Vitamin K deficient bleeding in cystic fibrosis

We would like to report a female infant (initially breast fed and subsequently formula fed) who had received two 1 mg doses of vitamin K orally, and presented at 9 weeks of age (initially breast fed and subsequently formula fed). Her weight had dropped from 25th to 9th centile at birth to her 2nd centile.

Her haemoglobin was 720 g/l, white blood cell count 13×10⁹/l, platelet count 523×10⁹/l, prothrombin time >10 seconds (normal range 0.8–1.2), activated partial thromboplastin time 109.4 seconds (normal range 24.0–34.0), and fibrinogen 4.5 g/l (normal range 0.8–1.2). She received 1 mg of vitamin K intravenously and repeat coagulation screen was then normal. Sweat osmolality was 110 mmol/l (normal range 17–80) and 105 mmol/l on repeat testing. No chymotryptsin activity was found in the faeces. DNA analysis confirmed homozygosity for delta F 508.

Vitamin K deficiency can occur in undiagnosed cystic fibrosis (CF) infants due to malabsorption of fat soluble vitamins. It is uncommon, since vitamin K is given to all newborns in the UK. As universal screening for CF is not undertaken in the UK, asymptomatic CF patients can be missed and a bleeding diathesis may be the presenting symptom.

Torstenson and colleagues reported three cases of severe life threatening bleeding subsequently diagnosed as CF in infants less than 6 months of age, and Rashid and colleagues found that 78% of pancreatic insufficient patients had PIYKA-II concentrations >3 µg/l.

Deficiency of vitamin K in children with CF may be due to inadequate dietary intake, malabsorption, and malnutrition. Decreased intestinal synthesis of vitamin K following diarrhoeal disease or antibiotic administration can also be a contributing factor.

Our patient developed vitamin K deficient coagulopathy despite receiving oral supplementation and vitamin K from formula feed. The vitamin K deficiency can be attributed to malabsorption secondary to CF and emphasises the need to consider CF as a differential diagnosis in bleeding diathesis presenting in the first year of life. If a universal neonatal screening programme for diagnosing CF had been in place, a potentially life threatening complication may have been prevented.

Improving mental health through parenting programmes: are the results valid?

We read the article by Patterson et al with interest. Firstly, the percentage of questionnaires returned from the survey should have been 61.8% not 70%, as reported.

Secondly, mental health problems are prevalent in all social groups and socioeconomic class. Unfortunately, working class parents were seriously under-represented in the study. The results from educated and predominantly caucasian people from Oxford are not applicable to areas like ours. In the Camden and Islington boroughs of London, we work with parents of mostly lower socioeconomic class and of varied ethnicity—from Albania to Zaire—to whom these results are not relevant. We need more studies conducted in these people to know the best evidence.

Thirdly, the intervention effect is seen at 6 months (short term) follow up. We wonder whether the maturational effect seen in the control group will actually decrease the effect of parenting in the intervention group in the long term? Moreover the intervention effect is said to be statistically significant. But is it clinically significant as well? And there is no cost-benefit analysis given. Does this justify the considerable use of resources, especially in today’s cash strapped, staff depleted (fewer health visitors) NHS? Furthermore, parents in the intervention group might have believed that the parenting programme is efficacious, and consequently feel and perform better than those who were in the control group, as they were aware of group allocation. Also, unblinded study personnel who are measuring and recording outcomes (such as quality of life) may provide different interpretations of original findings, which can distort the results. We now know that negative, inconsistent parental behaviour in families with high levels of adversity are associated with emergence of problems in early childhood and later life. Hence we believe that parenting interventions should be applied in high risk populations. That is parents of children with ECBI scores of 127 or more and not children with 100 and above as included in the study. It would have been helpful if authors gave ECBI and SDQ scales as a web supplement to the above article.
The authors suggest that the changes we have observed in our trial could be a speeding up of a normal maturational effect. Half of the child outcomes we measured showed changes compatible with this interpretation, but the other half do not. The latter show either continuing improvement in both groups or more change in the intervention than control group at six month follow up. We will be publishing the results of our 12 month follow up.

The authors also ask whether our results are clinically significant. The differences between intervention and control group scores at 6 months represent effect sizes of around 0.3 (of a standard deviation). In clinical terms such changes are regarded as small. However, in public health terms a small change in a large group is often more important than a big change in a small group, so these differences are of public health significance.

Dr Srinivas and colleagues also ask about cost effectiveness. We did not undertake a formal economic analysis in this study, but the costs of the intervention were mainly in the staff time. Taking account of time spent in supervision, but not training, the costs fall somewhere between six and ten hours of staff time. Taking account of time spent in supervision, but not training, the costs fall somewhere between six and ten hours of staff time.

In response to comments by Pearce and Mabin on Professor Russell's editorial on our paper, we doubt that our survey underestimated the true scale of the problem. We can inform them that this is not the case. Since our survey was completed we have notified of a further seven cases (five children, two adults). All but one of the children had been taking fluticasone in similar dosages to those reported in our survey. These children were clinically ill; four had required intensive care and an 8-year-old girl died due to adrenal crisis. The remaining child was only 20 months old and had been given budesonide in extremely high doses of 2000–8000 mcg/day. Both adults had been taking fluticasone (1000 mcg/day, 2250 mcg/day).

Case reporting clearly plays a much greater role than clinical studies in post license surveillance, particularly when there is not a single study showing clinical benefit and which would explain why only 2 cases of adrenal crisis have been reported in literature before the introduction of fluticasone propionate allowing Russell to make a claim in 1994 that “there is no firm evidence that any child has died of adrenal crisis as a result of adrenal suppression induced by inhaled corticosteroid therapy”.

Further, some cases reported in our survey had previously been taking very high doses of either beclometasone or budesonide but only developed adrenal crisis some time after changing to fluticasone.

Finally, it is unfair to blame doctors for prescribing fluticasone “off label”. Almost half of all drug prescriptions for children in hospital are either unlicensed or off label. Prescribers have every right to expect a reasonable margin of safety with a drug that should only be used when there is no alternative. Bearing in mind that there have now been two reported deaths and many intensive care admissions, the risks of prescribing fluticasone should be balanced against the possible benefits for patients, and we will have serious medicolegal implications for doctors, particularly when there is not a single study showing better efficacy for fluticasone compared with other available inhaled corticosteroids.

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Adrenal crisis due to inhaled steroids is underestimated

References

Moderately high doses still need to be considered for very young children.

In relation to the question of adrenal suppression when using higher doses of inhaled corticosteroid, I believe there is an aspect of dose selection which has not been mentioned by previous authors.

There are limited data on the question of intra-pulmonary drug deposition in children under 3 years but the studies that have been published seem to indicate that around 1–2% of the drug released into the spacer reaches the airways, compared to 15–17% in an adult using the same device. Based on this figure, it seems reasonable to prescribe similar doses to very young children and adults alike.

I note that none of the cases of adrenal impairment have been reported in children under 3 years of age; most of them are significantly older. This could be partly because higher doses are not being used in this age group, but might also be confirmation that a smaller fraction of the drug reaches the airways.

I would argue that there are good reasons to use higher doses, at least initially, when treating very young children. The diagnosis of asthma is exceptionally difficult here, and if a “trial of treatment” is ineffective, one wishes to be reasonably confident that the reason for the negative response was not related to an inadequate dose. A negative response allows the clinician to withdraw ineffective steroid treatment in those infants who may well not have asthma at all. If there is an excellent response, the dose of steroid should be stepped down to the minimum required to control symptoms.

Finally, for clarity, the doses I am referring to are budesonide/lipocortin one 800 mcg/day or fluticasone 500 mcg/day.

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Cultural representation of newborn feeding

Nicoll and Williams suggested that attitudes to breast feeding need to change. “everyone (not just women) needs to see breast feeding as normal and education needs to start early”. In Italy breastfeeding rates are low. Numerous training initiatives have been set up to heighten awareness with the aim of promoting breastfeeding. These initiatives have been based on implementation of the Baby Friendly Hospital Initiative; three hospitals in the country being nominated “Baby Friendly”.

I was recently invited to discuss the importance of breastfeeding for newborns with two 4th year junior school classes (41 children in total, 17 girls and 24 boys), aged between 9 and 10. Before talking to the children, I asked them to draw on a sheet of paper everything they thought was necessary for a baby to grow up healthy. All except four drew a feeding bottle next to a baby; 15 children drew a baby alone with a bottle; only three children drew a baby in her/his mother’s arms, but all these the babies were still holding a bottle. Only two drawings showed the baby with both parents and in without a bottle; the other two drawings without a bottle depicted a scene in the hospital. When I asked how many of them thought that formula milk was the same as mother’s milk, 28 out of 41 raised their hands. I believe this reflects the widespread tendency, also reported in other countries, not only to consider breastfeeding the same as artificial feeding, but “artificial” as “natural”.

In an historic and ever pertinent editorial, the Lancet hoped a warm chain for breastfeeding could be created, and warned about the ambivalent messages often encouraged by the marketing campaigns of formula manufacturers. I feel that the implementation of interventions aimed at supporting breastfeeding should not be limited to the healthcare system, but should cover a wider range of activities, aimed at changing the cultural representation of newborn feeding and at defending breastfeeding.

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References