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.

Keywords: hypocalcaemia; meningococcal infections; critical care

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

Hypocalcaemia is often found in critically ill patients, although 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. 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. 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.

Chelation of calcium by high concentrations of citrate in blood derived colloid (blood, fresh frozen plasma, and human albumin solution) 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, 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, which has been validated for children with meningococcal disease, and the Glasgow meningococcal prognostic score (GM-SPS). Previous work in this institution has shown that children with a GM-SPS score of 8 or more have a group mortality of 30%. 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 orthocresolphthalein calcium complex, having bound the magnesium with 8-hydroxyquinoline. Total calcium concentrations were not adjusted for serum albumin concentrations. Inorganic total phosphate was measured spectrophotometrically at 340 nM, as the unreduced phosphomolybdate complex. Total magnesium was measured by absorbance of a magnesium chelate with xylidyl blue at 660 nM.
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 pmol/l). There was no relation of calcitonin concentration on admission to total or ionised calcium concentration.
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 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 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.7

We found a good relation of ionised to total calcium concentrations. Children who had low ionised calcium had low total calcium. Previous work13 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.5 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

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

**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).
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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.

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