

PostScript

LETTERS

If you have a burning desire to respond to a paper published in *ADC* or *F&N*, why not make use of our "rapid response" option?

Log on to our website (www.archdischild.com), find the paper that interests you, click on "full text" and send your response by email by clicking on "submit a response".

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on "read eLetters" on our homepage.

The editors will decide, as before, whether to also publish it in a future paper issue.

Another case of HBV associated membranous glomerulonephritis resolving on lamivudine

Connor and colleagues¹ (see page 446) report rapid resolution of a hepatitis B associated membranous glomerulopathy and nephrotic syndrome after two months of oral lamivudine. We would like to add our experience with lamivudine in a similar case.

A 5 year old female of Vietnamese origin presented with a two week history of periorbital swelling and weight gain. She had 3 plus protein, 10-20 dysmorphic red blood cells, and red blood cell casts in her urine. Serum albumin was low at 19 g/L, cholesterol was 9.8 mmol/L, and serum complement C3 and C4 were reduced (0.61 g/L and <0.1 g/L, respectively). She was hepatitis B surface antigen positive and hepatitis B surface antibody negative. The physician caring for her at that time placed her on prednisone 60 mg/m²/day in three divided doses, and referred her to our service six weeks later, as the nephrotic syndrome was unresponsive to steroids. Her viral load initially was 1090 pg/ml of hepatitis B DNA in peripheral blood, and rose to >2000 pg/ml after four weeks of steroids, when ALT peaked at 72 U/L. A renal biopsy revealed stage II membranous glomerulonephritis. A liver biopsy showed focal lobular and portal inflammation and changes consistent with a mild chronic hepatitis.

She was started on lamivudine at a dose of 50 mg once daily (2.5 mg/kg), with steroids being weaned off over four weeks. Two weeks later the hepatitis B DNA dropped to 1686 pg/ml, decreased to 7 pg/ml two months later, and was undetectable at three months. She continued to be hepatitis e antigen positive without detectable e antibodies. The patient's proteinuria was cleared after three months of treatment, and serum albumin remained normal thereafter. She continued to take lamivudine for 13 months without rebound proteinuria. Six months after discontinuing lamivudine she remained clinically well, her urinalysis showed 0.04 g of protein per 24 hours, and there was microscopic haematuria. Hepatitis B DNA rose to >2000 pg/ml, indicating continued active viral replication. A repeat renal biopsy showed multiple electron dense deposits which had been

incorporated into the lamina densa with fragmentation of the latter, consistent with a membranous glomerulonephritis stage II/III. She has evidence of hyperfiltration with a glomerular filtration rate of 163 ml/min/1.73 m² as determined by ⁹⁹Tc DTPA clearance.

The ideal treatment for hepatitis B associated membranous nephropathy in children is yet to be determined. There is one retrospective analysis of six studies comprising a total of 82 children that showed 60% complete remission 12 months after the diagnosis, 7.3% renal failure, 2.4% end stage renal failure, and 30% persistent disease.² Steroid therapy should not be used as it does not appear to be beneficial, and the steroids may enhance viral replication in mononuclear cells.³ The average duration of proteinuria is 30 months.⁴ We believe that treatment with lamivudine in this case likely suppressed the virus and resulted in early remission of clinical nephrotic syndrome; however, the subsequent rebound in viral load and renal biopsy results probably indicates loss of viral suppression, leading to the subclinical relapse. It is unknown at this time if the strain of hepatitis B has developed resistance to lamivudine. Effective viricidal agents may be needed to prevent relapses of hepatitis B induced membranous glomerulonephritis. Finally, further work is needed to investigate the efficacy of this treatment in a larger cohort and to establish guidelines about the duration of such therapy.

G Filler, J Feber, G Weiler, N Le Saux

Children's Hospital of Eastern Ontario, Department of Paediatrics, 401 Smyth Road, Ottawa, ON, K2H 7M9, Canada

Correspondence to: Prof. G Filler, Professor of Paediatrics, Head, Division of Nephrology, Children's Hospital of Eastern Ontario, University of Ottawa, 401 Smyth Road, Ottawa, ON K1H 8L1, Canada; filler@cheo.on.ca

References

- 1 Connor FL, Rosenberg AR, Kennedy SE, et al. HBV-associated nephrotic syndrome: resolution with oral lamivudine. *Arch Dis Child* 2003;88:446-9.
- 2 Lai KN, Li PKT, Lui SF, et al. Membranous nephropathy related to hepatitis B virus in adults. *N Engl J Med* 1991;324:1457.
- 3 Lin CY, Lo S. Treatment of hepatitis B virus-associated membranous nephropathy with adenine arabinoside and thymic extract. *Kidney Int* 1991;39:301.
- 4 Gilbert R, Wigginklinken J. The clinical course of hepatitis B virus-associated nephropathy. *Pediatr Nephrol* 1994;8:11.

PCD or not PCD

In response to the leading article on primary ciliary dyskinesia (PCD)¹ and the commentary by Dr Andrew Boon, we write as clinicians with an interest in PCD who work in general paediatrics and neonatology.

We agree with Dr Boon that the identification of an uncommon medical disorder from the large number of children presenting with common symptoms and signs is a major challenge for the general paediatrician. We also support the view that it is undesirable and certainly impractical to refer every child with recurrent episodes of cough, rhinitis, and serous otitis media for further investigation.

However, we believe that the aim of the editorial by Professor C O'Callaghan and Dr A

Bush was to provide information on subtle differences in the clinical presentation of PCD to help us differentiate these patients from those with common non-specific childhood respiratory problems. For example, it is uncommon for a term infant to be admitted to a neonatal unit with significant respiratory concerns following a vaginal delivery but common in infants with PCD. We performed an as yet unpublished questionnaire survey of individuals belonging to the PCD support group which identified that 47% had been admitted to a neonatal unit with unexplained respiratory problems following a normal vaginal delivery. Rhinitis is also very rarely seen in normal neonates but is extremely common in patients with PCD. Other subtle clues increasing the likelihood of PCD are the characteristic of the cough and middle ear problems especially the development of persistent otorrhoea after tympanostomy tube insertion.

There is of course no doubt that a cheap reliable screening test would significantly help promote early diagnosis of PCD but it is not yet on the horizon. A detailed history especially of the neonatal period will help those working in neonatology or general paediatrics to highlight the patient that should be referred for further investigations including cilia studies.

M Meeks

Department of Neonatology, Leicester General Hospital, UK

M Coren

Department of Paediatrics, St Mary's Hospital, Paddington, UK

Correspondence to Dr Meeks; maggie.meeks2@virgin.net

References

- 1 Bush A, O'Callaghan C. Primary ciliary dyskinesia. *Arch Dis Child* 2002;87:363-5.
- 2 Coren ME, Meeks M, Morrison I, et al. Primary ciliary dyskinesia: age at diagnosis and symptom history. *Acta Paediatr* 2002;91:667-9.

Hazards in the epidemiological study of sudden infant death syndrome

The study of Platt and Pharaoh, confirms the increased risk of SIDS in twins compared with singletons.¹ They point out that a major component of that higher accrued risk is that twins tend to be of low birthweight. Their finding that like-sex twins are at no greater risk than unlike-sex twins adds to the substantial evidence concerning the very limited role of genetic susceptibility for SIDS, and the rarity of recurrence in siblings of victims.²

The authors illustrate the gratifying fall in the number of SIDS during the six years of their 1990s study. As the number of infants categorised each year as SIDS in England and Wales comes nearer to that of 200, so it becomes more important for those involved in epidemiological studies to be sure that the categorisation (i.e. the diagnosis) is correct.

I refer to infants who, a few years after they have been categorised as SIDS, have been re-assessed, usually because of a subsequent child being abused or killed, and, in the course of court proceedings, findings are made that

the previous infant(s) were killed by the parent, rather than dying of natural causes. Currently, there does not seem to be a mechanism for correcting the national childhood mortality statistics when later, correct diagnoses are made. For instance, in the 1990s, I am aware of at least 20 infants who were initially categorised as SIDS, but who in later years, after extensive child protection investigations, were deemed to have been killed, usually by smothering. Colleagues will know of other cases: the true number will be higher. It is unfortunate that the official statistics do not seem to be altered retrospectively, and remain a misleading figure for any research worker. I should add that, since none of the cases of parental killing of which I am aware involves twins, the conclusions of Platt and Pharoah are more likely to have been strengthened rather than weakened by such false diagnosis. However, as the number of SIDS continues to fall, it will become ever more difficult for research workers to compare small subgroups of SIDS within national mortality statistics unless the statistics are revised retrospectively in response to later correct diagnosis.

It is appropriate to warn of an additional hazard for research workers in this field. In the same issue of *Archives* there was an interesting letter from epidemiologists in Paris concerning the possibility of vagal overactivity as a cause of sudden infant death.³ They referred to a "positive family history of SIDS". A particular hazard there is that, unless details of that family history are verified in considerable detail, mistakes may be made. In recent years I have been involved with families in which parents who have repetitively smothered or killed children have provided to paediatricians, genetic counselling services, and to SIDS research workers, a false family history of SIDS—for instance, mother saying that two of her own siblings "died of SIDS". Such statements invariably are taken at face value and become part of the medical history: they are included in family trees in the hospital notes, and they have been quoted and displayed in published research concerning SIDS, yet subsequent questioning of the relevant grandparent has revealed that no such infant deaths occurred. Presumably, the mother responsible for smothering or killing her child has invented the family history, either to gain more medical attention for herself, or as a cover to distract from her actions. A second reason for verifying the alleged previous infant deaths in more detail is that, even if a death has occurred, it is necessary to explore the extent of the contemporary investigation and pathological examination. In one of Professor Emery's studies of infants initially categorised as SIDS, detailed re-assessment pointed to either a definite natural cause, or abuse, in two thirds of cases.⁴

S Roy Meadow

Room 4.13, Clinical Sciences Building, St James's University Hospital, Leeds LS9 7TF, UK; medmj@leeds.ac.uk

References

- 1 Platt MJ. Pharoah PO. The epidemiology of sudden infant death syndrome. *Arch Dis Child* 2003;**88**:27–9.

- 2 Hunt CE. Sudden Infant Death Syndrome and other causes of infant mortality. *Am J Respir Crit Care Med* 2001;**164**:346–57.
- 3 Shojaei-Brosseau T, Bonaiti-Pellie C, Lyonnet S, et al. Vagal overactivity: a risk factor of sudden infant death syndrome? *Arch Dis Child* 2003;**88**:88.
- 4 Walkind S, Taylor EM, Waite AJ, et al. Recurrence of unexpected infant death. *Acta Paediatr* 1993;**82**:873–6.

Use of inhaled corticosteroids in children

I read with interest the article Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom by Todd *et al* and the accompanying editorial in the December issue of *Archives*.

In the reported cases, the children had been administered substantially (up to 5 times) higher than the Glaxo SmithKline (GSK) Core Data Sheet recommended Flixotide dose of 400 mcg/day and use of fluticasone (FP) at such doses is certainly not endorsed by GSK. Within the recommended doses, there are a wealth of data from controlled clinical trials that Flixotide is a well tolerated and effective drug in adults and children.^{1–3} There are a number of recent studies in children which identified no cases of adrenal crisis and no effect on growth following 12 months treatment with FP at licensed doses.^{4–8}

There are also a number of methodological deficiencies in this survey, the most important being that the survey is not case-controlled and lacks information on true incidence against the overall FP use or exposure. In addition, it is unclear from the survey what attempts were made to closely monitor any adrenal suppression with increasing doses of FP or whether patients were down-titrated to the lowest effective FP dose, as routinely recommended.

The survey data also imply that fluticasone has been implicated in the great majority of cases of adrenal failure even though it is the least frequently prescribed form of inhaled corticosteroid. Prescribing data in relation to fluticasone from the UK DINLINK (Doctors Independent Network) database, shows that it is in fact the most commonly prescribed inhaled corticosteroid in children with moderate and severe asthma.⁹ DINLINK is an amalgamated database of the anonymised computer records of a panel of 300 general practitioners spread across the UK selected to represent the demographic population of the UK.

In addition, the authors' contention that adrenal effects with FP are due to its greater lipophilicity and hence accumulation over prolonged periods is misconceived and inaccurate. There are studies to show that there is no accumulation of FP at a steady state.¹⁰ It is the clearance value which determines the amount of FP in the body at steady state, and lipophilicity per se in not a relevant factor.¹¹

I also wanted to take this opportunity to comment on the editorial by Dr Russell. The last line of the editorial recommends that if high dose inhaled corticosteroid is considered necessary, that it is advisable not to use fluticasone. The recent publication by the CSM "Current Problems in Pharmacovigilance"¹² states that adrenal suppression is a dose

related class effect of inhaled steroids, and that all inhaled corticosteroids are associated with an increased risk of adrenal crisis when used at higher than licensed doses.

In conclusion, inhaled corticosteroids have an important place in asthma management throughout the world, and this paper by Todd *et al* should be reviewed in this context. Any inhaled corticosteroid used at such high doses has the potential to cause systemic effects, and paediatricians should be encouraged to treat their patients using the lowest effective dose, down-titrating as appropriate.

M Devoy

Vice President, Respiratory Clinical Development & Medical Affairs, GlaxoSmithKline Research & Development Ltd, Greenford Road, Greenford, Middlesex UB6 0HE, UK; Mike.B.Devoy@gsk.com

References

- 1 Barnes NC, Hallett C, Harris TAJ. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;**92**:95–104.
- 2 Ferguson AC, Spier S, Manjra A, et al. Efficacy and safety of high-dose inhaled steroids in children with asthma: a comparison of fluticasone propionate with budesonide. *J Pediatr* 1999;**134**:422–7.
- 3 Roorda RJ, Mezei G, Bisgaard H, et al. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol* 2001;**108**:540–6.
- 4 Rao R, Gregson RK, Jones AC, et al. Systemic effects of inhaled corticosteroids on growth and bone turnover in childhood asthma: a comparison of fluticasone with beclomethasone. *Eur Respir J* 1999;**13**:87–94.
- 5 De Benedictis FM, Teper A, Green RJ, et al. Effects of 2 inhaled corticosteroids on growth: Results of a randomized controlled trial. *Arch Pediatr Adolesc Med* 2001;**155**:1248–54.
- 6 Bidat E, Desfougeres J, Minini P, et al. Equivalent bone safety and better efficacy of fluticasone propionate compared to nedocromil sodium in asthmatic children. Results of a 2-year randomised study. *ERJ* 2002;**20**(Suppl 38):1443.
- 7 Bisgaard H, Allen D, Milanowski J, et al. Evaluation of long-term safety, growth and efficacy of fluticasone propionate 100mcg bd compared with sodium cromoglycate 5mg qds in asthmatic children aged 12–47 months. *ERJ* 2002;**20**(Suppl 38):1444.
- 8 de Benedictis FM, Teper A, Green R, et al. Effects of 2 inhaled corticosteroids on growth: results of a randomized controlled trial. *Arch Pediatr Adolesc Med* 2001;**155**:1248–54.
- 9 DIN-LINK Data, Compufile Ltd, (March 2002).
- 10 Meibohm B, Mollmann H, Wagner M, et al. The clinical pharmacology of fluticasone propionate. *Rev Contemp Pharmacother* 1998;**9**:535–49.
- 11 Mackie AE, McDowall JE, Falcoz C, et al. Pharmacokinetics of fluticasone propionate inhaled via the Diskhaler and the Diskus powder devices in healthy volunteers. *Clin Pharmacokinet* 2000;**39**(Suppl 1):23–30.
- 12 Committee on the Safety of Medicines. Inhaled corticosteroids and adrenal suppression in children. *Current Problems in Pharmacovigilance* 2002;**28**:7.