

LETTERS TO THE EDITOR

Outcome in antenatally diagnosed renal pelvis dilatation

EDITOR,—Dr Nicholl raises some pertinent points in his letter¹ regarding our paper.² The nub of the matter is whether asymptomatic vesico-ureteric reflux (VUR), detected as a result of antenatal ultrasound findings is clinically important or not. The answer to this question is not yet known and will require a trial that looks at what, 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 renal pelvis dilatation, and treat accordingly. As stated in our study,¹ this judgement is partly based on the fact that the prevalence of asymptomatic 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 scarring 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 pelvi-ureteric 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.

MERVYN S JASWON
Department of Paediatrics
The Whittington Hospital
Highgate Hill
London N19 5NF

- 1 Nicholl RM. Antenatally diagnosed renal pelvis dilatation. *Arch Dis Child Fetal Neonatal Ed* 1999;81:F160.
- 2 Jaswon MS, Dibble L, Purie S, et al. Prospective study of outcome in antenatally diagnosed renal pelvis dilatation. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F135–8.
- 3 Marra G, et al. Mild fetal hydronephrosis indicating vesicoureteric reflux. *Arch Dis Child Fetal Neonatal Ed* 1994;70:F147–50.

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.*¹ They described a 13 week, one unit study in Derby as finding that two thirds of all neonatal prescriptions (294 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.²

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 data sheet information is advisory 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 academy guidelines recommend doses that differ from those in the data sheets. The authors note that 36 prescriptions for caffeine, morphine, or parenteral nutrition had to be made up in the local pharmacy aseptic service unit, and the products were therefore classes 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 news media to latch on to this report before most clinicians had had their chance to read the paper for themselves? Were headlines such as "Doctors raise alarm over drugs given to babies," and "Babies used as drug guinea pigs" really what you hoped to generate? Coming only a week after an article in the *New Scientist*,³ inspired by a steer from the Derby clinicians, the journal article led the BBC to report that "Doctors are calling for stricter controls to ensure children are not given dangerous doses of adult drugs." Such manipulation of the news media does a serious disservice to a serious subject. Professor Aynsley-Green's subsequent letter,⁴ 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 everyone 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 most people currently do, but what most do is not necessarily right.

The neonatal use of gentamicin typifies some of the key issues, as Conroy has herself highlighted.⁵ The drug has been in neonatal use for over 30 years, but the best dose is still a matter for debate. High trough concentrations frequently cause concern, but there are actually very 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 10 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 pressure 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 approached by an appropriate and responsible professional body. Why, then, does the Royal College of Paediatrics and Child Health not do this?

For most of the drugs listed by Conroy, there is no need for further research, or more papers stating that drug data sheets are out of step with current practice. Nor do "they" need to tighten the prescribing rules and restrict 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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Department of Child Health,
Royal Victoria Infirmary,
Newcastle upon Tyne NE1 4LP

- 1 Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F142–5.
- 2 Conroy S. Developments in relation to unlicensed and off label drug use. *Paediatric and Perinatal Drug Therapy* 1998;2:23–6.
- 3 Fricker J. Too much too young. *New Scientist* 1999.
- 4 Aynsley Green A. Is it shameful that children's health is still in its infancy. *The Guardian* 1999.
- 5 Conroy S. Optimal dosing schedules with gentamicin are needed for premature neonates. *BMJ* 1998;317:204–5.

Drs 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 as 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 industry, and the government. Dr Hey states that data sheet information is "advisory," but 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 ototoxicity following the use of gentamicin in neonates, as it is difficult to definitely attribute such problems to the drug. However, this does not mean that gentamicin does not cause such problems. We note that renal insufficiency is not uncommon in acutely ill preterm infants and that long term hearing problems occur in babies who have been through neonatal intensive care. We do not know how many of these problems are associated with gentamicin use because the babies

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.¹

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.² 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.³

It is clear that many health professionals now accept the need for 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—for example, cystic fibrosis, leukaemia, cardiac defects, etc. When seeking funding for research on the extent and risk of unlicensed and off label drug use in children⁴ 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 prescribing^{4,5} and the consequences of such prescribing⁷ 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.

- 1 de Hoog M, Mouton J W, van den Anker J. The use of aminoglycosides in newborn infants. *Paediatric Perinatal Drug Therapy* 1998;2:48–56.
- 2 Turner S, Nunn A J, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off label drugs on paediatric wards: a prospective study. *Acta Paediatr* (in press).
- 3 Bonati M, Choonara I, Hoppu K, Pons G, Seyberth H. Closing the gap in drug therapy. *Lancet* 1999;353:1625.
- 4 Turner S, Longworth A, Nunn A J, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. *BMJ* 1998;316:343–5.
- 5 Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;80: F142–5.

Editors' comments

We issue press releases on articles of public interest with the aim of helping journalists understand the material. The press releases are seen in advance by authors who have an opportunity to make changes, and are issued with an embargo date, to avoid media publicity before the Journal's publication date. However, we have no control over how the media choose to headline this information. The public and the media have access to articles in scientific journals once they are published and if we did not issue press releases we believe there would be even greater scope for misinterpretation.

Glycosaminoglycans in neonatal urine

EDITOR.—Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by deficiency of the enzymes catalysing the

stepwise degradation of glycosaminoglycans (GAG). Bone marrow transplantation can slow down or reverse some of the features of these diseases. Enzyme replacement (ERT) studies in several animal models of MPS disorders have shown promising results^{1–3}; human clinical trials of ERT in MPS type I have only recently become possible.⁴ The clinical symptoms of MPS usually become evident only between the second and third years of life. This therefore argues for early therapeutic intervention before the development of irreversible changes.

Quantitative measurement of urinary GAG (glycosaminoglycans) can be used to diagnose MPS. We investigated the change in urinary excretion of GAG to use for early diagnosis.

Random urine samples were obtained from 570 neonates on days 2–6 of life. The samples were obtained from 320 boys and 250 girls with birthweights of mean 3137 (SD 374) g and gestational ages of 39.7 (1.1) weeks. Urine specimens were collected from 85 neonates on day 2; 254 on day 3; 92 on day 4; 65 on day 5; and 74 on day 6. The babies had been born after an uneventful pregnancy and delivery and were not known to have any specific clinical abnormalities. Urine samples were also obtained from 1328 infants aged between 1 and 12 months old who had no symptoms of MPS, and from five MPS patients aged 1 month or less (MPS type II, 15 days old, 978 mg GAG/g creatinine; MPS type II, 26 days old, 940 mg GAG/g creatinine; MPS type II 1 month old, 1177 mg GAG/g creatinine; MPS type III, 1 month old, 1180 mg GAG/g creatinine; MPS VII, 1 month old), 205 mg GAG/g creatinine.

The urine collector (ATOM pediatric urine collector, ATOM medical Co, Japan) was removed as soon as it was full of urine; it was then immediately stored at –20°C until analysis. After thawing at room temperature the urine were analysed as follows. Urinary excretion of GAG was measured using the DMB method⁵ and the urinary creatinine concentration was measured using the Jaffe method.⁶ Both measurements were performed using an MR 5000 plate reader (Dynatech, USA). The Wilcoxon rank sum test for unpaired data was used to compare groups.

Figure 1 shows the urinary GAG:creatinine ratio for normal neonates and infants and for five MPS patients. Urinary excretion of GAG decreased each day after birth until day 5 of

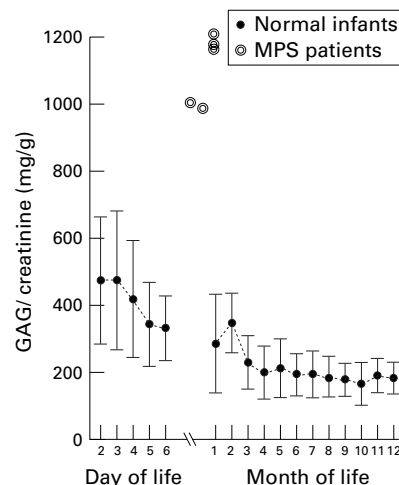


Figure 1 Urinary GAG:creatinine excretion ratios for normal infants and MPS patients. Circles indicate means; bars SD.

life. The median for the GAG:creatinine ratio was 459.0, 446.4, 400.0, 323.0, and 311.5 mg/g on days 2, 3, 4, 5 and 6, respectively. Between days 2 and day 4 of life, the decrease was significant. Urinary excretion of GAG in the normal neonates was much lower than in the five MPS patients: type II, 15 days of age, 978 mg GAG/g creatinine; type II, 26 days old, 940 mg GAG/g creatinine; type II, 1 month old, 1177 mg GAG/g creatinine; type III, 1 month old, 1180 mg GAG/g creatinine; type VII, 1 month old 1205 mg GAG/g creatinine.

The GAG:creatinine ratio in MPS patients was much higher than in normal infants. We conclude that these results might be useful for the early diagnosis of MPS.

SHOKO IWATA

KAZUKO SUKEGAWA

MIE KOKURYU

SHUNJI TOMATSU

NAOMI KONDO

Department of Paediatrics,

Gifu University School of Medicine,

40 Tsukasa-machi,

Gifu 500-8705,

Japan

S IWASA

Iwasa Hospital,

161-1 Nagara Fukumitsu,

Gifu 502-0817,

Japan

T ORII

Department of Human Welfare,

Chubu Gakuin University,

4909-3 Kurachi,

Seki,

Gifu 501-3936,

Japan

- 1 Hugh-Jones K, Hobbs JR, Vellodi A, *et al.* Long-term follow-up of children with Hurler's disease treated with bone marrow transplantation. In: Hobbs JR, ed. *Correction of certain genetic diseases by transplantation*. London: Cogent, 1989:103–11.
- 2 O'Connor LH, Erway LC, Vogler CA, *et al.* Enzyme replacement therapy for murine mucopolysaccharidosis type VII leads to improvements in behaviour and auditory function. *J Clin Invest* 1998;101:1394–400.
- 3 Crawley AG, Niedzieiski KH, Isaac EL, *et al.* Enzyme replacement therapy from birth in a feline model of mucopolysaccharidoses type VI. *J Clin Invest* 1997;99:651–62.
- 4 Kakkis E, Muenzen J, Tiller G, *et al.* Recombinant α -iduronidase replacement therapy in mucopolysaccharidosis I: Result of a human clinical trial. *Am J Hum Genet* 1998;63(suppl):A25.
- 5 Iwata S, Sukegawa K, Sakaki T, *et al.* Mass screening test for mucopolysaccharidoses using the 1,9-dimethylmethylen blue method: Positive interference from paper diapers. *Clin Chim Acta* 1997;264:245–50.
- 6 Bosnes RW, Taussky HH. On the colorimetric determination of creatinine by the Jaffe reaction. *J Biol Chem* 1945;158:581–91.

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:

2 Todd DA, Jane A, John E. Chronic oxygen dependency in infants born at 24–32 weeks' gestation: the role of antenatal and neonatal factors. *J Paediatr Child Health* 1997;33:402–7. From there on all references should be renumbered accordingly.