LETTERS TO THE EDITOR

Outcome in antenatally diagnosed renal pelvis dilatation

EDITOR,—Dr Nicholl raises some pertinent points in his letter regarding our paper.1 The hub of the matter is whether antenatal diagnosis of vesicoureteric reflex (VUR), detected as a result of antenatal ultrasound findings is clinically important or not. The answer to this question is not yet known and we require a trial to look at, if any, difference treatment makes to outcome, as judged by the development of renal scars.

Until this matter is resolved, however, we feel it appropriate to look for VUR when there has been antenatal pelvis dilatation, and treat accordingly. As stated in our study,1 this judgement is partly based on the fact that the prevalence of symptomatic VUR is around 1%, as described by Bailey, in contrast to an incidence of 20% in our study, implying that our findings were significant.

We accept that in a review of the published findings, from which Bailey acquired his data, the radiological techniques used may have differed from those currently in use, but as can be imagined, it is not easy to acquire information about the incidence of VUR in healthy children, and Bailey’s work is, to our knowledge, the currently accepted reference.2

With regard to the specific points raised by Nicholl around 50% of the babies with VUR in our study, have now undergone further imaging at the age of 3 years. Their reflux had resolved and, more importantly, no renal scar had been incurred. In those babies where both postnatal ultrasonography and the mic- turating cystogram were normal, the infants were discharged from further follow up, as we saw no further indication for continuing their surveillance.

The fact that only one baby required surgical intervention reflects that VUR, which is generally treated medically, was the most common finding, and a more conservative approach is now adopted in cases of pelviureteric junction obstruction.

In table 1 of our study we included, under the diagnosis of “idiopathic dilatation” only those infants in whom persisting renal pelvis dilatation was > 10 mm, because in those (n=22) in whom it was 5–10 mm and the mic- turating cystogram was normal, we did not feel an MAG III renogram was indicated; therefore, they did not strictly fulfil our criteria for this diagnostic label.

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Unlicensed and off label drug use in neonates

EDITOR,—Most papers in this journal have a commendable clear “take home” message, but this was not really true of the recent paper by Conroy et al.3 They described a 13 week, one unit study in Derby as finding that two thirds of all neonates (148 out of 455) involved the use of a drug in a way that the manufacturers had no license to recommend. The authors do not say what should be done about it.

They note that 84 prescriptions for vitamins and 77 for penicillin or an aminoglycoside used a dose other than the one mentioned in the drug data sheet. But they must be aware, surely, that changing a written rule is not the same in nature. Secondly, an immense amount of information has been published on these issues since the data sheets were first prepared. Thirdly, many UK college and American acadmy guidelines recommend doses that differ from those in the data sheets. The authors note that 36 prescriptions for caffeneine, morphine, or parenteral nutrition had to be made up in the local pharmacy aseptic service unit, and the products were therefore classified as unlicensed. They do not suggest, however, how they would prefer to see the prescribing and dispensing of these drugs handled.

What was the intended message when arrangements were made for the production of a media does a serious disservice to a serious adult drugs.” Such manipulation of the news media does a serious disservice to a serious subject. Professor Aynsley-Green’s subsequent letter, contrasting the lack of support for paediatric pharmacology in the UK with the establishment of 13 such centres in North America, rather suggests that it was a simple bid for money.

Readers who turned to Professor Sir David Hull’s commentary in the same issue will have found little enlightenment. His main message seemed to be that one should buy Medicines for Children. However, any suggestion that this would be the first reference text to clearly identify unlicensed and off label paediatric drug use in the UK would be misleading. Even should that be the case, it wouldn’t get us very far: the new consensus driven text may tell us what “we” can do. What is needed is sensible, sustained, and constructive dialogue between the profession, the licensing authorities, and the manufacturers, to get drug sheets revised at regular intervals, so that they reflect all the additional information that becomes available in the years after the product first comes on the market. My message is, that it is up to the profession to start the ball rolling.

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Dr Conroy et al respond:

We welcome the opportunity to clarify our “take home” message. This is actually very simple: drugs used in children should be tested scientifically to ensure that age dependent changes in pharmacokinetics and pharmacodynamics are known, the likely side effects are anticipated, and that the minimum effective dose can be given.

We expect the Medicines Control Agency to ensure that neonates receive drugs that are carefully evaluated for efficacy, safety, and quality as the drugs given to adults. We also expect the pharmaceutical industry to provide drugs that are appropriate for use in neonates and children as well as in adults. We accept that health professionals involved in the care of neonates have a responsibility to contribute to this process. It requires a joint effort between healthcare staff caring for children, the indus- try, and the government. Dr Hey states that data sheet information is “a matter for debate”. This is the only information that the pharmaceutical manufacturer will take responsibility for, anything else is on the head of the prescriber.

There may be few published reports of renal or other few reports of neonatal renal or ototoxicity. Low peak concentrations, on the other hand, often go unremarked.

Six separate papers have been published over the past few years, which show that a therapeutic peak concentration will not be achieved for 12 to 24 hours using any standard policy, unless an initial loading dose is given—the volume of distribution being particularly high at birth—but such a strategy is still only recommended in a few reference texts.

This is not an area where more money is needed for research. More than 200 papers have already been published on this topic over the past decade. There is no commercial pres- sure on the manufacturer to modify the data sheet: they are generic products unprotected by patents. Nor does the Medicines Control Agency believe that it should take the initiative over this, although it would be very willing to review the case for voluntary modification with manufacturers if it felt appropriate to do so. We would recommend that the profession, the licensing authorities, and the manufacturers, to get drug sheets revised at regular intervals, so that they reflect all the additional information that becomes available in the years after the product first comes on the market. My message is, that it is up to the profession to start the ball rolling.

4 Aynsley Green A. Is it shameful that children’s health is still in its infancy. New Scientist 1999.

have many other potentially contributory problems. Research is needed to establish the dose and frequency required to provide therapeutic, non-toxic serum concentrations of this drug for babies of all gestations.

We were surprised by the media interest in our paper and responded to requests for interviews accordingly. Unfortunately, we cannot be held responsible for the headlines or tone of the published newspaper reports.

The extent of drug toxicity from unlicensed and off label drug use in neonates is unknown. We know that severe adverse drug reactions in children are more likely to occur with unlicensed and off label treatment than licensed drugs. The scientific study of drug treatment in neonates has been relatively neglected by both doctors and pharmacists in the UK and Europe. However, there are positive developments: the British Forum for the Use of Medicines in Children and the European Network for Drug Investigation in Children are trying to both encourage and coordinate clinical trials in this area.

It is clear that many health professionals need to be informed about research in paediatric therapeutics. We are not simply bidding for money but trying to raise the profile of a neglected area of research. Historically, research has been centred on disease in specific areas such as diabetes, cystic fibrosis, leukaemia, cardiac defects, etc. When seeking funding for research on the extent and risk of unlicensed and off label drug use in children we were told by a major children’s charity that they did not consider it an appropriate area for research and that they would not even consider an application for funding. We hope that the studies documenting the extent of unlicensed and off label drug prescribing and the consequences of such prescribing will convince the Department of Health and the major charities that this is an important area of research, and that the use of drugs in the neonate should be evidence based.


CORRECTION

Please note that the authors of Gilbert et al (Role of Ureaplasma urealyticum in lung disease of prematurity: 1999;81:F162-7) have noted a discrepancy in the reference list for this article. Reference 2 should read:
pelvis dilatation

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