3 mmol/kg/day of chloride and 3 mmol/kg/day of acetate. Other sources of chloride (drugs and other intravenous solutions) were also included when calculating the daily intake.

The caloric content of the full solution was 97 kcal/kg/day with a standard protein intake of 2.5 g/kg/day, lipid at 3 g/kg/day, and a fluid intake between 150 and 200 ml/kg/day depending on clinical circumstances.

The outcome measure on which trial size was calculated was a reduction in the incidence of hyperchloraemia from around 90% to around 60%, which required a sample size of 29 per group to have 80% power to detect a significant ($\alpha = 0.05$) difference.

Additional outcome measures were blood base excess (as a measure of metabolic acidosis), pH, and duration of assisted ventilation (if any), total dose of human albumin solution (4.5%) infused (for plasma volume expansion), total dose of sodium bicarbonate given (mmol/kg) and number of babies requiring inotropic support with either dopamine or dobutamine. All of the above variables were recorded from day 1 to day 10, or until death or discharge. Duration of assisted ventilation was measured in all neonates. Hence data from days 1 to 2 were collected retrospectively and those from days 3 to 10 prospectively. Blood samples were obtained from indwelling arterial catheters or by capillary sampling. Where a number of samples had been taken in a day, the first recorded value after 1200 hours was used. Blood gas measurements were undertaken in a side room on the neonatal unit using an Instrumentation Laboratories Blood Gas Analyser which is calibrated daily, and electrolytes were measured using a Bayer Axon Analyser which is used for clinical measurements. Although they were not primary outcomes, blood sodium and blood carbon dioxide concentrations were also measured.

Where continuous variables were normally distributed, they were described by mean and standard deviation (SD). Comparison between the standard and acetate groups was then made using Student's *t* test. Where data were not normally distributed, variables were described as median and range. Intergroup comparisons were then made using the Mann-Whitney U test. The normality of distribution was assessed using P-P normality plots, and like the other analyses, this was undertaken using the SPSS for Windows statistical program. It was planned to correlate the dose of acetate with the degree of metabolic acidosis (base deficit), chloride concentration, and carbon dioxide tension. χ^2 tests were used to analyse proportional data.

Assignment to parenteral nutrition type was done using sealed numbered envelopes stratified into two groups (<1 kg and ⩾1 kg). The randomisation was in blocks of two and four, themselves randomly arranged. The assignment was made when the request to start parenteral nutrition was made on day 3. The assignment was made and the parenteral nutrition manufactured at a separate hospital, the pharmacy staff there being unaware of the clinical state of each child. Each assignment was masked. The parenteral nutrition delivery sets were identical and there was no indication of their chloride or acetate status. The parenteral nutrition was ordered on-line by computer and the doctor was asked to prescribe the quantities of various cations required, the anions being calculated as detailed above. The trial code was kept at the distant pharmacy department. This code did not have to be broken during the trial. The clinical care team had access to all of the usual biochemical data and although they remained blind to the initial allocation, by interpreting routine biochemical and clinical variables, they might have been able to guess which allocation had been made. We did not confirm whether this had occurred. The clinical staff could not be blinded to these results for obvious reasons and we also wished to measure their therapeu-

Table 1 Characteristics of both groups

Variables	Groups	
	Standard (n=30)	*Acetate (n=28)*
Median gestation (range) (weeks)	27 (24-31)	28 (24-31)
Median weight (g) (range)	1060 (660-1690)	1010 (660-1670)
Number needing assisted ventilation	29	28
Number dying	2	4
Day of death	3,7	2,3,6,9
Number transferred out before end of trial	2	3
Day of transfer	5,7	4,4,4

tic response to the biocemical changes caused by the intervention.

All parenteral nutrition solutions were filtered during the trial to prevent particulate matter entering the circulation.

The study was approved by the Liverpool Children's Research Ethics Committee based at Alder Hey Children's Hospital, Liverpool.

Results

Thirty babies were randomly allocated into each group. In two infants randomised to acetate, assignment was unsuccessful due to a clerical error and these infants received standard parenteral nutrition. Two babies in the standard group and four in the acetate group died. Details of babies transferred out during the study are shown in table 1. Data up to the point of transfer were included.

Table 1 shows that the stratified randomisation was successful in producing comparable groups. There was no significant difference in gestation or birthweight between the two groups. There was no significant difference in the proportion being ventilated, dying, or being transferred to other neonatal units before 10 days of life.

The acetate group had a similar and non-significantly different chloride intake to the standard group before starting acetate. From day 3 onwards the median chloride intake in the standard group was 7.3 (range 3.9 to 18.9) mmol/kg/day, compared with 4.1 (1.2 to 8.5) mmol/kg/day (P <0.001). There was no difference in plasma sodium concentration between the groups at any time. The dose of acetate delivered increased from a median of 2.6 (range 0 to 6.3) mmol/kg/day on day 4 to 4.1 (0 to 14.2) on day 8 in the acetate group.

The incidence of hyperchloraemia (>115 mmol/l) in the acetate group (25%; 7 out of 28) was significantly less than that in the standard group (77%; 23 out of 30) (P<0.001). The mean base deficit (normally distributed) was significantly greater in the standard group from days 5 through 10 (P<0.001 days 5,7–10 and P <0.01 day 6) (table 2). The pH, which was also normally distributed, was similar in both groups until day 5. On day 5 (P <0.02) and days 8–10 (P<0.001), the pH was significantly higher in the acetate group (table 2). There was no significant difference in partial pressure of CO_2 between the groups until day 6 when a significant increase was observed in the acetate group (P <0.001 on day 6, P <0.015 day 8, and P <0.03 on day 10) (table 2).

The median therapeutic dose of bicarbonate administered to the standard group (4.8 mmol/kg; range 0 to 37.7 mmol/kg) was greater (P<0.0001) than in the acetate group (0 mmol/kg range 0 to 8.5 mmol/kg), representing a median of 3.5 (0 to 13) administrations in the former and 0 (0 to 4) in the latter. Neonates receiving standard parenteral nutrition received a median of 95.5 ml/kg of human albumin solution (range 0–204 ml/kg), compared with 41.0 ml/kg (0–165 ml/kg) in the acetate group (P <0.0001) which represented 5.5 (0–19) administrations in the standard group and 1 (0–7) in the acetate group. There was no difference in the degree of inotrope administration between the two groups. A maximum of nine babies in the acetate group received inotropic support compared with eight in the standard group.

Although there was a large difference in the median duration of ventilation—4.5 (range 1 to 34) days in the acetate group *vs* 12 (1 to 55) days in the standard group, because of the large variability in this variable, this was not significant,

Base deficit (r = −0.77, P <0.0001) and blood chloride concentration were negatively (r=−0.63 P <0.0001) correlated and blood partial pressure of carbon dioxide was positively (r=0.58, P <0.0001) correlated with acetate dose on day 8 (equation: pCO_2 (mm Hg) =45.7+1.7 × acetate dose (mmol/kg/day)).

Discussion

The primary hypothesis, that partial acetate replacement of chloride in neonatal parenteral nutrition for preterm neonates would reduce the incidence of hyperchloraemia, was proved: the reduction was from around three quarters to one quarter of infants. There were also beneficial changes in acid base status. Such changes could have arisen by two mechanisms: by replacement of chloride anion and by

Table 2 Blood gas and acid base characteristics of the two groups from day 5 of life to day 10, showing mean values, intergroup difference, and (standard error) of the difference

Variable	Allocation	Age (days)					
		5	*6*	*7*	*8*	*9*	*10*
Base excess (mmol)	Standard	−5.7	−5.3	−5.3	−5.8	−4.5	−4.9
	Acetate	−2.1	−1.5	0.6	2.2	3.4	5.0
	Difference (SE)	3.6 (0.8)	3.8 (1.4)	5.9 (1.4)	8.0 (1.1)	7.9 (1.3)	9.9 (2.0)
pH	Standard	7.30	7.20	7.28	7.26	7.27	7.30
	Acetate	7.35	7.29	7.33	7.34	7.34	7.36
	Difference (SE)	0.05 (0.02)	0.09 (0.11)	0.05 (0.03)	0.08 (0.02)	0.07 (0.02)	0.06 (0.02)
pCO_2 (kPa)	Standard	5.3	5.2	5.7	6.1	6.1	6.0
	Acetate	5.6	6.8	6.5	7.1	6.9	7.3
	Difference (SE)	0.3 (0.3)	1.6 (0.5)	0.8 (0.4)	1.0 (0.3)	0.8 (0.5)	1.3 (0.5)

metabolism of acetate to base. Hyperchloraemic metabolic acidosis during parenteral nutrition seems to mimic the situation in renal tubular acidosis, when hyperchloraemia and a normal anion gap are associated with low blood bicarbonate concentration and a failure of urinary acidification. The immaturity of the renal tubules in the preterm neonate may exacerbate this problem directly through failure of urinary acidification, and it may also contribute through high sodium loss,[1–2] which is replaced therapeutically as the chloride salt.

The improvement in pH and fall in base deficit in the acetate group was accompanied by a steady rise in blood carbon dioxide tension. Presumably this was due to a reversal in the equilibrium of the reaction catalysed by carbonic anhydrase. The rise in pCO_2 was balanced by the increase in blood pH.

The methodology of this study—a prospective randomised blinded control trial—is superior to the methodology used for the previously published study of such an intervention with acetate.[3] That study was a historical control study, with data gathered either side of an intervention and as such is open to all of the criticisms of that approach. The finding of improved acid base status in that study has been confirmed by this study and it is now possible to be more certain about the magnitude of the change, given the better methodology.

As a consequence of the changes in the biochemical and physiological varaibles they observed, the medical staff reacted differently to the acetate group, managing metabolic acidosis in a systematic way using human albumin solution and sodium bicarbonate. The reduced incidence of acidosis led them to use significantly less of these two interventions. Inotropes, which are more specifically indicated for hypotension, were used in a similar way in both groups.

We had hypothesised that because of an improvement in pH in the acetate group, that the degree of assisted ventilation would be decreased. Not only was total duration of assisted ventilation not reduced, but number of ventilator days in the first 10 days was similar and there were no differences on any day in ventilator rate or peak inspired pressure. It may be that the clinicians' perceptions of pH were counterbalanced by the tendency to increased pCO_2 in the acetate group. The study was not designed to detect a difference in ventilation and the possibility of a type II error remains.

The results of this study are now being put into practice on a systematic basis on this neonatal unit. The only change has been the definition of a maximum dose of acetate of 6 mmol/kg/day, because of concerns over hypercarbia. A daily dose at this level represents a mean blood pCO_2 of 8 kPa. The anion regimen is therefore the first 3 mmol provided as chloride, the next 6 mmol as acetate, and thereafter as chloride again. These are guidelines and can of course be amended if individual clinical circumstances permit.

We thank the Pharmacy Departments at Liverpool Women's Hospital and Alder Hey Children's Hospital for their assistance with this study. The study was funded by the North West Regional Health Authority Research Funding Scheme.

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