

LETTERS TO THE EDITOR

Oesophageal atresia, VACTERL association: Fanconi's anaemia related spectrum of anomalies

EDITOR,—The VACTERL association and Fanconi's constitutional anaemia have in common several congenital anomalies as shown in Perel *et al*'s report.¹ Although differentiating these two entities is usually easy, they can sometimes be confused.² We reported in 1996 the association of Fanconi's constitutional anaemia and VACTERL association.³ The pancytopenia in our patient was diagnosed at the age of 3 years, Fanconi's anaemia was confirmed by the increased chromosomal breakages with mitomycin and, as with Perel *et al*'s case, there was no associated hydrocephalus as described in previous reports.

Although the association of these two entities is being described more frequently, the value of routine screening of all neonates with oesophageal atresia or VACTERL for chromosomal breakages deserves to be studied. We agree with Peel *et al* that a high index of suspicion for an association with Fanconi's anaemia should be maintained in these neonates. Although surgical correction of life threatening anomalies in these infants will still be undertaken in the neonatal period, early diagnosis of associated Fanconi's anaemia would allow early surgical correction of some skeletal or renal anomalies before the onset of pancytopenia. Genetic counselling and family education for the associated risk of bone marrow aplasia and malignancy should be undertaken, and preparations for allogeneic bone marrow or umbilical cord blood transplantation can be made at an early stage.

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- 1 Perel L, Butenandt, Carrere R, *et al*. Oesophageal atresia, VACTERL association: Fanconi's anaemia related spectrum of anomalies. *Arch Dis Child* 1998;78:375-6.
- 2 Poole SR, Smith AC, Hays T, *et al*. Monozygotic twin girls with congenital malformations resembling Fanconi anaemia. *Am J Med Genet* 1992;42:780-4.
- 3 Narchi H, Mallouh A. Fanconi's constitutional anaemia and VACTER association. *Annals of Saudi Medicine* 1996;16:94-5.

Polio vaccine: is it time for a change?

EDITOR,—The arguments against and for the continued use of live attenuated oral polio vaccine (OPV) put forward by Finn and Bell¹ and Heath *et al* in their ensuing commentary had previously been considered carefully by the Joint Committee on Vaccination and Immunisation. The committee came down on the side of Heath *et al*, recommending the continuing use of OPV.

Finn and Bell suggest the introduction of Salk inactivated polio vaccine (IPV) as an opportunity to harmonise immunisation schedules in Europe and, by implication, are suggesting that we should lengthen the intervals between immunisation to two months,

thereby immunising with diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, and IPV at 2, 4, and 6 months of age. This might lead to the prevention of one to two cases of vaccine associated paralytic poliomyelitis each year, but any such gain would be offset against the possibility of an increase in deaths from pertussis, and possibly *Haemophilus influenzae* type b infection, as later immunisation would leave children vulnerable to these diseases for longer than afforded with the present immunisation schedule.

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- 1 Finn A, Bell F. Polio vaccine: is it time for a change? *Arch Dis Child* 1998;78:571-4.

"Can I have a letter for the housing, doctor?"

EDITOR,—The annotation by McKenzie¹ on housing and health offers a useful review of the literature, and some sensible advice. However, the ensuing commentary by Paton depicts housing departments as uncaring, ill informed, and reluctant to spend money or take action unless forced to do so by superior medical expertise or threats of litigation.

We suggest that this attitude is out of step with current thinking about multiagency working and collaboration between health and local authorities. While we do not doubt that there are housing officers like those known to Dr Paton, doctors may find that they can help their patients more by seeking a constructive relationship with the housing department. They will find that housing officers are valuable professional colleagues who in their own field are as up to date and well informed as most health professionals, and whose wish to do a good job is also constrained by shortage of resources.

In Sheffield City Council's Housing Service, assessments for rehousing on medical grounds are carried out in the applicants' own homes by staff who are generally trained nurses and have a broad experience of the council's housing stock.

Most people are well able to describe their own medical conditions and how these relate to their housing. Where there is any doubt, the rehousing visitor consults the relevant health professional. If the applicant requests a review or appeal of the original decision, the Housing Service initially consults a consultant in public health medicine and then a local general practitioner before reaching a final decision.

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- 1 McKenzie S. "Can I have a letter for the housing, doctor?" *Arch Dis Child* 1998;78:505-7.

Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis

EDITOR,—The paper by Vic and colleagues¹ provides useful pharmacokinetic data on the use of once daily aminoglycoside treatment in

children with cystic fibrosis. However, their conclusions regarding efficacy and safety must be viewed with caution. They did not perform a power calculation and therefore they cannot exclude the possibility of a type 2 error—that is, one regimen may be more effective but insufficient patients have been studied to demonstrate this. In an equivalence study conventional tests of significance are inappropriate and the results should be expressed as a confidence interval wherein the true difference may lie.²

This study is also too small to make any meaningful comments about toxicity. Ototoxicity appears to be an uncommon complication, and a study of 22 patients will not establish its prevalence with either regimen. Children with cystic fibrosis differ from most other patient groups in that they may receive multiple courses of aminoglycosides and the effects of cumulative toxicity must be measured in any evaluation of once daily treatment. Children with cystic fibrosis who have received large cumulative doses of aminoglycosides have been found to have hearing impairment when sensitive tests such as acoustic emissions have been used.³ Vic *et al* have studied nephrotoxicity by measuring lysozyme and β_2 microglobulin in urine. However, they have not looked for clinically important manifestations of renal tubular toxicity such as hypomagnesaemia, which are known to occur with cumulative dosages of aminoglycosides.⁴

Unfortunately, this study does not provide the information needed to bring about a change in practice, allowing the routine use of a once daily regimen in children with cystic fibrosis. There is urgent need for a large, adequately powered study of once *v* three times daily aminoglycosides for pulmonary exacerbations in adults and children with cystic fibrosis.

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- 1 Vic P, Ategbro S, Turck D, *et al*. Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. *Arch Dis Child* 1998;78:536-9.
- 2 Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996;313:36-9.
- 3 Mulheran M, Degg C. Comparison of distortion product OAE generation between a patient group requiring frequent gentamicin therapy and control subjects. *Br J Audiol* 1997;31:5-9.
- 4 Green CG, Doershuk CF, Stem RC. Symptomatic hypomagnesaemia in cystic fibrosis. *J Pediatr* 1985;107:425-8.

Dr Vic and colleagues comment:

Our goal was not to show that a once daily regimen was safer and more effective than the conventional regimen, but to study its safety and efficacy on a short term basis. Obviously, a larger number of patients would have enhanced the power of our study and we welcome the suggestion of a larger study comparing once and three times daily tobramycin. We are now able to give some more information on ototoxicity and nephrotoxicity after a three to four year follow up of our patients. Audiometry and assessment of kidney function (serum creatinine, creatinine clearance, 24 hour proteinuria with electro-

phoresis, lysozymuria, β_2 microglobulinuria, and urinary N-acetyl- β -D-glucosaminidase activity) was performed in 16 of the 30 cystic fibrosis patients who had taken part in our two studies of once daily amikacin and tobramycin.^{1,2} Median age was 12 years (range 8–27 years) and the mean number of antibiotic courses with once daily aminoglycosides was 8 (range 2–15). No cochlear or renal abnormalities were found in these patients, suggesting the absence of cumulative toxicity. Even if these preliminary results strongly suggest that the use of once daily aminoglycosides is safe on a long term basis, we recommend that cochlear and renal function must be examined at least every year in cystic fibrosis patients receiving repeated antibiotic courses with once or thrice daily aminoglycosides.

1 Vic P, Ategbo S, Turck D, *et al*. Tolerance, pharmacokinetics and efficacy of once-daily amikacin for treatment of *Pseudomonas aeruginosa* pulmonary exacerbations in cystic fibrosis patients. *Eur J Pediatr* 1996;155:948–53.

2 Vic P, Ategbo S, Turck D, *et al*. Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. *Arch Dis Child* 1998;78:536–9.

Brief neonatal exposure to cows' milk and atopy

EDITOR.—The study by de Jong *et al* tries to demonstrate that the administration of three or more cows' milk supplements to healthy full term newborn infants during the first three days of life does not increase the risk of atopy in the first two years.¹ In our opinion, the study does not demonstrate this hypothesis.

Allergy to cows' milk can occur as an IgE mediated anaphylactic reaction. This is well documented in infants given cows' milk in the first months of life after being sensitised in the first few days.^{2,3} Anaphylactic reactions are rare and limited to infants at risk, and we think that this study does not have the power to rule out this negative effect of cows' milk. Delayed allergy is more common, but it probably depends on a larger and sustained exposure to the antigens of cows' milk. The three feeds given to the study infants may not be sufficient to trigger this mechanism and increase the risk of atopic symptoms. The studies reporting an increased incidence of atopy were generally based on the sustained administration of cows' milk in the first few months of life.⁴ In addition, de Jong *et al* do not consider the incidence of atopy in a group of exclusively breast fed infants, which might be as low as 0.5% per year.⁵

- their study subjects were, by definition, not exclusively breast fed by WHO criteria⁶
- they do not say what they mean by exclusive breast feeding after the end of the intervention
- in the absence of a clear definition, they do not report how the 46% of infants

classified as not exclusively breast fed to six weeks of age were distributed in the two groups.

The potential bias introduced by an unequal distribution of this ill defined variable in the two groups might outweigh the effect of the brief earlier intervention. For all these reasons, we are not surprised by the findings and we think that this trial will keep the more than 50 year old controversy unresolved.⁶

Suppose the conclusion of the authors is true—that is, that early and brief exposure to cows' milk in breast fed children does not increase the risk of atopic disease. This may be enough to save the lives of midwives who (inadvertently?) administer formula supplements to healthy, full term, newborn babies,⁷ but it is certainly not enough to justify such a common non-evidence-based practice. The advantages of exclusive breast feeding are so many, well beyond the postulated effect on atopy, and the role of early supplements in decreasing the duration of exclusive breast feeding is so clear that prescribing supplements without indication should still be considered inappropriate.⁸ In fact, we wonder whether it is ethical, despite the approval of an ethics committee, to give supplements without indication as done in this trial. Finally, we believe that it would have been preferable that this study be carried out without the support of a party (a baby food company) with obvious interests in the use of formula supplements.

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- 2 Ventura A, Longo G, Tamburlini G. Reaginic hypersensitivity to cow's milk proteins. *Helv Paediatr Acta* 1981;36:237–40.
- 3 Høst A, Husby S, Østerballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. *Acta Paediatr Scand* 1988;77:663–70.
- 4 Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995;346:1065–9.
- 5 Division of Diarrhoeal and Acute Respiratory Disease Control. *Indicators for assessing breast-feeding practices*. Geneva: World Health Organisation, 1991.
- 6 Kramer MS. Does breast feeding help protect against atopic disease? Biology, methodology, and a golden jubilee of controversy. *J Pediatr* 1988;112:181–90.
- 7 David TJ. Infant feeding causes all cases of asthma, eczema, and hay fever. Or does it? *Arch Dis Child* 1998;79:97–8.
- 8 Division of Child Health and Development. *Evidence for the 10 steps to successful breastfeeding*. Geneva: World Health Organisation, 1998.

Dr de Jong *et al* comment:

Cows' milk allergy is a problem, even in exclusively breast fed infants; therefore, investigation of possibilities to decrease the incidence is unlikely to be questioned. Induction of immunological tolerance by early oral antigenic stimulation is a well established concept in mucosal immunology and supported by data from Lindfors and Enocksson.¹ However, such an approach is in marked contrast to the “dangerous bottle” hypothesis and therefore requires careful attention to its possible risks.²

Our results are disappointing to some extent, in the sense that the protocol we used did not induce specific tolerance. On the other hand, our results are positive in that we did not find support for the “dangerous bottle”. This result is relevant both for a number of practical issues as well as from the conceptual point of view: it facilitates the testing of other tolerance induction protocols—of course, any such an investigation should not be embarked on lightly.

Our scientific approach vis a vis the dangerous bottle hypothesis is fully in line with the principles of evidence-based practice: a double blind, placebo controlled study to substantiate a notion based on anecdotal information. The power of the study is indicated by the 95% confidence intervals; even if the analysis is restricted to the per protocol analysis, the power is sufficient to conclude that the relative risk is less than 1.7.

Tamburlini *et al* seem to be disappointed by our results, because they feel it weakens the case for breast feeding. However, as they justly point out, the scientific case in favour of breast feeding is strong, so there is no need to be sorry for the loss of a non-evidence-based argument.

We accept that the introduction of food or drink other than breast milk should be discouraged as a general practice, but in our study 90% of the mothers who intended to breast feed actually did at two weeks after delivery.

We did not investigate the effect of prolonged exposure to cows' milk and thus did not address the controversy discussed in Kramer's famous review.³

We are currently involved in a follow up of the cohort, so we hope to be able to report on the effects (if any) of brief early exposure to cows' milk at the more informative age of 6 years.

- 1 Lindfors A, Enocksson E. Development of atopic disease after early administration of cow's milk formula. *Allergy* 1988;43:11–16.
- 2 Høst A, Husby S, Østerballe O. A prospective study of cow's milk allergy in exclusively breast fed infants. *Acta Paediatr Scand* 1988;77:663–70.
- 3 Kramer MS. Does breast feeding help protect against atopic disease? Biology, methodology and a golden jubilee of controversy. *J Pediatr* 1988;112:181–90.