LETTERS TO THE EDITOR

A variant TATA box in the bilirubin UDP-glucuronosyltransferase 1 gene promoter does not contribute to neonatal jaundice in the Japanese population

EDITOR,—A variant TATA box (A[TA]₇TAA, designated as TA-7) in the promoter region of the bilirubin UDP-glucuronosyltransferase 1 (BUGT1) gene has been reported to accelerate the increase in bilirubin concentration during the first two days of life.¹ However, the relation between TA-7 and peak bilirubin concentration in the neonatal period has not been clarified, and it is also unclear as to whether TA-7 influences bilirubin metabolism in infants of different ethnic groups.

To investigate whether TA-7 is one of the risk factors for neonatal jaundice in the Japanese population, we performed genotyping analysis of the BUGT1 gene in 74 Japanese newborn infants, and measured bilirubin concentrations at 4–5 days of age in healthy infants (n=55) and peak bilirubin concentrations in infants with jaundice requiring treatment, phototherapy, or exchange transfusion (n=19).

Informed consent was obtained from parents, and infants were enrolled at birth. All infants were born at 37–42 weeks of gestation and weighed more than 2500 g. They showed no blood incompatibility, had a negative direct Coombs test; they had no clinically significant antenatal and intrapartum complications, and no clinically detectable pathology except for jaundice. In healthy infants serum bilirubin concentrations were measured at 4–5 days after birth. In infants with jaundice requiring treatment, peak bilirubin concentrations were used in the analysis.

The TATA box region of the BUGT1 promoter was amplified with the polymerase chain reaction (PCR) using the primers BUGT1-A (5'-TAACTTGGTGTATCGATTGGTTTTTG-3') and BUGT1-B (5'-ACAGCCATGGCGCCTTTGCT-3'). BUGT1-B was labelled with a fluorescent dye, 6-carboxy-X-rhodamine. An aliquot of each PCR product was electrophoresed on a genetic analyser (ABI PRISM 310; Perkin-Elmer Applied Biosystems, Foster City, CA, USA) and then analysed using the GeneScan analysis software package (Perkin-Elmer Applied Biosystems). The electrophoretogram clearly separated the peaks for a normal TATA box (A[TA]₆TAA, designated as TA-6, 90 base pairs of PCR product size) and TA-7 (92 base pairs of PCR product size).

The results of genotyping analysis of the BUGT1 gene in 55 healthy infants are given in table 1. The one variant homozygote was omitted from the statistical analysis. The serum bilirubin concentration at 4 days of age in this infant was 9.1 mg/dl. In the healthy infants no significant difference was detected in serum bilirubin concentrations at 4 to 5 days of age between normal homozygotes (10.0 (2.7) mg/dl; mean (SD)) and heterozygotes (9.2 (1.5) mg/dl) ($p = 0.43$, unpaired Student's t test).

We also analysed 19 infants with jaundice requiring treatment; 18 normal homozygotes and one heterozygote. Thus the TA-7 allele was found in only one of 19 cases. The peak serum bilirubin concentrations in the 18 normal homozygotes were 18.8 (2.29) mg/dl and that in the heterozygote was 15.7 mg/dl. TA-7 allele frequency was calculated to be 0.07, significantly lower than the value of 0.4 found in the North American and Eastern Scottish populations ($p < 0.001$, χ^2 analysis with one degree of freedom).^{2,3} The genotype distribution in the 74 Japanese infants was also significantly different from that found in the North American and Eastern Scottish populations ($p < 0.001$, χ^2 analysis with two degrees of freedom).

Ethnic differences in the incidence of neonatal jaundice have been reported. Neonatal jaundice occurs more often in East Asian infants than in Caucasian infants.^{4–6} Even if the presence of TA-7 could affect the metabolism of bilirubin in the neonatal period, it does not explain the high incidence of neonatal jaundice in Japanese infants, because the TA-7 allele frequency is very rare in the Japanese population. In the 74 infants in this study, we detected only one who was homozygous for TA-7, which happened to be a baby who was in the healthy control group. In the 19 infants with jaundice requiring treatment, we found a TA-7 allele in only one heterozygous case.

In conclusion, our findings indicate that the variant TATA box in the promoter region of the BUGT1 does not contribute to the high incidence of neonatal jaundice in the Japanese population.

SHOZO WAKU
YASUHIRO TAKESHIMA
HAJIME NAKAMURA
Department of Paediatrics
Kobe University School of Medicine
7-5-1 Kusunoki-cho
Chuo-ku, Kobe
650-0017 Japan
HISAHIDE NISHIO
KIMIYAKI SUMINO
Department of Public Health

- 1 Bancroft JD, Kreamer B, Gourley GR. Gilbert syndrome accelerates development of neonatal jaundice. *J Pediatr* 1998;132:656–60.
- 2 Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med* 1995;333:1171–5.

- 3 Monaghan G, Ryan M, Seddon R, Hume R, Burchell B. Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. *Lancet* 1996;347:578–81.
- 4 Brown WR, Boon WH. Ethnic group differences in plasma bilirubin levels of full-term, healthy Singapore newborns. *Pediatrics* 1965;36:745–51.
- 5 Horiguchi T, Bauer C. Ethnic differences in neonatal jaundice: comparison of Japanese and Caucasian newborn infants. *Am J Obstet Gynecol* 1975;121:71–4.
- 6 Linn S, Schoenbaum SC, Monson RR, Rosner B, Stubblefield PG, Ryan KJ. Epidemiology of neonatal hyperbilirubinemia. *Pediatrics* 1985;75:770–4.

Randomised controlled trial of cisapride in preterm neonates for gastric emptying time

EDITOR,—We read with interest the study on the randomised controlled trial of cisapride in preterm infants reported by McClure *et al.*¹ We have recently concluded a randomised, double blind, placebo controlled study to evaluate the effect of cisapride on feed tolerance and gastric emptying of preterm neonates. (P S Reddy, A K Deorari, C S Bal, V K Paul, M Singh. Abstract 1705 presented to the Society of Pediatrics Research meeting, 1–4 May 1999, San Francisco, USA). After obtaining informed parental consent a total of 44 preterm neonates stratified by gestation into 29–32 weeks and 33–34 weeks, and randomly allocated to receive either cisapride or placebo at a dose of 0.2 mg/kg every 8 hours. The babies were enrolled once they were stable and receiving oral feeds amounting to 25 per cent of their fluid requirements.

The feeds were increased gradually in a stepwise manner, around 20 ml/kg/day. Gastric emptying time was measured on days 6 to 8 after enrolment using a dynamic technetium scan using 100 μ Ci of radioactivity. This results in only 0.2 mSV of whole body absorbed dose.² To offset the effect of type of feeding on gastric emptying, the two feeds before the nuclear study were of uniformly expressed breast milk. Gastric emptying time (mean (SD) and median) in the cisapride group (58.1 (32.2 mins) 48.8 mins) was not significantly different from that of the control group (53.8 (34.6 mins) 43.4 mins). Clinically significant gastro-oesophageal reflux was seen in 50% of babies in each group. Cisapride had no effect on either the number of episodes of feed intolerance or the length of feed intolerance. Weight gain and the day on which the total enteral feeding began were also comparable in the two groups.

Our observations support the findings of McClure *et al.*, that cisapride does not improve gastric emptying in preterm neonates and that its use for establishing enteral feeds is not warranted.

A K DEORARI
P S REDDY
V K PAUL
Department of Paediatrics
All India Institute of Medical Sciences
New Delhi 110029
India
C S BAL
Department of Nuclear Medicine

Table 1 Clinical data and DNA polymorphism of all infants

	Healthy infants			Infants with jaundice	
	TA-6/TA-6	TA-6/TA-7	TA-7/TA-7	TA-6/TA-6	TA-6/TA-7
Number of subjects	47	7	1	18	1
Male/female	22/25	2/5	0/1	10/8	0/1
Birthweight (g) (mean (SD))	3079 (350)	3001 (184)	2658	3059 (255)	2676
Gestational weeks (mean (SD))	39.8 (1.1)	39.6 (1.4)	38.9	39.0 (1.2)	38.0
Breast fed/formula fed	25/22	5/2	1/0	10/8	1/0
Bilirubin (mg/dl)*	10.0 (2.7)	9.2 (1.5)	9.1	18.8 (2.29)	15.7

*Bilirubin concentrations at 4–5 days old in healthy infants and the peak bilirubin in infants with jaundice.

- 1 R J McClure, J H Kristensen, A Grauaug. Randomised controlled trial of cisapride in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F174–F7.
- 2 Heyman S. Gastroesophageal reflux, gastric emptying, gastrointestinal motility. In: Treves ST, ed. *Pediatric Nuclear Medicine*. 2nd Edn. Springer-Verlag, New York, 1994: 430–52.

Use of laryngeal masks in the resuscitation of a neonate with difficult airway

EDITOR,—Neonates with mandibulo-facial anomalies and respiratory distress present a challenge for neonatologists. We report a newborn boy with severe micrognathia who failed to breathe adequately immediately after birth. Tracheal intubation was unsuccessful, but he was ventilated for several hours using a laryngeal mask.

Case report

The boy was born to a 29 year old primigravida after 39 weeks of gestation. During the pregnancy, absence of the corpus callosum had been noted at 33 weeks of gestation, and genetic amniocentesis had indicated a microdeletion of chromosome 21. No other malformation had been verified. Caesarean section was performed because of intrauterine growth retardation and breech presentation.

At birth the boy weighed 2300 g, had multiple contractures of the limbs, bilateral coloboma of the iris, severe mandibular hypoplasia with a small oral orifice and a massive glossoptosis, and a systolic heart murmur. He made feeble attempts to cry, but remained cyanotic and bradycardic despite the jaw thrust manoeuvre and bagging. Oro-tracheal intubation with a 3 mm and a 2 mm tracheal tube failed twice. A lubricated number 1 laryngeal mask was easily put into the right position while holding the tongue with a Magill forceps. After sedation with fentanyl and midazolam he tolerated intermittent mechanical ventilation well for three hours while investigations were carried out. At ventilator settings of PI 25 cm H₂O, PEEP 4 cm H₂O, RR 60 per minute, FIO₂ 0.4, I:E ratio of 1:2, flow rate of 12 l/min, capillary blood gas analysis was pH 7.3, pCO₂ 4, pO₂ 95, base excess -5 mmol/l. Blood pressure and heart rate were within the normal range.

Echocardiography revealed a severely hypoplastic distal aortic arch with a wide open ductus arteriosus, and cranial echocardiography confirmed the absence of the corpus callosum.

In view of the poor prognosis the parents requested the withdrawal of intensive care, and at necropsy the diagnoses were confirmed, with the addition of a micro larynx and a large pharyngo-oesophageal cleft. No signs of damage to the hypopharynx were found.

The use of the laryngeal mask in our patient gained us time to perform investigations to establish prognosis. In patients with isolated cranio-facial and mandibulo-facial malformations such as Goldenhar, Treacher-Collins, or Pierre-Robin syndromes, the laryngeal mask could be used to establish a definite airway either through bronchoscopic intubation or tracheotomy. The usefulness of the laryngeal mask during anaesthesia in such cases has been well documented,¹⁻³ but we believe that the mask could also be a valuable tool for neonatologists who unexpectedly face a difficult airway.

RUDOLF TRAWÖGER
CHRISTIAN MANN

Department of Paediatrics
University Hospital Innsbruck
Innsbruck A-6020
Austria

MANFRED MÖRTL
Department of Anaesthesiology

KARIN RIHA
Department of Obstetrics

- 1 Brimacombe J. Use of the laryngeal mask airway in very small neonates. *Anesthesiology* 1994; **81**:1302.
- 2 Rabb MF, Minkowitz HS, Hagberg CA. Blind intubation through the laryngeal mask airway for the difficult airway in infants. *Anesthesiology* 1996;**84**:1510-11.
- 3 Ofer R, Dworak H. Die Kehlkopfmaske-ein wertvolles Instrument bei erschwelter kindlicher Intubation. *Anaesthetist* 1996;**45**:268-70.

Multicentre trial of high frequency ventilation

EDITOR,—Cools and Offringa's recent meta-analysis of elective high frequency ventilation (HFV) in preterm infants with respiratory distress syndrome¹ concludes that HFV reduces the risk of chronic lung disease (CLD) at 36 weeks of postconceptional age, but may be associated with an increased risk of severe intraventricular bleeding. Several areas of uncertainty remain, however, and they suggest that new clinical trials should be done in very preterm infants to evaluate the usefulness of elective HFV, using a high lung volume strategy, started as soon as possible after birth. We are currently running exactly such a trial in the UK—the United Kingdom Oscillation Study (UKOS).

This is a multicentre trial comparing high frequency oscillatory ventilation (HFOV) with conventional ventilation in preterm infants < 29 weeks of gestation. Previous trials have included more mature babies, but we have restricted recruitment to those babies with the highest incidence of chronic lung disease and of neurological complications. We expect to recruit 1200 babies over two years, making this the largest study of its kind so far, with the greatest statistical power. To avoid selection bias, treatment allocation is by a central telephone randomisation service. Infants are given their allocated mode of ventilation within one hour of birth (up to 15 hours in previous studies) to assess the effect of early intervention with HFOV, which has been shown to be most beneficial in animal studies.² Long term neurodevelopmental and pulmonary outcome will be evaluated up to 2 years of corrected gestational age; only two previously published studies^{3,4} have done this.

Keszler and Dunn in North America (personal communication) also have an ongoing study of a similar nature, and we hope that the results of these trials will provide the evidence for future ventilation policy for very preterm infants.

A JOHNSON

S CALVERT

N MARLOW

A GREENOUGH

UKOS STUDY GROUP

St George's Hospital Medical School
London SW17 0RE

- 1 Cools F, Offringa M. Meta-analysis of elective high frequency ventilation in preterm infants with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F15-F20.
- 2 Meredith KS, de Lemos RA, Coalson JJ, et al. Role of lung injury in the pathogenesis of hyaline membrane disease in premature baboons. *J Appl Physiol* 1989;**66**:2150-8.
- 3 Hi Fi Study Group. High frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *N Engl J Med* 1989;**320**:88-93.

- 4 Ogawa Y, Miyasaka K, Kawano T, et al. A multicentre randomised trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure. *Early Hum Dev* 1993;**32**:1-10.

Antenatally diagnosed renal pelvis dilatation

EDITOR,—I read with interest the study by Jaswon *et al* on outcome in antenatally diagnosed renal pelvis dilatation.¹

The cohort was recruited antenatally from pregnancies where renal pelvis dilatation had been diagnosed mostly on the 20 week ultrasound scan. VUR was described as being "the most common clinically significant pathology" (23 out of 104 cases). Presumably all of the babies were asymptomatic. How can the authors be sure that this VUR was either clinically significant or indeed pathological?

Figure 2 shows that nine out of 23 babies had grade III or IV VUR despite a normal postnatal renal ultrasound scan. Is anything known of the natural history of these nine babies? The reference regarding the possible prevalence of VUR in infants is a "literature review"² (method not stated by the author) of 14 papers published between 1916 and 1967—that is, predating the era of antenatal ultrasonography.

One baby went on to have pyeloplasty at 18 months of age, because of deteriorating renal function, due to PUJ obstruction, not VUR (table 1). This low rate of surgical intervention (one baby out of 139 pregnancies over 18 months) reinforces the notion that these findings are largely benign.^{3]}

The longer term follow up, or outcome, of the other 103 babies is not stated—for example, if the postnatal renal ultrasound scan and MCU were normal, n=60/104, the infant was discharged. This suggests follow up only of babies with "abnormal" findings.

Information has been collected regarding the prevalence of VUR, PUJ obstruction, and renal dysplasia in the first three months of life in this cohort. What is the evidence that these diagnoses have clinically important long term adverse outcomes?

The conclusion states that babies with antenatal renal pelvis measurements of 5 mm or greater should be investigated, as they may have VUR. However, I am unclear as to what long term outcome measures will be improved by these sometimes invasive investigations.

Table 1 also contains data on 25 babies, but the text refers to persisting renal pelvis dilatation in 47 babies.

R M NICHOLL

Department of Paediatrics
North West London Hospitals NHS Trust
Northwick Park Campus
Harrow
HA1 3UJ

- 1 Jaswon MS, Dibble L, Purie S, Davis J, Young J, Dave R, Morgan H. Prospective study of outcome in antenatally diagnosed renal pelvis dilatation. *Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F135-8.
- 2 Bailey RR. Vesicoureteric reflux in healthy infants and children. In: Hodson J, Kincaid Smith P, eds. *Reflux Nephropathy*. New York: Masson, 1979:57-61.
- 3 Koff S, Campbell K. Non-operative of unilateral neonatal hydronephrosis. *J Urol* 1992;**148**: 525-3.