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 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 90th centile at birth to the 2nd centile.

Her haemoglobin was 720 g/l, white blood cell count 13×10^9/L, platelet count 523×10^9/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 1.7–4.5). 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 chymotrypsin activity was found in the faeces. DNA analysis confirmed homozygosity for delta F508.

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.

Torpstenson 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 PIVKA-II concentrations >3 µg/L.

Deficiency of vitamin K in children with CF may be due to inadequate dietary intake, malabsorption, and malabsorption. 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.

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References


Authors’ reply

Drs Srinivas, Gada, Shanker, and Kanumakala make a number of useful points about our trial. Firstly, they query our response rate. This rate can be calculated using either the number of families or the number of children as the denominator. The rate we quoted 800/1155 is the proportion of families responding. The rate we quoted 61.8% (1105/1788) relates to the proportion of children. Given that this was a trial about parents and parenting we decided that the family based response rate was the most appropriate to report.

Secondly, they point out that this trial was carried out in Oxford and that the socioeconomic mix was somewhat biased towards middle class parents. Although all social groups were well represented in the trial, the point Dr Srinivas and colleagues make is valid. However, behaviour problems are common in all social groups, and because of the distribution of children in each social class, there are considerably more children with behaviour problems in middle class families than there are in families living in social deprivation. An important finding in this trial was that those who consented to take part were more likely than those who did not to have a child with problem behaviour. We feel that this validates our population approach. At the same time, it is true that our results may not be totally transferable to Islington. That does not stop them, however, being both valid and important.

Dr Srinivas says that more studies of programmes with parents from lower socioeconomic groups are needed. In fact, the great majority of trials of parenting programmes have been conducted with high risk groups and we know from these trials that they are valuable with families living in social deprivation. We are currently completing a systematic review of parenting programmes for minority ethnic families and have found no evidence that parenting programmes are less effective with parents from such groups than they are with those from majority ethnic groups.
The authors suggest that the changes we have observed in our trial could be a speeding up of a normal maturation 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 on staff time. Taking account of time spent in surveillance of new drugs. In an international role than clinical studies in post license surveillance of some of these outcomes, such approaches greatly increase the cost of studies and were not possible with the funding we had available.

Finally, and perhaps most importantly, Dr Srinivas and colleagues suggest that unless NHS resources should be concentrated were they are needed most, and not on relatively well middle classes. There will be many readers who agree with them. The pros and cons of population versus high risk approaches are well middle classes. There will be many readers who agree with them. The pros and cons of population versus high risk approaches are.

Adrenal crisis due to inhaled steroids is underestimated

In response to comments by Pearce and Mabin on Professor Russell's editorial on our paper.

They doubt that our survey underestimated the true scale of the problem. I 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 cases were in critically ill 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 of some of these outcomes, such approaches greatly increase the cost of studies.

Finally, it is unfair to blame doctors for prescribing fluticasone “off label”. We have responsible doctors prescribing fluticasone when considered necessary or appropriate.

References


Pearce and Mabin correctly state that “individuals have differing sensitivities to inhaled corticosteroids. Idiosyncratic responses to inhaled corticosteroids may occur even at licensed doses.” I agree, however, such patients “disappear” in large multicentre studies, particularly when the pharmaceutical company will not make available data on individual patients. This is of concern as there is evidence that fluticasone is associated with significantly more indiscriminately low cortisol values than other inhaled steroids. Also, over 75% of patients developed adrenal crisis greater than one year after starting fluticasone, and it is known that length of time taking inhaled steroids is a major factor in determining the frequency of side effects. How many studies of fluticasone have lasted greater than one year?

Pearce and Mabin correctly state that in recent years, when paediatricians are faced with high doses of inhaled corticosteroids are necessary, more are choosing to prescribe fluticasone propionate. However, they need to explain why only 2 cases of adrenal crisis (one adult) in over 30 years of prescribing inhaled corticosteroids had ever 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 ever come to harm 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” after 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 they decide to use. Labeling and off label decisions are a major factor in determining the frequency of side effects.

We have reported 10% adrenal suppression and 352 mcg/day can produce 50% adrenal suppression, a considerably greater degree than the equipotent dosage of beclometasone, leading those authors to conclude that increasing the dose beyond this point of maximum efficacy... resulted in increasing systemic effect, especially with fluticasone metered dose inhaler with its CFC propellant—exactly what we have reported.

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References


PostScript


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 withhold 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/beclomethasone 800 mcg/day or fluticasone 300 mcg/day.

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Reference

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 with 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 his/her 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


3 Cattaneo A, Buzzetti R, on behalf of the Breastfeeding Research and Training Working Group (Conti Nibali S, et al). Effect on rates of breast feeding of training for the Baby Friendly Hospital Initiative: three hospitals in the country being nominated “Baby Friendly”.


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