Persistent pulmonary hypertension and abnormal prostaglandin E levels in preterm infants after maternal treatment with naproxen

ANDREW R. WILKINSON, A. AYNLEY-GREEN, AND M. D. MITCHELL

Department of Paediatrics and Nuffield Department of Obstetrics, John Radcliffe Hospital, Oxford

SUMMARY Twins and a singleton were born at 30 weeks' gestation although naproxen (d-2 (6'methoxy-2-naphthyl) propionic acid) had been given to the mothers in an attempt to delay parturition. Inhibition of prostaglandin synthesis was shown by very low plasma concentrations of prostaglandin E and the ductus arteriosus remained closed despite signs of pulmonary hypertension with severe hypoxaemia. Abnormalities in blood clotting, renal function, and bilirubin metabolism were also found and one infant died. Further studies of the benefits and risks of the inhibition of prostaglandin synthesis are required before this treatment of preterm labour is accepted.

Indomethacin and salicylates are prostaglandin synthetase inhibitors (PGSI), which suppress uterine activity in animals and humans (Wigvist *et al.*, 1975). Some workers have used PGSI to treat women after the onset of preterm labour (Zuckerman *et al.*, 1974), but experiments in lambs (Heymann and Rudolph, 1976; Levin *et al.*, 1979) show that these drugs cross the placenta and cause great changes in the fetal circulation with closure of the ductus arteriosus and an increase in pulmonary arterial pressure. Postnatal persistent pulmonary hypertension has been described after maternal treatment with indomethacin and salicylates (Manchester *et al.*, 1976; Csaba *et al.*, 1978; Levin *et al.*, 1978). We report 3 premature infants with this syndrome who were born to mothers who had been given naproxen (d-2 (6'methoxy-2-naphthyl) propionic acid) which is another potent PGSI.

Case 1

A girl weighing 1.28 kg was born at 30 weeks' gestation to a 28-year-old mother. There had been recurrent vaginal bleeding throughout pregnancy and at 28 weeks uterine contractions became

frequent. Naproxen 250 mg was given orally 8-hourly for 6 days and contractions became less frequent but 48 hours after stopping naproxen spontaneous labour recurred. The baby was delivered by caesarean section because of breech presentation. The Apgar score was 2 and the baby was resuscitated with oxygen and positive pressure ventilation, but cyanosis persisted and tachypnoea developed. Artificial ventilation was continued and at 40 minutes while breathing 50% oxygen arterial pH was 7.04, P_{aO_2} 3.0 kPa (23 mmHg), and P_{aCO_2} 7.9 kPa (59 mmHg). Breath sounds were normal and no heart murmurs were heard. The haematocrit was 52% and blood glucose concentration normal. Parenchymal and vascular markings and the heart size were normal on chest x-ray. The inspired oxygen concentration was raised to 100% and ventilation pressure to 30 cmH₂O with 4 cmH₂O end-expiratory pressure. Fig. 1 shows that despite these changes, the P_{aO_2} could not be raised above 6.7 kPa (50 mmHg) until 6 hours after birth. At 10 hours, right radial and umbilical artery blood-gas tensions were identical (Fig. 1). She required assisted ventilation until 63 hours of age and additional oxygen until the fifth day. There was no evidence of pneumonia, hyaline membrane disease, or aspiration. Urine was not passed until 24 hours and plasma bilirubin rose to 252 μ mol/l (14.7 mg/100 ml). Bleeding time was prolonged but platelet count and clotting studies were within normal limits. At discharge, age 61 days, she weighed 2.2 kg and examination was normal.

John Radcliffe Hospital, Oxford
Department of Paediatrics

A. R. WILKINSON, lecturer in paediatrics

A. AYNLEY-GREEN, lecturer in paediatrics

Nuffield Department of Obstetrics

M. D. MITCHELL, MRC senior research fellow

Fig. 1 Inspired oxygen concentration ($F_{I O_2}$)—continuous line, and arterial oxygen tension ($P_{a O_2}$)—dotted line. Hatched area shows normal range of $P_{a O_2}$. Effect of tolazoline hydrochloride is shown in Cases 2 and 3. S = identical gas tensions in umbilical and right radial arterial blood and blood samples taken for prostaglandin assay. Conversion: SI to traditional units 1 kPa $\approx$ 7.5 mmHg

Cases 2 and 3

Twin girls were delivered by caesarean section at 30 weeks' gestation to a 20-year-old mother after a pregnancy complicated by vaginal bleeding and preterm labour. 30 hours before delivery naproxen 250 mg 8 hourly had been begun. A total of 1 g was given, the last dose 5 hours before delivery.

The first twin weighed 1.18 kg. The Apgar score was 1 and positive pressure ventilation was given immediately. At 30 minutes while breathing 80% oxygen arterial pH was 7.05, $P_{a O_2}$ 6.7 kPa (51 mmHg), and $P_{a C O_2}$ 10.8 kPa (81 mmHg). The lung

fields were clear and the heart size normal on chest x-ray. Haematocrit and blood glucose concentration were normal and the lecithin/sphingomyelin ratio (L/S) was 2.0 in the pharyngeal aspirate. The hypercarbia was rapidly corrected by artificial ventilation but $P_{a O_2}$ remained low despite pressures up to 35 cmH₂O and 100% oxygen. Simultaneous right radial and umbilical blood-gas tensions taken when the baby was unresponsive were identical at 40 hours (Fig. 1). Tolazoline hydrochloride (2 mg/kg, IV) produced an immediate improvement in oxygenation (Fig. 1) which was maintained by an infusion (2 mg/kg per hour) for 20 hours. Assisted

ventilation was necessary for 5 days after which chronic lung disease with oxygen dependency persisted for 12 weeks. During the first 2 days plasma bilirubin rose to 225 $\mu\text{mol/l}$ (13.2 mg/100 ml) and bleeding time, prothrombin time, and partial thromboplastin time were prolonged. Urine volume was markedly reduced until the third day.

The second twin was delivered 2 minutes later and weighed 1.26 kg. The Apgar score was 1 and severe hypoxaemia rapidly developed. Treatment and investigations were similar to those in the first twin. The L/S ratio was 3.1, and within the first 24 hours the bilirubin rose to 230 $\mu\text{mol/l}$ (13.5 mg/100 ml). Bleeding from the umbilical stump and heel punctures was prolonged and the clotting studies were abnormal. At 3 hours an intracranial haemorrhage was suspected. At 10 hours tolazoline hydrochloride (2 mg/kg, IV) rapidly improved oxygenation (Fig. 1) and during the next 60 hours ventilatory assistance was gradually withdrawn. However, at 80 hours she suddenly became apnoeic with a distended abdomen and poor peripheral perfusion. Cardiac arrest occurred and resuscitation was unsuccessful. Necropsy showed a subarachnoid haemorrhage and blood in both ventricles. Multiple gastric ulcers were present and there was blood throughout the intestine. The ductus arteriosus was short and constricted and hyaline membranes were not seen in sections of the lungs.

Assay of plasma prostaglandins. The plasma concentrations of prostaglandins E and F (PGE and

Fig. 2 Plasma concentration of PGE, PGF, and PGFM (pg/ml) (open circles), compared with concentrations in preterm infants without cardiopulmonary disease (closed circles).

PGF), and 13, 14-dihydro-15-keto-PGF (PGFM) (the major circulating metabolite of PGF), were measured by methods described previously and in Fig. 2 the values at 10, 40, and 10 hours age are compared with the levels found in preterm infants of the same age who were not ill (Mitchell *et al.*, 1978).

Discussion

Persistent pulmonary hypertension presents during the first hours of life with arterial oxygen desaturation in the absence of parenchymal pulmonary disease or cardiac malformation. The mechanisms responsible are not known but an altered structure or abnormal response of the smooth muscle of the pulmonary arterioles has been suggested (Levin *et al.*, 1978). The condition has been associated with birth asphyxia, hypoglycaemia, hypocalcaemia, and hyperviscosity. The 2 infants who survived (Cases 1 and 2) were not hypoxaemic at birth. Umbilical cord vein Po_2 was 4.1 and 2.9 kPa (31 and 22 mmHg). In Case 3 the umbilical cord was so friable that blood could not be obtained. Undoubtedly hypoxaemia after birth contributed to maintaining the high pulmonary vascular resistance. Cassin *et al.* (1978) showed that this effect of hypoxia is potentiated by indomethacin and meclofenamate (another PGSI). In their experiments with goats the response to indomethacin was more pronounced in the premature than mature newborn. They also reported that an infusion of PGE abolishes the response to hypoxia and can reverse the effect of the PGSI.

Constriction of the ductus arteriosus and pulmonary arterial hypertension after maternal indomethacin administration in fetal lambs has been reported by Levin *et al.* (1979). This effect was also reversed promptly but temporarily by an infusion of PGE. In the 3 infants described here the identical gas tensions in blood drawn simultaneously from both sides of the ductus arteriosus (Fig. 1) and the absence of a ductal flow murmur suggests that the ductus arteriosus had constricted. The very low concentrations of prostaglandin E in all 3 babies (Fig. 2) supports the view that this prostaglandin plays an important role in maintaining relaxation of the ductus arteriosus *in utero* and that constriction may follow inhibition of prostaglandin synthesis.

The association between pulmonary hypertension and inhibition of prostaglandin synthesis in humans was first suggested by Manchester *et al.* (1976) who described 2 cases after treatment with indomethacin, and the report by Zuckerman *et al.* (1974) included 5 infants who died within 48 hours. Csaba *et al.* (1978) reported 2 deaths in 5 infants after indomethacin and Levin *et al.* (1978) reported 2 deaths, one each after salicylate and indomethacin treatment, in which they found an increase in pulmonary arterial smooth

muscle and a decrease in the number of pulmonary vessels. This report is the first to implicate naproxen in a similar role.

When the severe hypoxaemia of the twins (Cases 2 and 3) was refractory to other treatment we gave tolazoline hydrochloride which caused a large rise in Pao_2 (Fig. 1). There was a pronounced skin flush and fall in systolic blood pressure from 58 to 35 mmHg and 69 to 39 mmHg which was restored immediately by infusing albumin and blood. Tolazoline is a potent pulmonary and systemic vasodilator and blood pressure must be continuously monitored to detect severe hypotension. The gastric ulceration and bleeding found at necropsy (Case 3) was probably due to the histaminic action of tolazoline on gastric secretion. It is less certain whether the cerebral bleeding preceded the infusion of tolazoline or not.

The role of naproxen in the aetiology of early hyperbilirubinaemia, the abnormalities in blood clotting, and the impairment of renal function remain to be defined.

There is no universally effective and safe way of delaying preterm labour, and only when details of all the effects of PGSI are known will it be possible to decide whether there is any benefit to the fetus from this form of treatment. At present the possible hazards outweigh the theoretical advantage taking into account the improved prognosis for premature infants with current management.

We thank Professor F. Dray (Pasteur Institute, Paris) for prostaglandin antisera, Dr J. E. Pike (Upjohn Company, Kalamazoo, USA) for prostaglandin standards, Mrs J. D. Brunt for assay work, and Professor A. C. Turnbull and Dr A. Anderson for advice.

This work was supported in part by an MRC programme grant awarded to Professor A. C.

Turnbull, and A.R.W was supported by the National Foundation, The March of Dimes, USA. M.D.M holds the Staines Medical Research Fellowship at Exeter College, Oxford.

References

- Cassin, S., Tyler, T., and Leffler, C. (1978). Pulmonary vascular responses to prostaglandins and prostaglandin synthetase inhibitors in perinatal goats. In *Advances in Prostaglandin and Thromboxane Research*, volume 4, pp. 249–256. Edited by F. Cocceani and P. M. Olley. Raven Press: New York.
- Csaba, I. F., Sulyok, E., and Ertl, T. (1978). Relationship of maternal treatment with indomethacin to persistence of fetal circulation syndrome. *Journal of Pediatrics*, **92**, 484.
- Heymann, M. A., and Rudolph, A. M. (1976). Effects of acetylsalicylic acid on the ductus arteriosus and circulation in fetal lambs *in utero*. *Circulation Research*, **38**, 418–422.
- Levin, D. L., Fixler, D. E., Morriss, F. C., and Tyson, J. (1978). Morphological analysis of the pulmonary vascular bed in infants exposed *in utero* to prostaglandin synthetase inhibitors. *Journal of Pediatrics*, **92**, 478–483.
- Levin, D. L., Mills, L. J., Parkey, M., Garriott, J., and Campbell, W. (1979). Constriction of the fetal ductus arteriosus after administration of indomethacin to the pregnant ewe. *Journal of Pediatrics*, **94**, 647–650.
- Manchester, D., Margolis, H. S., and Sheldon, R. E. (1976). Possible association between maternal indomethacin therapy and primary pulmonary hypertension in the newborn. *American Journal of Obstetrics and Gynecology*, **126**, 467–469.
- Mitchell, M. D., Lucas, A., Etches, P. C., Brunt, J. D., and Turnbull, A. C. (1978). Plasma prostaglandin levels during early neonatal life following term and preterm delivery. *Prostaglandins*, **16**, 319–326.
- Wigvist, N., Lindström, V., and Green, K. (1975). Premature labor and indomethacin. *Prostaglandins*, **10**, 515–526.
- Zuckerman, H., Reiss, U., and Rubinstein, I. (1974). Inhibition of human premature labor by indomethacin. *Obstetrics and Gynecology*, **44**, 787–792.

Correspondence to Dr A. R. Wilkinson, Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU.

Received 13 March 1979