Downloaded from http://fn.bmj.com/ on April 29, 2017 - Published by group.bmj.com
ADC-FNN Online First, published on April 29, 2017 as 10.1136/archdischild-2016-311107


# Severe hypercalcaemia and hypophosphataemia with an optimised preterm parenteral nutrition formulation in two epochs of differing phosphate supplementation

Shaveta Mulla,[1] Susan Stirling,[2] Sarah Cowey,[1] Rosie Close,[1] Sara Pullan,[1] Rosalind Howe,[1] Lynne Radbone,[3] Paul Clarke[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/archdischild-2016-311107).

[1]Neonatal Intensive Care Unit, Jenny Lind Children's Hospital, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK
[2]Norwich Clinical Trials Unit, Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK
[3]East of England Neonatal Operational Delivery Network, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

**Correspondence to**
Dr Paul Clarke, Consultant Neonatologist, Neonatal Intensive Care Unit, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich NR4 7UY, UK; paul.clarke@nnuh.nhs.uk

These data were presented orally in abstract form at the Spring meeting of the Neonatal Society, March 2015, and at the jENS Congress, Budapest, September 2015.

Received 26 April 2016
Revised 23 November 2016
Accepted 9 March 2017

**To cite:** Mulla S, Stirling S, Cowey S, *et al. Arch Dis Child Fetal Neonatal Ed* Published Online First: [*please include* Day Month Year]. doi:10.1136/archdischild-2016-311107

## ABSTRACT

**Objective** To compare in two epochs of differing phosphate provision serum calcium, phosphate, potassium, and sodium concentrations and the frequency of abnormality of these electrolytes and of sepsis in preterm infants who received an optimised higher amino acid-content formulation.

**Design and setting** Retrospective cohort study at a single tertiary-level neonatal unit.

**Patients** Preterm infants given parenteral nutrition (PN) in the first postnatal week during two discrete 6-month epochs in 2013–2014.

**Interventions** In epoch 1 the $Ca^{2+}$:$PO_4$ molar ratio of the PN formulation was ~1.3–1.5:1 (1.7 mmol $Ca^{2+}$ and 1.1 mmol $PO_4$ per 100 mL aqueous phase) and in epoch 2 was 1.0:1 via extra phosphate supplementation (1.7 mmol $Ca^{2+}$ and 1.7 mmol $PO_4$ per 100 mL).

**Main outcome measures** Peak calcium and nadir phosphate and potassium concentrations, and proportions with severe hypercalcaemia ($Ca^{2+}$ >3.0 mmol/L), hypophosphataemia ($PO_4$<1.5 mmol/L), and hypokalaemia ($K^+$ <3.5 mmol/L) within the first postnatal week.

**Results** In epoch 2, peak calcium concentrations were lower than in epoch 1 (geometric means: 2.83 mmol/L vs 3.09 mmol/L, p value<0.0001), fewer babies were severely hypercalcaemic (10/49, 20%, vs 31/51, 61%, p value<0.0001); nadir plasma phosphate concentrations were higher (means: 1.54 mmol/L vs 1.32 mmol/L, p value=0.006), and there were fewer cases of hypophosphataemia (17/49, 35% vs 31/51, 61%, p value=0.009) and hypokalaemia (12/49, 25% vs 23/51, 45%, p value=0.03).

**Conclusions** Reverting from a PN $Ca^{2+}$:$PO_4$ molar ratio of 1.3–1.5:1 to a ratio of 1.0:1 was associated with a lower incidence and severity of hypophosphataemia and hypercalcaemia. For preterm infants given higher concentrations of amino acids (≥2.5 g/kg/day) from postnatal day 1, an equimolar $Ca^{2+}$:$PO_4$ ratio may be preferable during the first postnatal week.

### What is already known on this topic?

- High amino acid intakes from parenteral nutrition (PN) in the first postnatal week may improve growth, but uncertainty remains about optimal intakes, safety and associated later neurodevelopmental outcomes.
- High early amino acid intakes with inadequate accompanying phosphate provision or a suboptimal calcium:phosphate ratio may lead to severe hypercalcaemia, hypophosphataemia and hypokalaemia.
- Severe biochemical derangements occurred frequently following introduction of a new regional neonatal PN formulation that met current international recommendations for amino acids, calcium and phosphate.

### What this study adds?

- Increasing the PN phosphate content to match its higher calcium content mole-for-mole was associated with a reduction in the observed incidence and severity of hypercalcaemia and hypophosphataemia.
- For preterm infants receiving higher amounts of amino acids (≥2.5 g/kg/day) in the first postnatal week, an equimolar (1:1) $Ca^{2+}$:$PO_4$ ratio appears preferable to that currently recommended (1.3–1.7:1).
- Prospective audit of neonatal biochemistry is important following any changes to PN formulations.

## INTRODUCTION

Parenteral nutrition (PN) is essential to meet the nutritional requirements of many preterm babies until enteral feeds are established. Higher amino acid intakes in the first postnatal week have been recommended to meet their accelerated ex utero metabolic demands,[1] and may improve somatic and brain growth.[2] Yet uncertainty remains about ideal early amino acid intakes for optimal growth and whether higher early protein intakes are safe and improve neurodevelopmental outcomes.[3]

Current European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines have, since 2005, recommended PN provision for growing preterm infants of amino acids up to 4 g/kg/day, $Ca^{2+}$ 1.3–3.0 mmol/kg/day and $PO_4$ 1.0–2.3 mmol/kg/day, with a $Ca^{2+}$:$PO_4$ ratio in the range 1.3–1.7:1.[1] Between 2006 and 2012 our neonatal intensive care unit (NICU) aimed to


Copyright Article author (or their employer) 2017. Produced by BMJ Publishing Group Ltd (& RCPCH) under licence.

Downloaded from http://fn.bmj.com/ on April 29, 2017 - Published by group.bmj.com



provide this amino acid intake via a preterm PN formulation with a higher amino acid concentration of 3.2 g per 100 mL of aqueous phase PN. It had equivalent $Ca^{2+}$ and $PO_4$ concentrations, each of 1.0 mmol/100 mL, and thus an equimolar (1.0:1) $Ca^{2+}$:$PO_4$ ratio. Electrolyte disturbances appeared uncommon in this era.

In January 2013, a new PN formulation was introduced into all neonatal units in the East of England region to better accord with the ESPGHAN guidelines for higher calcium and amino acid intakes for growing preterm infants.[1] In the ensuing months, our neonatal unit and several others reported frequent cases of severe hypercalcaemia and hypophosphataemia occurring during the first postnatal week. Our hypothesis was that these biochemical disturbances were secondary to inadequate phosphate provision in the PN leading to a 'refeeding-type syndrome'.[4] Because a recent report had associated severe hypophosphataemia with sepsis in preterm infants,[5] the NICU of the Norfolk and Norwich University Hospital introduced an urgent temporising workaround measure that aimed to alleviate the incidence of these biochemical abnormalities. The change, made in December 2013 with the approval of our hospital's Paediatric Nutrition Support Team, involved the daily addition of extra phosphate to each baby's PN on an individualised basis to match the $Ca^{2+}$ concentration, so effectively reverting to our NICU's former equimolar (1:1) $Ca^{2+}$:$PO_4$ ratio.

This retrospective study reports the incidence of electrolyte disturbances of $Ca^{2+}$, $PO_4$, $K^+$ and $Na^+$ and the incidence of sepsis in preterm infants who received PN in periods before and after our bespoke additional $PO_4$ supplementation of the new regional PN formulation.

## METHODS

We reviewed PN provision of amino acids and electrolytes and the associated incidence and severity of abnormalities of $Ca^{2+}$, $PO_4$, $K^+$ and $Na^+$ in babies born within two discrete 6-month epochs. Epoch 1 was 1 June to 29 November 2013 during which the newly introduced regional PN aqueous phase formulation contained 1.7 mmol $Ca^{2+}$ and 1.1 mmol $PO_4$ per 100 mL; including the $PO_4$ provision from lipid, this delivered an overall $Ca^{2+}$:$PO_4$ molar ratio of ~1.5:1 from day 1 of PN and ~1.3:1 on days 2–7 (table 1). Epoch 2 was 5 December 2013 to 31 May 2014, the period of bespoke daily additional $PO_4$ supplementation to match the higher calcium provision thereby achieving an overall $Ca^{2+}$:$PO_4$ ratio of 1.0:1 (1.7 mmol $Ca^{2+}$ plus 1.7 mmol $PO_4$ per 100 mL less the $PO_4$ contribution from lipid). In epoch 2, the additional $PO_4$ was added to the PN aqueous phase by our hospital pharmacy's sterile production unit as sodium glycerophosphate (Glycophos Sterile Concentrate, [Fresenius Kabi, Runcorn, UK], containing phosphate 20 mmol and $Na^+$ 40 mmol per 20 mL phial); this thereby provided additional supplementation of 2 mmol $Na^+$ for every mmol of added $PO_4$. Amino acid provision remained unchanged (3.3 g per 100 mL aqueous phase) and, except for the supplementary sodium glycerophosphate, the PN formulation regime was identical to that in epoch 1 (table 1).

We included in our analyses all admitted preterm infants (<37 weeks gestational age) that received any PN during their first postnatal week, excluding those who died aged <1 week. In both epochs our NICU's practice for delivering PN was to commence amino acids and lipid in infants eligible for PN on the first postnatal day, ideally within 6 hours of birth. The duration of 'day 1' was variable, commencing from the time of birth and ending at the first 24:00 hours. Using a standardised protocol (supplementary file S2), amino acid intake commenced on day 1 at 2.5 g/kg/day, and increased daily to reach a maximum of 4.3 g/kg/day by day 5 (table 1). Supplementary sodium 3.0 mmol and potassium 1.9 mmol per 100 mL aqueous phase was provided from day 1. Enteral feeding with human milk was commenced from day 1 and increased gradually over subsequent days according to our regional standardised feeding protocol (see online supplementary file S2).

We reviewed case notes, PN charts, and daily biochemistry results during the first postnatal week, and microbiology results up to discharge. We recorded actual aqueous phase volumes delivered in each infant on each day during the first week, from which we derived the daily amino acids and electrolytes intake received. The main outcome measures were incidences in the first week of severe hypercalcaemia (plasma $Ca^{2+}$ >3.0 mmol/L), hypophosphataemia (plasma $PO_4$ <1.5 mmol/L), severe hypophosphataemia ($PO_4$ <1.0 mmol/L) and hypokalaemia (plasma $K^+$ <3.5 mmol/L), and the peak plasma $Ca^{2+}$ and nadir $PO_4$ and $K^+$ concentrations. Secondary outcomes were peak plasma $Na^+$ concentration, incidence of hypernatraemia (plasma $Na^+$ >150 mmol/L), and incidence of sepsis as defined by a

**Table 1** Standardised regimen for incremental fluid, PN and electrolyte intakes over the first five postnatal days

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5* |
|---|---|---|---|---|---|
| Fluids, mL/kg/day | 80 | 100 | 120 | 135 | 150 |
| Aqueous phase, mL/kg/day | 75 | 90 | 105 | 120 | 130 |
| Lipid phase, g/kg/day† | 0.9 | 1.8 | 2.7 | 2.7 | 3.6 |
| Amino acid, g/kg/day | 2.5 | 3.0 | 3.5 | 3.8 | 4.3 |
| Nitrogen, g/kg/day | 0.35 | 0.42 | 0.49 | 0.54 | 0.61 |
| Protein, g/kg/day | 2.2 | 2.7 | 3.1 | 3.4 | 3.8 |
| Calcium, mmol/kg/day | 1.3 | 1.5 | 1.8 | 2.0 | 2.2 |
| Phosphate, mmol/kg/day | 0.8 | 1.0 | 1.2 | 1.3 | 1.4 |
| $Ca^{2+}$:$PO_4$ ratio‡ | 1.5:1 | 1.3:1 | 1.3:1 | 1.3:1 | 1.3:1 |
| Potassium, mmol/kg/day | 1.4 | 1.7 | 2.0 | 2.3 | 2.5 |
| Sodium, mmol/kg/day | 2.3 | 2.7 | 3.2 | 3.6 | 3.9 |

Data shown are for epoch 1; intakes for epoch 2 were identical apart from an increased daily phosphate supplementation given to match the daily calcium intakes ($Ca^{2+}$:$PO_4$ ratio 1.0:1), plus the resultant extra sodium.

*Prescribed provision on days 6 and 7 was same as for day 5.

†Each 1 g/kg/day of lipid (5 mL/kg/day intralipid) contributed an additional 0.08 mmol/kg/day of phosphate to overall intake.

‡Overall $Ca^{2+}$:$PO_4$ ratio from PN when including lipid phase phosphate content. Further nutritional details of the aqueous phase content and the common daily parenteral provision of vitamins, trace elements and micronutrients provided across the study period are available in online supplementary file S1.

PN, parenteral nutrition.

Downloaded from http://fn.bmj.com/ on April 29, 2017 - Published by group.bmj.com



**Table 2** Baseline characteristics of preterm infants who received parenteral nutrition in two epochs of different phosphate supplementation

| | Epoch 1 n=51 | Epoch 2 n=49 | p Value‡ |
|---|---|---|---|
| Gestational age, weeks | 29.9 (29.0–30.8) | 28.7 (27.8–29.6) | 0.07 |
| Birth weight, g* | 1182 (1075–1299) | 1061 (945–1192) | 0.16 |
| Male gender, n (%) | 23 (45) | 22 (45) | 0.98 |
| Small for gestational age, n (%) | 20 (39) | 13 (27) | 0.18 |
| Postnatal day PN started† | 1 (1–2) | 1 (1–1) | 0.46 |
| Postnatal age PN commenced, hours† | 12 (6–41) | 9 (6–23) | 0.18 |
| PN days in first week† | 6 (5–7) | 7 (6–7) | 0.20 |

*Geometric mean (95% CI) presented for birthweight data.
† Median (IQR).
‡t-tests, Mann-Whitney U test and $\chi^2$ test used, as appropriate.
Data are arithmetic mean (95% CI) or n (%) unless otherwise stated.
PN, parenteral nutrition.

positive blood or cerebrospinal fluid culture with accompanying antibiotic treatment for ≥5 days between birth and discharge. We used t-tests, Mann-Whitney U test and the $\chi^2$ test to compare data between the two cohorts. Multivariable logistic and linear regression models were used to adjust for potential confounding factors. This study was registered as a clinical audit and service evaluation and did not require formal ethics approval.

**Table 3** Plasma calcium, phosphate, potassium and sodium concentrations and proportions of infants affected by electrolyte derangement and sepsis in the two epochs of different phosphate supplementation

| | Epoch 1 n=51 | Epoch 2 n=49 | p Value‡ |
|---|---|---|---|
| Calcium | | | |
| Peak $Ca^{2+}$ concentration, mmol/L* | 3.09 (3.02–3.17) | 2.83 (2.78–2.89) | <0.0001 |
| Postnatal day of peak $Ca^{2+}$ concentration† | 5 (4–7) | 6 (5–7) | 0.73 |
| $Ca^{2+}$ >3.0 mmol/L, n (%) | 31 (61) | 10 (20) | <0.0001 |
| Phosphate | | | |
| Nadir $PO_4$ concentration, mmol/L | 1.32 (1.21–1.43) | 1.54 (1.42–1.65) | 0.006 |
| Postnatal day of nadir $PO_4$ concentration† | 5 (4–6) | 5 (2–7) | 0.29 |
| $PO_4$ <1.5 mmol/L, n (%) | 31 (61) | 17 (35) | 0.009 |
| $PO_4$ <1.0 mmol/L, n (%) | 11 (22) | 7 (14) | 0.34 |
| Potassium | | | |
| Nadir $K^+$ concentration, mmol/L | 3.6 (3.4–3.7) | 3.7 (3.5–3.8) | 0.25 |
| $K^+$ <3.5 mmol/L, n (%) | 23 (45) | 12 (25) | 0.03 |
| Sodium | | | |
| Peak $Na^+$ concentration, mmol/L | 146 (145–147) | 148 (146–149) | 0.13 |
| $Na^+$ >150 mmol/L, n (%) | 9 (18) | 14 (29) | 0.19 |
| Sepsis, n (%) | 8 (16) | 5 (10) | 0.42 |

Data are arithmetic mean (95% CI) or n (%) unless otherwise stated.
*Geometric mean (95% CI) presented for peak $Ca^{2+}$ concentration data.
Median (IQR) or n (%).
‡t-test, Mann-Whitney U test and $\chi^2$ test used, as appropriate.

## RESULTS

Over the 12-month study period, 101 preterm infants received PN. One 23-week gestation infant who died aged 12 hours postnatally was excluded from analysis. Of 100 included infants, 26 were transferred in from other hospitals and commenced or continued PN on arrival which was usually within 24–48 hours of birth. Baseline characteristics (table 2) and PN nutrient and electrolyte intakes within the first week (see online table A, supplementary file S3) were similar across epochs, excepting the extra sodium glycerophosphate provided in epoch 2.

Table 3 shows peak plasma $Ca^{2+}$ and nadir plasma $PO_4$, $K^+$, and peak $Na^+$ concentrations, and the incidence of hypercalcaemia, hypophosphataemia, hypokalaemia, hypernatraemia and sepsis within the two epochs. In epoch 2 compared with epoch 1, peak calcium concentrations were lower ($p<0.0001$) and fewer babies were severely hypercalcaemic (20% vs 61%). Correspondingly, nadir plasma phosphate concentrations were higher ($p=0.006$) and there were fewer cases of hypophosphataemia (35% vs 61%), severe hypophosphataemia (14% vs 22%) and hypokalaemia (25% vs 45%). Adjusting for (1) birth weight and gestation, and (2) small-for-gestational age status (birth weight <10th centile) made very little difference to our univariate findings of differing incidences of hypercalcaemia, hypophosphataemia and hypokalaemia, and of differing plasma calcium and phosphate concentrations, between epochs 1 and 2 (table B, supplementary file S4). Peak sodium concentrations and proportions with hypernatraemia were not significantly different between epochs (table 3). Eight babies (16%) in epoch 1 and five babies (10%) in epoch 2 had culture-positive sepsis before discharge.

## DISCUSSION

In our region, severe biochemical disturbances of calcium and phosphate occurred frequently in preterm infants given an optimised PN formulation that was introduced with good intentions to better accord with ESPGHAN recommendations for amino acid and calcium content. While this quasi-optimised PN preparation improved provision of calcium, its comparatively low phosphate content led to unanticipated metabolic derangements despite achieving a recommended $Ca^{2+}$:$PO_4$ ratio of 1.3:1. However, after we increased ad hoc the phosphate concentration of the PN formulation to match calcium in an equimolar ratio, we observed a reduction in the incidence of severe hypercalcaemia, hypophosphataemia and hypokalaemia. For preterm infants receiving PN with a higher amino acid content in the first postnatal week, an equimolar (1:1) $Ca^{2+}$:$PO_4$ ratio would thus appear preferable to that currently recommended (1.3–1.7:1). Our data support current expert opinion that an adequate $Ca^{2+}$:$PO_4$ molar ratio in neonatal PN in the first postnatal week should be close to or below 1.0 for higher amino acid intakes >2.5 g/kg/day starting from the first postnatal day,[6] and also the suggestion that the current PN guidelines for preterm infants need revision.[7]

In epoch 1, peak $Ca^{2+}$ and nadir $PO_4$ concentrations had often already occurred by postnatal day 5, highlighting the importance of sufficient early $PO_4$ provision to achieve a 1:1 $Ca^{2+}$:$PO_4$ ratio and avoid deficit within the first few days. While the additional phosphate supplementation and 1:1 $Ca^{2+}$:$PO_4$ molar ratio in epoch 2 was associated with a reduction in the observed incidence of hypophosphataemia and hypercalcaemia, it did not

Downloaded from http://fn.bmj.com/ on April 29, 2017 - Published by group.bmj.com



completely abolish all cases. Thus, some babies in epoch 2 affected by hypophosphataemia needed still further increased $PO_4$ supplementation to achieve resolution. This was provided via a higher molar concentration of $PO_4$ compared with $Ca^{2+}$ (ie, a 'reersed' $Ca^{2+}$:$PO_4$ ratio), and was often required for several days.

Several reports have already highlighted the risk of hypercalcaemia and hypophosphataemia with an 'aggressive' PN approach[4 5 7–11] and that small-for-gestational age infants appear particularly prone.[9–11] The prime cause of these biochemical disturbances is postulated as inadequate early phosphate and potassium supply and/or inadequate proportions of calcium, phosphate and potassium delivered alongside higher amino acid concentrations.[4] Phosphate is used rapidly for production of energy within the cell and for tissue growth in very low birthweight infants with limited reserves. Severe hypophosphataemia accentuates mobilisation of calcium from bone, leading to hypercalcaemia.[4 5] One prospective study showed that severe hypophosphataemia due to a low phosphate content in the PN during the first postnatal week led to increased urinary calcium excretion and a high urinary $Ca^{2+}$:creatinine ratio, and the associated risks of poor bone mineralisation and nephrocalcinosis.[12] Provision of adequate calcium and phosphorus in PN during the first weeks after birth significantly reduces bone demineralisation in preterm infants and helps preserve short-term bone strength.[13]

Severe hypophosphataemia potentially increases the risk of infection because it inhibits the production of ATP leading to impairment of phagocytic responses, bactericidal activity and chemotaxis.[14] Recruitment to one randomised controlled trial (RCT) of enhanced feeding of very low birthweight infants was curtailed early due to an increased rate of neonatal sepsis associated with enhanced feeding and first-week hypophosphataemia.[5] Others have reported the same association.[10] Yet it remains unclear for preterm infants whether low plasma phosphate is a risk factor for sepsis independent of being extremely low birthweight.

The importance of adequate early $Na^+$ and $K^+$ provision when providing higher amino acid concentrations to preterm neonates has been highlighted.[5 7] It is unclear why fewer babies in epoch 2 had hypokalaemia. Better $PO_4$ and $K^+$ retention related to greater nitrogen retention cannot explain the finding because protein and $K^+$ intakes remained the same across epochs. Babies coped well with the inadvertent extra sodium provided via the extra phosphate supplementation in epoch 2, because plasma $Na^+$ concentrations and proportions with hypernatraemia remained similar.

The Nutritional Evaluation and Optimisation in Neonates (NEON) trial, to date the largest RCT of PN in preterm neonates, compared two regimens of first-week amino acid intakes which provided averaged daily protein intakes from day 1 of either 2.2 g/kg/day or 2.9 g/kg/day.[15] Initial $Ca^{2+}$ and $PO_4$ provisions from PN were both 1.0 mmol/kg/day (1:1 ratio), and then 1.5 mmol/kg/day $Ca^{2+}$ and 2.0 mmol/kg/day $PO_4$ from day 3 (1:1.3 ratio) (personal communication, Dr Uthaya). In comparison, infants in the present study received an averaged protein intake of ~2.4 g/kg/day (table A, supplementary file S3). Our epoch 2 infants had a similar incidence of hypophosphataemia (17/49, 35%) as in the NEON study incremental-amino acids groups (33/84, 39%). Yet significantly more infants in our epoch 2 cohort had severe hypercalcaemia (10/49, 20%) than in either of the NEON study amino acid cohorts: vs NEON incremental-amino acid groups (0/84, 0%), $p<0.0001$, Fisher's exact test; versus NEON immediate-recommended daily amino acid groups (5/85, 6%), $p=0.02$, $\chi^2$ test. This disparity may predominantly reflect the higher average daily first-week planned calcium provision with our PN regimen compared with that of the NEON study (~1.9 mmol/kg/day (table 1) versus 1.4 mmol/kg/day), because the intended average daily phosphate provision in epoch 2 was essentially the same as that in the NEON study (~1.9 mmol/kg/day).

Study strengths include this being the first to report the incidence and severity of biochemical abnormalities associated with neonatal PN formulations that differed only in respect of phosphate (and sodium) content, and that complete data collection was achieved from all eligible infants. Limitations include that this was a retrospective, single-centre review covering two separate although essentially contiguous epochs. Also, as an observational study rather than an RCT, our findings cannot indicate definite causality from the intervention. Nevertheless we believe our data provide useful information to help guide the preferred $Ca:PO_4$ ratio in early neonatal PN. Our experience also highlights the potential pitfalls of widely introducing standardised PN solutions that have not been subject to the rigorous testing of RCTs or careful prospective audit.

## CONCLUSIONS

For preterm infants given higher concentrations of amino acids (≥2.5 g/kg/day) starting on the first postnatal day, increasing the phosphate provision of the PN solution to match $Ca^{2+}$ content was associated with a reduction in the incidence and severity of both hypophosphataemia and hypercalcaemia in the first postnatal week. An equimolar (1.0:1) $Ca^{2+}$:$PO_4$ ratio therefore appears preferable to a ≥1.3:1 ratio for preterm PN during the first postnatal week. Our study findings support calls to review current international recommendations regarding early phosphate and calcium provision in PN for preterm infants. Our study also emphasises the importance of careful prospective audit of neonatal biochemistry following any changes to PN formulations.

**Acknowledgements** The authors thank Dr Mary-Anne Morris and the Jenny Lind Nutritional Support Team for their support of this project. The authors also thank Jacqui Jones, ANNP, for help with data collection, and Allan Clark (UEA statistician) for kind advice. The authors especially thank Dr Sabita Uthaya and the anonymous referees and statistical reviewer for their very helpful constructive comments on earlier versions of the manuscript.

**Contributors** PC conceived the idea for this project. SM, SC, RC and RH undertook the data collection. LR and SP provided intellectual input. SS provided statistical expertise and analysed the data. PC and SM wrote the first manuscript draft and PC wrote the final draft. All authors contributed to manuscript revisions and approved the final version. PC is guarantor.

**Competing interests** PC served as an independent member of the Trial Steering Committee for the NEON study.

**Ethics approval** This study was undertaken as a clinical audit and service evaluation. Formal ethics approval was not required under the contemporaneous NRES guidance.

**Provenance and peer review** Not commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

1 Koletzko B, Goulet O, Hunt J, *et al*; Parenteral Nutrition Guidelines Working Group: European Society for Clinical Nutrition and Metabolism; European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); European Society of Paediatric Research (ESPR). 1. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Cinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005;41 Suppl 2:S1–S4.

Downloaded from http://fn.bmj.com/ on April 29, 2017 - Published by group.bmj.com




2 Morgan C, McGowan P, Herwitker S, *et al*. Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study. *Pediatrics* 2014;133:e120–e128.
3 Cester EA, Bloomfield FH, Taylor J, *et al*. Do recommended protein intakes improve neurodevelopment in extremely preterm babies? *Arch Dis Child Fetal Neonatal Ed* 2015;100:F243–F247.
4 Bonsante F, Iacobelli S, Latorre G, *et al*. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants--it is time to change the composition of the early parenteral nutrition. *PLoS One* 2013;8:e72880.
5 Moltu SJ, Strømmen K, Blakstad EW, *et al*. Enhanced feeding in very-low-birth-weight infants may cause electrolyte disturbances and septicemia--a randomized, controlled trial. *Clin Nutr* 2013;32:207–12.
6 Pieltain C, Rigo J. Early mineral metabolism in very-low-birth-weight infants. *J Pediatr Gastroenterol Nutr* 2014;58:393.
7 Senterre T, Abu Zahirah I, Pieltain C, *et al*. Electrolyte and mineral homeostasis after optimizing early macronutrient intakes in VLBW infants on parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2015;61:491–8.
8 Moe K, Beck-Nielsen SS, Lando A, *et al*. Administering different levels of parenteral phosphate and amino acids did not influence growth in extremely preterm infants. *Acta Paediatr* 2015;104:894–9.
9 Ichikawa G, Watabe Y, Suzumura H, *et al*. Hypophosphatemia in small for gestational age extremely low birth weight infants receiving parenteral nutrition in the first week after birth. *J Pediatr Endocrinol Metab* 2012;25:317–21.
10 Brener Dik PH, Galletti MF, Fernández Jonusas SA, *et al*. Early hypophosphatemia in preterm infants receiving aggressive parenteral nutrition. *J Perinatol* 2015;35:712–5.
11 Boubred F, Herlenius E, Bartocci M, *et al*. Extremely preterm infants who are small for gestational age have a high risk of early hypophosphatemia and hypokalemia. *Acta Paediatr* 2015;104:1077–83.
12 Christmann V, de Grauw AM, Visser R, *et al*. Early postnatal calcium and phosphorus metabolism in preterm infants. *J Pediatr Gastroenterol Nutr* 2014;58:398–403.
13 Pereira-da-Silva L, Costa A, Pereira L, *et al*. Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. *J Pediatr Gastroenterol Nutr* 2011;52:203–9.
14 Craddock PR, Yawata Y, VanSanten L, *et al*. Acquired phagocyte dysfunction. A complication of the hypophosphatemia of parenteral hyperalimentation. *N Engl J Med* 1974;290:1403–7.
15 Uthaya S, Liu X, Babalis D, *et al*. Nutritional evaluation and optimisation in neonates (NEON) trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double-blind controlled trial. *Efficacy and Mechanism Evaluation* 2016;3:1–80. http://www.journalslibrary.nihr.ac.uk/eme/volume-3/issue-2.

Downloaded from http://fn.bmj.com/ on April 29, 2017 - Published by group.bmj.com

# Severe hypercalcaemia and hypophosphataemia with an optimised preterm parenteral nutrition formulation in two epochs of differing phosphate supplementation

Shaveta Mulla, Susan Stirling, Sarah Cowey, Rosie Close, Sara Pullan, Rosalind Howe, Lynne Radbone and Paul Clarke

*Arch Dis Child Fetal Neonatal Ed* published online April 29, 2017

Updated information and services can be found at:
**http://fn.bmj.com/content/early/2017/04/29/archdischild-2016-311107**

*These include:*

**References** This article cites 15 articles, 2 of which you can access for free at:
**http://fn.bmj.com/content/early/2017/04/29/archdischild-2016-311107#BIBL**

**Email alerting service** Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

## Notes

To request permissions go to:
**http://group.bmj.com/group/rights-licensing/permissions**

To order reprints go to:
**http://journals.bmj.com/cgi/reprintform**

To subscribe to BMJ go to:
**http://group.bmj.com/subscribe/**