Hypocalcaemia in severe meningococcal infections

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Abstract

Aim—To determine the incidence of hypocalcaemia in critically ill children with meningococcal disease.

Methods—In a prospective cohort study, 70 of 80 patients admitted consecutively with a clinical diagnosis of meningococcal disease to intensive care had measurements of total and ionised calcium on admission. Parathormone and calcitonin were measured in a proportion of the children.

Results—Total and ionised calcium concentrations were low in 70% of the children. There was a weak relation of calcium concentration to the volume of blood derived colloid which had been given, but a good relation to disease severity, where sicker children had lower calcium concentrations. Although the parathormone concentration was higher in children with lower calcium concentrations, some children had low ionised calcium concentrations, without an increase of parathormone concentration. Serum calcitonin concentration was not related to calcium concentrations.

Conclusion—Hypocalcaemia is common in meningococcal disease.

(Arch Dis Child 2000;83:510–513)

Keywords: hypocalcaemia; meningococcal infections; critical care

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Accepted 6 June 2000

frozen plasma, and human albumin solution)⁶ may cause ionised hypocalcaemia, though this is usually transient. However, as some of the children receive up to 200 ml/kg or more of fluid resuscitation over the first 24 hours,⁷ perhaps more severe hypocalcaemia may result.

We sought to estimate the incidence of hypocalcaemia in critically ill children with meningococcal disease, and to determine its cause. To determine the importance of chelation of calcium by citrate in blood derived colloid we compared the volume of blood derived colloid used in resuscitation with the calcium concentration observed on intensive care admission.

Methods

Blood was obtained on admission to paediatric intensive care from children with a clinical diagnosis of meningococcal disease. These children had a petechial or purpuric rash with evidence of infection (raised temperature or abnormal white cell count). In those children where meningococcal disease was not confirmed microbiologically, no other bacteria were isolated. The study predates the routine use of polymerase chain reaction in the diagnosis of meningococcal disease in this region. The volume of blood derived colloid (blood, 4.5% human albumin solution, and fresh frozen plasma) given prior to admission to the intensive care unit was recorded. Children were excluded if they had already received calcium therapy.

In some children total calcium was not measured and in those children who did not have an arterial or venous blood gas measurement, ionised calcium was not measured. The study was approved by the local research ethics committee.

Disease severity of the children was scored using PRISM,⁸ which has been validated for children with meningococcal disease,⁹ and the Glasgow meningococcal prognostic score (GM-SPS).¹⁰ Previous work in this institution has shown that children with a GMSPS score of 8 or more have a group mortality of 30%.¹¹

Heparinised blood was analysed in the laboratory for total calcium, magnesium, and phosphate, using a Bayer Axon multichannel analyser. Total calcium was measured by absorbance of light at 575 nm of an ortho-cresolphthalein calcium complex, having bound the magnesium with 8-hydroxy-quinoline. Total calcium concentrations were not adjusted for serum albumin concentrations. Inorganic total phosphate was measured photometrically at 340 nm, as the unreduced phosphomolybdate complex. Total magnesium was measured by absorbance of a magnesium chelate with xyldil blue at 660 nm.

Meningococcal sepsis is an important cause of disease in children. There is a strong relation between the concentration of meningococcal endotoxin and disease severity.¹ The cytokine response² correlates well with the severity of illness.

Hypocalcaemia is often found in critically ill patients,³ though its incidence has not been described in meningococcal disease. Calcium is found in the plasma in three forms: free or ionised calcium, normally 50% of the total; protein bound, usually 40% of the total; and complexed, usually 10% of the total.⁴ Ionised calcium is the active component which is controlled by parathormone, calcitonin, and vitamin D. The intracellular concentration of calcium is maintained at much lower concentrations of around 100 nanomolar.³ This is regulated by active transport, both extracellularly and into the sarcoplasmic reticulum. The results of hypocalcaemia are uncertain, though hypotension is a common feature of critically ill children with meningococcal disease, and correction of hypocalcaemia will raise the blood pressure of critically ill adults.⁵

Chelation of calcium by high concentrations of citrate in blood derived colloid (blood, fresh

Blood taken into a balanced heparin syringe was immediately analysed for ionised calcium using a Chiron diagnostics blood gas analyser. The ionised calcium was measured electrochemically using a silver chloride electrode separated from the blood sample by a PVC membrane with a calcium selective ionophore.

Calcitonin was assayed in serum frozen at -70°C by chemiluminescence using a commercially available method (Nicholls Institute Diagnostics). Parathormone was assayed in serum frozen at -70°C , using a commercially available two site immunoradiometric assay (Nicholls Institute Diagnostics).

Statistical analysis was performed using Stata (Stata Corp Texas). The results were described using non-parametric tests and relations were described using regression and correlation coefficients.

Results

We report the results of measurements of calcium on admission to a regional paediatric intensive care in 70 of 80 children admitted consecutively with a clinical diagnosis of

meningococcal disease. In these 80 children, meningococcal disease was confirmed microbiologically in 35. Of the 70 children, five died. The median risk of mortality assessed by PRISM was 0.115, with interquartile range 0.03 to 0.34.

Accepting a lower limit of total calcium of 2.12 mmol/l ,¹³ 49 of the 70 children with meningococcal disease had a low calcium (median 1.97 , interquartile range 1.58 to 2.17 mmol/l).

Accepting a lower limit of normal for ionised calcium of 1.1 mmol/l ,¹² 49 of the 66 children who had ionised calcium concentrations measured had ionised hypocalcaemia. The median ionised calcium was 0.99 mmol/l , with interquartile range from 0.85 to 1.1 mmol/l . Analysis of only those children who had microbiological confirmation of meningococcal disease, showed that 80% had low concentrations of both ionised and total calcium.

The ionised calcium concentration paralleled the total calcium concentration. Children with low ionised calcium also had a low total calcium concentration (fig 1; regression coefficient 1.15 , $p < 0.001$).

There was a good relation of disease severity to the total calcium concentrations, where children with higher PRISM score had lower calcium concentration (fig 2, regression coefficient -0.908 , $p < 0.001$). This relation remained when only those children with microbiological confirmation of meningococcal disease were studied (regression coefficient -0.932 , $p < 0.001$). There was also a good relation when the disease severity was expressed using GMSPS (Spearman correlation coefficient -0.746 , $p < 0.0001$).

There was a statistically significant relation between the total amount of blood, 4.5% human albumin solution, and fresh frozen plasma administered prior to admission to intensive care and the first measurement of ionised or total calcium concentration (fig 3; regression coefficient -0.002 , $p = 0.027$ for ionised calcium; Shapiro-francia test for normality $p = 0.048$ and regression coefficient -0.004 , $p = 0.005$ for total calcium), though the magnitude of the response is unimpressive. Neither was there an impressive relation of the total amount of these fluids administered to children with meningococcal disease and bound calcium (bound calcium being the ionised calcium subtracted from the total calcium), though again this was statistically significant (regression coefficient -0.003 , $p = 0.035$). Using forward or backward stepwise regression analysis, with total calcium and the total amount of blood derived colloid and risk of mortality, the fluid volume was eliminated, leaving the risk of mortality as the explanatory variable in the model.

Calcitonin was measured on admission in 23 children with meningococcal disease. The median calcitonin concentration was 3.1 pmol/l , with interquartile range 2.3 to 5.8 pmol/l (normal range $< 4\text{ pmol/l}$). There was no relation of calcitonin concentration on admission to total or ionised calcium concentration.

Figure 1 Relation of total and ionised calcium on intensive care admission in children with meningococcal disease; x axis line at the lower limit of normal total calcium (2.12 mmol/l); y axis line at the lower limit of normal ionised calcium (1.1 mmol/l).

Figure 2 Total calcium on admission to intensive care and risk of mortality (PRISM) in children with meningococcal disease.

Figure 3 Relation of ionised calcium to volume of blood derived colloid given to children with meningococcal disease on admission to intensive care.

Children who had worse disease on either GMSPS or PRISM scoring had higher calcitonin concentrations (Spearman correlation coefficient 0.59, $p = 0.003$ for PRISM).

The median parathormone concentration of 24 children with meningococcal disease admitted to the intensive care was 6.6 pmol/l, with interquartile range 3.1 to 9.4 pmol/l. There was an inverse relation between ionised calcium and parathormone concentration on admission to intensive care (fig 4; regression coefficient -0.015 , $p = 0.003$). However, accepting an upper limit of normal of parathormone of 4.9 pmol/l, only 12 of the 20 children with low ionised calcium (less than 1.1 mmol/l) had raised parathormone concentrations. The children with low calcium concentrations and low parathormone concentrations did not have lower magnesium concentrations than children with a raised parathormone concentration in response to hypocalcaemia (median magnesium concentration in those with low parathormone was 0.77 mmol/l, range 0.43–1.12 mmol/l; and 0.76 mmol/l, range 0.43–0.91

Figure 4 Ionised calcium and parathormone concentration on admission to intensive care in children with meningococcal disease; x axis line at the lower limit of normal of ionised calcium (1.1 mmol/l); y axis line at the upper limit of normal of parathormone concentration (4.9 pmol/l).

mmol/l in those with high parathormone concentrations).

The median phosphate concentration in 71 children was 1.47 mmol/l (interquartile range 1.1 to 1.82 mmol/l). Children with a low risk of mortality on PRISM had lower than normal phosphate concentrations. Eighteen children had a phosphate lower than normal (<1.13 mmol/l); none of the children died. Children with low calcium had high phosphate concentrations and vice versa (regression coefficient -0.128 , $p = 0.001$). The median magnesium concentration was 0.79 mmol/l, with interquartile range 0.72 to 0.87 mmol/l. There was no relation of magnesium concentration to risk of mortality predicted by PRISM, nor to the concentration of ionised or total calcium.

Discussion

We have shown that hypocalcaemia, both total and ionised, is common in critically ill children with meningococcal disease. Hypocalcaemia has been described previously in critically ill children, though the incidence of hypocalcaemia (74%) is higher in this study of meningococcal disease than in other studies of critically ill children. Gauthier *et al* reported an incidence of ionised hypocalcaemia of 14% in 45 critically ill children,¹² and Cardenas-Rivero *et al* reported an incidence of ionised hypocalcaemia of 18%,¹³ though as they measured ionised calcium concentrations only in the children with low concentrations of total calcium (49%), this may be an underestimate. Zaloga summarised the incidence of total hypocalcaemia at 70–90% and of ionised hypocalcaemia at 15–50% in critically ill adults.³

We found a good relation of ionised to total calcium concentrations. Children who had low ionised calcium had low total calcium. Previous work^{3 13} has emphasised the poor association between ionised and total calcium concentrations.

We have shown a good relation of both ionised and total calcium concentrations to disease severity, when stratified either by GMSPS or PRISM. The total calcium concentration is one of the components which are used in the calculation of the PRISM score.⁸ However, the lowest concentration of calcium (<1.75 mmol/l) contributes six points to a potential total of 74 points, which would not explain the relation seen here.

The cause of the hypocalcaemia is uncertain. The children were generally previously well, without prior disease or drug therapy. Urinary calcium losses were not measured, but as most of these children had oliguria, urinary losses were likely to be minimal. Sanchez *et al* measured urinary calcium excretion in four critically ill children with hypocalcaemia and found normal calcium:creatinine ratios.¹⁴ We supposed that calcium is chelated by the citrate remaining in blood derived products.⁶ Citrate may be present in concentrations up to 15 mmol/l in 4.5% human albumin solution. That this is not the case is shown because both total and ionised calcium concentrations are decreased, and because there is an unimpressive relation between the volume of blood derived

colloid administered and the reduction of total or ionised calcium concentrations. Most probably, the calcium redistributes intracellularly, for which there is evidence from both animal models and studies of human lymphocytes and erythrocytes.¹⁴⁻¹⁶

In some of the children with ionised hypocalcaemia (60%) the parathormone concentrations are raised, though in some children even with low concentrations of ionised calcium the parathormone concentrations are not raised. This suggests the aetiology of the hypocalcaemia is twofold: in some children a failure to increase the parathormone concentrations in response to ionised hypocalcaemia, and in other children a failure of the action of parathormone to elevate calcium concentrations. Low magnesium concentrations may prevent parathormone secretion in response to hypocalcaemia.⁴ This was not the case in our patients, where the concentrations of serum magnesium in those children who had hypocalcaemia with a parathormone concentration within the normal range were the same as the magnesium concentrations in children with a raised parathormone in response to hypocalcaemia.

There was no relation of calcitonin to calcium concentrations. This is counter to the inverse relation of calcitonin to ionised calcium concentration described by Sanchez *et al* in critically ill children.¹⁷ We did find a relation of disease severity to calcitonin concentrations. This has been described by other groups.¹⁸

Although we have shown that the incidence of hypocalcaemia is common in meningococcal infections we have not studied the role of correction of hypocalcaemia. Information supporting the correction of hypocalcaemia in critically ill patients is limited. Vincent's group showed that correction of hypocalcaemia increased blood pressure of critically ill adults, without increasing cardiac output or oxygen delivery.⁴ In critically ill adults recovering from cardiopulmonary bypass, calcium was found to reduce the response to adrenaline.¹⁹ Administration of calcium to endotoxic rats increased mortality, whereas therapy with calcium chelators decreased mortality.²⁰

In conclusion, we have shown that hypocalcaemia occurs in 70% of critically ill children

with meningococcal disease. This is unlikely to be caused by chelation of calcium by citrate in blood derived colloid, but is related to disease severity, with sicker children having lower concentrations of calcium.

Paul Baines was funded by the Johanne Holly Meningitis Fund.

- 1 Brandtzaeg P, Kierulf P, Gaustad P, Skulberg A, Bruun JN, Halvorsen S, Sorensen E. Plasma endotoxin levels as a predictor of multiple organ failure and death in systemic meningococcal disease. *J Infect Dis* 1989;159:195-204.
- 2 Waage A, Halstensen A, Espevik T. Association between tumour necrosis factor in serum and outcome in patients with meningococcal disease. *Lancet* 1987;100:355-7.
- 3 Zaloga GP. Hypocalcaemia in critically ill patients. *Crit Care Med* 1992;20:251-62.
- 4 Bushinsky DA, Monk RD. Electrolyte quintet: calcium. *Lancet* 1998;352:305-11.
- 5 Vincent JL, Bredas P, Jankowski S, Kahn RJ. Correction of hypocalcaemia in the critically ill: what is the haemodynamic benefit? *Intensive Care Med* 1995;21:838-41.
- 6 Denlinger JK, Nahrwold ML, Gibbs PS, Lecky JH. Hypocalcaemia during rapid blood transfusion in man. *Br J Anaesth* 1976;48:995-9.
- 7 Mercier JC, Beaufils F, Hartman J-F, Azema D. Hemodynamic patterns of meningococcal shock in children. *Crit Care Med* 1988;16:27-33.
- 8 Pollack MM, Ruttiman UE. Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988;16:1110-16.
- 9 Algren JT, Lal S, Cutliff SA, Richman BJ. Predictors of outcome in acute meningococcal infection in children. *Crit Care Med* 1993;21:447-52.
- 10 Sinclair JF, Skeoch CH, Hallworth D. Prognosis of meningococcal septicaemia. *Lancet* 1987;ii:39.
- 11 Marzouk O. Clinical and laboratory aspects of meningococcal disease in children. MD Thesis. University of Liverpool, 1994.
- 12 Gauthier B, Trachtman H, Di Carmine F, *et al*. Hypocalcaemia and hypercalcaemia in critically ill children. *Crit Care Med* 1990;18:1215-19.
- 13 Cardenas-Rivero N, Chernow B, Stoiko MA, Nussbaum SR, Todres ID. Hypocalcaemia in critically ill children. *J Pediatr* 1989;114:946-51.
- 14 Zaloga GP, Washburn D, Black KW, Prielipp R. Human sepsis increases lymphocyte intracellular calcium. *Crit Care Med* 1993;21:196-202.
- 15 Hotchkiss RS, Karl IE. Calcium: a regulator of the inflammatory response in endotoxaemia and sepsis. *New Horizons* 1996;4:58-71.
- 16 Todd JC, Mollitt DL. Effect of sepsis on erythrocyte intracellular calcium homeostasis. *Crit Care Med* 1995;23:459-65.
- 17 Sanchez GJ, Venkataraman PS, Pryor RW, Parker MK, Fry HD, Blick KE. Hypercalcaemia and hypocalcaemia in acutely ill children: studies in serum calcium, blood ionized calcium, and calcium-regulating hormones. *J Pediatr* 1989;114:952-6.
- 18 Lind L, Ljunghall S, Bucht E. Pronounced elevation in circulating calcitonin in critical care patients is related to the severity of illness and survival. *Intensive Care Med* 1995;21:63-6.
- 19 Zaloga GP, Strickland RA, Butterworth JF, Mark LJ, Mills SA, Lake CR. Calcium attenuates epinephrine's β -adrenergic effects in postoperative heart surgery patients. *Circulation* 1990;81:196-200.
- 20 Malcolm DS, Zaloga GP, Holaday JW. Calcium administration increases the mortality of endotoxic shock in rats. *Crit Care Med* 1989;17:900-3.