Theophylline toxicity in a neonate

Theophylline and its derivatives have been widely used in the successful management of recurrent apnoeic attacks in preterm infants (Kuzemko and Paala, 1973; Shannon et al., 1975). Recently there have been reports of less beneficial metabolic sequelae of theophylline administration. Nobel and Light (1977) reported a diuresis in such an infant, theophylline infusion significantly raised blood glucose in 2 infants (Aranda and Dupont, 1976), and small infants may metabolise theophylline less efficiently than do adults (Aranda et al., 1976). We report a pair of twins, one of whom developed hyperglycaemia and glycosuria while receiving theophylline; these abnormalities were corrected within 48 hours of stopping theophylline. The other twin also received theophylline, but at a smaller dose, and did not develop hyperglycaemia or glycosuria.

Case histories

Twins were born to a 24-year-old Caucasian primigravida. Pregnancy was uncomplicated but spontaneous onset of labour occurred at 30 weeks' gestation and delivery of both twins was normal. Both twins were transferred to this unit from a referral hospital at 36 hours.

Twin 1 was a girl weighing 880 g. Apgar scores were 9 and 10 at 1 and 5 minutes respectively. Short apnoeic attacks occurred on the first day and were initially treated by stimulation and increased ambient O2 concentration. Treatment with oral choline theophyllinate at 2 mg/kg per day was begun on the 2nd day and a maximum plasma level of 4 μg/ml one hour after the dose was recorded.

No increase in dosage was necessary and no apnoeic attacks took place after the 7th day. Theophylline treatment was discontinued on the 28th day. No hyperglycaemia or glycosuria was recorded. The only metabolic abnormality was a nonrespiratory acidosis treated with oral sodium bicarbonate.

Twin 2 was a boy weighing 880 g; Apgar scores were 7 and 10 at 1 and 5 minutes respectively. Early symptoms of respiratory distress developed and despite ambient O2 concentration of 40–50%, recurrent apnoeic attacks occurred after 15 hours. At 30 hours intubation and intermittent positive pressure ventilation (IPPV) were required. The initial clinical and x-ray findings were compatible with hyaline membrane disease and IPPV was continued for 3 days; this was followed by a further 9 days of continuous positive airways pressure (CPAP). Apnoeic attacks initially resolved by the 10th day but were again present by the 20th day. On this occasion they were associated with copious pharyngeal and tracheal secretions and radiological evidence of pulmonary consolidation. Serratia marcescens and Escherichia coli were grown from tracheal aspirates on separate occasions and appropriate treatment was given. An enterobacter septicaemia occurred on the 14th day and was treated with a 7-day course of flucloxacillin and gentamicin.

IPPV was again necessary from day 27 to day 34 followed by a period of nasal CPAP. Apnoeic attacks were not recorded after day 42. Oral choline theophyllinate was given from the 3rd day at an initial dosage of 2 mg/kg per day. Because of inadequate control of apnoeic attacks despite the intermittent use of CPAP the dosage was increased by 1 mg/kg per day at approximately weekly intervals. Plasma levels were checked at similar intervals one hour after the dose and maximum plasma levels of 4 μg/ml were obtained. Hyperglycaemia and glycosuria occurred on two occasions (Figure). The first episode was related to the use of 10% dextrose IV in addition to a small dose of theophylline. During the second episode on the 34th day the infant was clear of infection and receiving 230 ml/kg of expressed breast milk daily. Maximum urine sugar concentration was 1% and blood glucose 15 mmol/l (270 mg/100 ml). On this occasion the abnormalities were corrected within 36 hours of stopping theophylline. A metabolic acidosis, responsive to bicarbonate, and hyponatraemia were also recorded. The hyponatraemia resolved with the introduction of sodium supplements, but choline theophyllinate was also discontinued at this time.

The infant was discharged to the referral hospital on the 45th day weighing 1·56 kg.

Discussion

Choline theophyllinate has been found of value in the management of apnoea of prematurity (Kuzemko and Paala, 1973; Shannon et al., 1975), but recent reports have suggested that it is not without risk (Aranda and Dupont, 1976; Aranda et al., 1976;
Nobel and Light, 1977). Although hyperglycaemia and glycosuria have been reported in older children suffering from theophylline poisoning (Vaucher et al., 1977), we do not know of any such reports in premature infants. However, in 2 such infants infusion of theophylline was shown to raise the blood glucose (Aranda and Dupont, 1976). In our twin 2, the second episode of hyperglycaemia and glycosuria was related to a recent increase in theophylline dosage despite a constant nutritional intake and without concomitant evidence of infection. Moreover, the decline in blood glucose corresponded with the time taken for elimination of theophylline from the body as judged from clearance studies made by Giacoia et al. (1976) and data from other cases (Vaicher et al., 1977).

The explanation for this hyperglycaemia is not clear; the recorded plasma levels of theophylline did not exceed 4 \( \mu g/ml \) (below the levels that Vaucher obtained in poisoned children), but as our levels were taken one hour after theophylline administration, it may be that peak levels were missed. Giacoia et al. (1976) and Aranda et al. (1976) have shown that in small preterm infants metabolism of theophylline is less efficient than in adults, thereby increasing potential toxicity. From their studies, Giacoia et al. (1976) recommended a theophylline dosage of 2 mg/kg per 12 h instead of the 2–3 mg/kg per 6 h suggested by Shannon et al. (1975).

In twin 2 the final dosage of theophylline exceeded this value at 2·5 mg/kg per 12 h and it is of interest that twin 1, of identical weight but receiving only 1 mg/kg per 12 h, did not develop hyperglycaemia and glycosuria. Twin 2 had episodes of infection requiring vigorous treatment but these seemed neither directly related to the hyperglycaemia or glycosuria nor to be the primary cause of the apnoea. Indeed, both infants fulfilled the criteria (Shannon et al., 1975) for theophylline administration when treatment was begun.

Although toxic levels of theophylline were not obtained in twin 2, it seems likely that the administration of theophylline was related to this infant's glycosuria and hyperglycaemia. What part the drug may have played in the other metabolic abnormalities of hyponatraemia and acidosis is conjectural. Clearly, care is needed in the use of theophylline in sick premature infants and more detailed studies are required to evaluate the clinical significance of the recorded disturbance of carbohydrate homeostasis.

**Summary**

One of a pair of preterm twins treated with theophylline (2 mg/kg per day) for apnoea developed episodes of hyperglycaemia and glycosuria.

**References**


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**Aortic homograft valve replacement for postendocarditis aortic incompetence in early childhood**

**A case report**

Acute bacterial endocarditis in infancy and early childhood has a high mortality. Its incidence and mortality increase if there is associated congenital heart disease. The mainstay of the clinical management of children with acute bacterial endocarditis has been chemotherapy in addition to drugs for congestive heart failure. Prosthetic valve replacement has been used in a few cases. Homograft valve replacement in a child under 2 years has apparently not been reported in the UK. We now report a case of bacterial aortic valvulitis with ventricular septal defect in a 21-month-old child, successfully treated by surgical closure of the septal defect and by homograft replacement of the aortic valve.

**Case report**

A 21-month-old girl was admitted to hospital, with a 2-week history of malaise, loss of appetite, listlessness, and irritability preceded by an attack of acute gastroenteritis. At age 3 months, a heart murmur attributed to a small ventricular septal defect had been noted. Clinical examination showed severe peripheral oedema and hepatomegaly; she was afebrile and acyanotic. Both ventricles were overactive on palpation; there were widespread precordial loud systolic and diastolic murmurs maximal at the left 4th interspace.

Despite treatment with digoxin and diuretics, her condition deteriorated and she developed a high pyrexia. Initial blood culture yielded no bacterial growth, but because of increasing heart failure, associated with pyrexia, anaemia, splenomegaly, and signs of aortic incompetence, acute bacterial endocarditis was suspected. Treatment with IV potassium penicillin and cloxacillin was therefore begun.

Laboratory investigations showed Hb 7·0 g/dl, WBC $14.2 \times 10^9$/l (14 200/mm$^3$) with 60% polymorphs, and ESR 57 mm in 1st hour. β-Haemolytic streptococcus group A was grown from a throat swab; blood cultures later yielded a growth of nonhaemolytic streptococcus.

Chemotherapy produced only an initial improvement. Cardiac catheterisation and angiography showed gross aortic incompetence through a tricuspid valve, an abscess of the interventricular septum in the subaortic region with a small left to right ventricular shunt, and a nonleaking aneurysm into the right atrium.

On admission to Harefield hospital, signs of aortic incompetence and congestive heart failure were confirmed. Medical treatment with IV penicillin and cloxacillin, oral digoxin, fruseamide, and spironolactone was continued. On the 10th day after admission she developed signs of cerebral embolism with left-sided hemiplegia. Five days later, she developed pulmonary oedema which responded to intensive medical treatment.

In view of the embolic phenomenon and the occurrence of pulmonary oedema, operation under moderate surface-induced hypothermia and cardiopulmonary bypass was performed on 8 April 1974.

**Operative findings.** These were: bicuspid and incompetent aortic valve whose cusps were covered with massive soft vegetations (Fig. 1); aneurysmal dilatation of the aortic root bulging into, but not entering, the right atrium; and a high ventricular septal defect, 3 mm in diameter.

Through a longitudinal aortotomy, the diseased valve was excised, and the ventricular septal defect closed by direct suturing. The aortic root was enlarged using 2 gussets of aortic wall homograft, to accommodate an aortic homograft 15 mm in diameter (Fig. 2). The valve homograft was inserted in the subcoronary position by the standard two suture-line procedure. The gussets were oversewn with a piece of woven dacron for extra support. Postoperative progress was uncomplicated. At the time of discharge full power and movements had returned to the upper limb. Clinical reviews show continued satisfactory physical, mental, and haemodynamic states.

**Discussion**

Congenital malformations of the heart and the great vessels are present in about two-thirds of all children...
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