Pharmacological closure of ductus arteriosus in preterm infants using indomethacin

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SUMMARY Patent ductus arteriosus (PDA) was diagnosed in 27 (21%) of 129 infants weighing ≤ 1500 g at birth presenting over 1½ years. The incidence of PDA in infants with pulmonary disease, particularly hyaline membrane disease, was higher than that in infants without such disease (31% compared with 16%). 16 (59%) infants with PDA developed congestive cardiac failure (CCF), of whom 12 were ≤ 1000 g at birth. Eight of these infants had persistent CCF despite aggressive antifailure treatment, and 8 were ventilator-dependent although stable on medical management. Pharmacological ductal closure with indomethacin was attempted in these 16 infants according to clinical and echocardiographic criteria. Complete or partial ductal closure with clinical and echocardiographic improvement was achieved in 75% of infants. Treatment with indomethacin failed in 4 infants all of whom were ≤ 1000 g at birth and had gestational ages ≤ 26 weeks. Two of these infants had surgical ligation of the PDA and recovered. No morbidity was attributed to indomethacin except for transient oliguria. Overall survival was 76%; this ranged from 50% in infants weighing 501–750 g, to 91% in infants weighing 1251–1500 g.

Results suggest that (1) extremely preterm infants are less likely to respond to indomethacin, (2) success is more likely in the first 10 days of life, (3) a total dose greater than 0.6 mg/kg will not increase the success rate, (4) selective morbidity from indomethacin is unlikely if the contraindications of bleeding tendency, hyperbilirubinaemia, and renal dysfunction are followed, although urinary output must be monitored carefully, (5) indomethacin is a useful alternative to surgical ligation although long-term prognosis from clinical trials has yet to be established.

Improvement in neonatal intensive care has resulted in greater survival of preterm infants, and increased diagnosis of disorders associated with prematurity—such as patent ductus arteriosus (PDA). Management of PDA has become one of the major problems in neonatal intensive care.¹ For most preterm infants with PDA, conservative medical management is satisfactory.^{2–3} If cardiac or respiratory failure is progressive and life-threatening despite aggressive medical management, immediate ductal closure is essential for infant survival.^{4–6} Small preterm infants ≤ 1500 g with or without hyaline membrane disease (HMD) often have a prolonged course of ductus shunting and characteristically require weeks of mechanical ventilation. A recent study showed

that early ductal closure led to earlier weaning from mechanical ventilation, decreased need for antifailure treatment, and earlier establishment of optimal nutrition via the enteric route.⁷ Friedman *et al.*⁸ and Heymann *et al.*⁹ have reported that inhibitors of prostaglandin synthesis (indomethacin and aspirin) are effective in closing the ductus.

Until June 1977, our management of infants with congestive cardiac failure (CCF) secondary to left-to-right shunting through a PDA was confined to conventional antifailure treatment using digoxin, frusemide, and respiratory support, and if this failed—surgical ligation. Between June 1977 and December 1978, indomethacin was used as an alternative to surgical ligation. If this failed surgery was used. This study reports the results of this trial.

Patients and methods

Study population. 129 infants ≤ 1500 g at birth were admitted between June 1977 and December 1978 to

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the neonatal unit of this centre. Their median birth-weight was 1190 g (range 570–1500) and median gestational age 29 weeks (range 24–36). 39 (30%) infants weighed between 501 and 1000 g. Overall survival was 76%. 16 (52%) of the 31 deaths occurred earlier than 72 hours of age, before the presence of PDA could be evaluated.

General management. Details of neonatal intensive care methods and the protocol for ventilatory assistance have been described in previous reports.^{10–11} Parenteral nutrition was given before establishment of enteric feeds. Total daily fluid administered during the first week was 100–150 ml/kg, and increased to 150–200 ml/kg by the second week depending on the clinical and biochemical hydration state. Details of the parenteral nutrition regimen, the formulation used, and its administration and monitoring have been reported.¹²

Diagnosis of PDA. Essential features were a systolic murmur maximal at the left sternal edge or below the left clavicle, or a continuous murmur, with bounding pulses. When an arterial catheter was *in situ* the increased pulse pressure was measured directly. Serial chest x-rays, ECGs, and echocardiograms were performed. Infants were designated as having 'symptomatic PDA' (sPDA) when CCF secondary to a large left-to-right ductus shunt developed. The clinical signs included tachycardia (>150/min), gallop rhythm, hyperdynamic praecordium with collapsing pulses, moist râles in the chest on auscultation, and hepatomegaly. A deterioration of respiratory function was often heralded by increasing apnoeic episodes and bradycardia. Infants already on mechanical ventilation experienced increased oxygen and ventilatory requirements. X-ray findings included prominent pulmonary vasculature and evidence of pulmonary oedema, ranging from hazy lung fields to complete white-out¹³ and cardiomegaly. Serial echocardiography showed significant increases in left ventricular end-diastolic (LVED) and left atrial (LA) dimensions, and a left atrial/aortic (LA/Ao) ratio >1.2:1.

Management of PDA. Infants with PDA and no CCF were treated with careful regulation of the volume of fluid administered (120 ml/kg per 24 hours). Infants who had CCF were treated with digoxin and frusemide. Fluids were restricted to 80–100 ml/kg per 24 hours. Digoxin 10 µg/kg IV was given initially followed by maintenance therapy 24 hours later of 5 µg/kg 12-hourly. Central haematocrit was maintained above 40% with transfusions of packed cells 10–15 ml/kg over 2 hours, followed by frusemide 1 mg/kg.

Indomethacin therapy. If, despite medical management, cardiac failure persisted or ventilatory requirement increased, indomethacin was administered. The initial dose of indomethacin was 0.3 mg/kg and this was repeated 24 hours later if the PDA murmur persisted. The course was repeated later if signs recurred. Because of drug insolubility, indomethacin was suspended in syrup BP and water vehicle (0.2 mg/ml) and given via a gastric tube. Hb, haematocrit, white blood count, platelet count, serum indirect bilirubin, stool guaiacum reaction, blood urea, and urine analysis were performed. Blood-gases and serum electrolytes were monitored routinely. Fluid intake, urinary output, and body weight were recorded daily. Serial chest x-rays, ECGs, and echocardiograms were performed. Contraindications to the use of indomethacin included bleeding tendency, necrotising enterocolitis, serum indirect bilirubin >150 µmol/l (8.8 mg/100 ml), and blood urea >8 mmol/l (48.2 mg/100 ml).

Results

Incidence. PDA was diagnosed in 27 (21%) of 129 infants ≤1500 g at birth. The incidence of PDA was higher in infants with lower birthweights: 16 (41%) infants weighing 501–1000 g compared with 11 (12%) in infants weighing 1001–1500 g. Birthweights and gestational ages of infants with and without PDA are given in Table 1. 59 (46%) infants had HMD. PDA was present in 16 (27%) of 59 infants with HMD compared with 11 (16%) of 70 without HMD. In addition, 2 infants with intrapartum pneumonia (group B β-haemolytic streptococcal infection) and one infant with Wilson-Mikity syndrome had PDA. The incidence of PDA in infants with pulmonary disease (31%) was higher than that in the infants without (16%) ($\chi^2=5.72$, $P<0.05$). The PDA murmur was first heard between 4 and 14 days after birth (median 6); 18 (67%) by the end of the first week, and 9 (33%) in the course of the second week.

Table 1 Birthweights and gestations of infants weighing ≤1500 g with and without PDA

	Infants		All infants (n=129)
	With PDA (n=27)	Without PDA (n=102)	
Gestation			
Mean	28	29	29
Median	27	29	29
Range	24–33	24–36	24–36
Birthweight			
Mean	1020	1180	1150
Median	940	1220	1190
Range	620–1400	570–1500	570–1500

Symptomatic PDA. 11 (41%) of the 27 infants with PDA had an uneventful course, uncomplicated by CCF or ventilator dependence, followed by spontaneous ductal closure. The remaining 16 (59%) developed CCF, 12 of whom weighed 501–1000 g. They fell into four clinical groups: (1) Three (19%) infants without respiratory disease developed PDA, CCF, and continued to deteriorate despite antifailure treatment and ventilation. (2) Two (12%) infants with HMD who after a few days of gradual improvement of their respiratory distress deteriorated after the appearance of PDA and CCF despite antifailure treatment, increased oxygen and ventilation. (3) Three (19%) with HMD or pneumonia developed PDA and CCF during the course of ventilatory treatment and continued to deteriorate despite antifailure treatment. (4) Eight (50%) infants with HMD developed PDA and CCF during the course of ventilatory therapy and, although stable on antifailure treatment, were ventilator-dependent.

Indomethacin therapy. The 16 infants with sPDA who had persistent CCF or were ventilator-dependent despite antifailure treatment were treated with indomethacin. Their median birthweight was 840 g (range 620–1340) and median gestational age 26 weeks (range 24–28). 12 of the infants weighed ≤ 1000 g. The first dose of indomethacin was administered between 8 and 22 days (median 10). Only 6 of 16 infants received the first dose before 10 days of age.

After the administration of indomethacin the time taken for clinical and echocardiographic evidence of ductal closure varied as did the number of doses needed to achieve this. Ductal closure with complete disappearance of both the PDA murmur and signs of CCF with return of echocardiogram to normal occurred in 9 (56%) infants. This was achieved within 24 hours of a single dose in 4 infants, and after a course of two doses in 5 infants. The murmur became softer and there was pronounced clinical and echocardiographic improvement in a further 3 (19%) infants. Four (25%) infants failed to respond to indomethacin despite two courses of treatment in 3 infants and three courses of treatment in the other. Two of these infants (birthweights 780 and 820 g) underwent surgical ligation of the ductus and recovered. The other 2 infants (birthweights 720 and 980 g) remained critical on respiratory treatment and subsequently died of intraventricular haemorrhage in the third week after birth, 8 and 10 days respectively after treatment with indomethacin. The PDA murmur recurred with evidence of a left-to-right shunt in 3 of the 8 infants whose ducts closed after the first course. This coincided with acute

hypoxaemia due to blockage of the endotracheal tube in one instance, increasing respiratory distress from pneumonia in another, and inadvertent sudden increase in the parenteral fluid infusion rate in the third. The effects of indomethacin on LVED and LA dimensions and the LA/Ao ratio are shown in Figs 1 to 3.

Morbidity and mortality. Urinary output fell in several infants receiving indomethacin after the first dose; 24 to 48 hours after the last dose, urine

Fig. 1 Left ventricular end-diastolic dimension before and after treatment with indomethacin.

Fig. 2 Left atrial dimension before and after treatment with indomethacin.

Fig. 3 Left atrial/aortic ratio before and after treatment with indomethacin.

Table 2 Survival rates of infants weighing ≤ 1500 g with and without PDA

Birthweight (g)	No. of infants				Total survivors	
	With PDA		Without PDA		No.	%
	Survived	Died	Survived	Died		
501-750 (n=10)	2	3	3	2	5	50
751-1000 (n=29)	9	2	10	8	19	66
1001-1250 (n=37)	3	0	23	11	26	70
1251-1500 (n=53)	8	0	40	5	48	91
Total (n=129)	22 (81%)		76 (75%)		98	76

flow returned to normal. Throughout the episodes of oliguria, serum electrolytes remained normal and excessive weight gain was prevented by appropriate restriction of fluid intake. No other complications of indomethacin administration were observed.

11 (9%) of the 129 infants ≤ 1500 g developed bronchopulmonary dysplasia (BPD) of whom 10 were ≤ 1000 g at birth. Eight (30%) of the 27 infants who had PDA developed BPD, the ductus in these cases remained patent for up to 8 to 20 days of age. Only 3 (3%) of 102 infants without PDA developed BPD. This association between PDA and subsequent development of BPD is significant ($\chi^2=16.2$, $P<0.001$).

Overall survival in this series was 76% (Table 2). Survival rates ranged from 50% in infants weighing 501 to 750 g, to 91% in the 751 to 1000 g weight group.

Discussion

Previous reports of PDA in preterm infants have ranged from 15 to 36% depending on the degree of prematurity, frequency of HMD, and incidence of early neonatal mortality.^{1,3,14-15} This compares with a 21% incidence of PDA reported in the present series of preterm infants ≤ 1500 g, with a higher incidence of 41% in infants 501-1000 g. In addition the incidence of PDA was significantly higher in infants with pulmonary disease, primarily HMD, compared with those without, as has been reported earlier.¹⁻²

Evaluating the magnitude of left-to-right shunts in preterm infants with PDA is of fundamental importance in their management. Since cardiac catheterisation may be a considerable risk to these seriously ill infants, a simple noninvasive method is invaluable. Silverman *et al.*¹⁶ described the echocardiographic measurement of the LA/Ao ratio as a valuable index of the size of left-to-right ductal shunts. However there are reports of infants with substantial left-to-right shunting across a PDA in whom absolute LA dimensions and LA/Ao ratios were within normal limits.¹⁷ In these reports the

LVED was more reliable. To avoid these pitfalls we performed serial echocardiography on these infants and used significant increases in LA/Ao ratio, LA and LVED dimensions in our echocardiographic evaluation. An LA/Ao ratio over 1.2:1 signified heart failure and a ratio of 1.5:1 was a critical value signifying the need to attempt closure of the ductus. Graphs previously obtained from 25 normal preterm infants served as normograms for LA and LVED dimensions. Serial echocardiographic assessment thus provided objective criteria which helped to determine the magnitude of L-R shunting and decide when ductal closure was required for the infant to survive.

Complete pharmacological closure of sPDA was achieved in 56% of preterm infants treated, and partial closure with reduced left-to-right shunting and clinical and echocardiographic improvement in a further 19%. Indomethacin failed to produce constriction in 25%. Heymann *et al.*⁹ reported success in over 90% of preterm infants treated. In their series only 5 out of 15 infants weighed ≤ 1000 g and most had gestational ages over 28 weeks. Merritt *et al.*⁴ reported success in 32 (91%) out of 35 infants. In their study 9 (26%) infants had birthweights over 1500 g, and only 10 (29%) were ≤ 1000 g. The morbidity and mortality rate related to PDA in infants weighing > 1500 g is slight and such babies rarely pose a problem in management. In the present series, 12 (75%) of the 16 infants treated with indomethacin were < 1000 g, all of whom had gestational ages between 24 and 28 weeks. All 4 infants who did not respond to indomethacin had gestational ages between 24 and 26 weeks and weighed ≤ 1000 g (range 720–980). Heymann *et al.*⁹ had one failure out of 5 infants weighing ≤ 1000 g when given indomethacin. It would therefore appear that while indomethacin is successful in constricting the PDA in preterm infants weighing > 1000 g with gestational ages > 28 weeks, it is less successful in more immature infants weighing ≤ 1000 g. Neal *et al.*¹⁴ have reported an 80% failure rate in preterm infants with HMD and PDA which they attributed to administering the drug after 10 days of age. In our series too, only 6 out of 16 infants were given the drug under 10 days. This was due to CCF being treated first with antifailure treatment and indomethacin administered only if this failed. Of the 4 infants who failed to respond to indomethacin, only one had it earlier than 10 days. This too may have contributed to the 25% failure rate (4 infants).

The association between PDA and the subsequent development of BPD in this study was striking. Three main factors have been implicated in the pathogenesis of BPD: barotrauma from mechanical ventilation,¹⁸ oxygen toxicity,¹⁹ and CCF secondary to left-to-right

shunting through a PDA.²⁰ Gay *et al.* showed that PDA and large left-to-right shunts over 2 days increased the risk of developing BPD.²⁰ Early ductal closure may shorten the duration of ventilatory assistance and thereby reduce the risk of BPD, besides increasing the chances of successful pharmacological closure.

Several principles have emerged from the experience in this and other recent studies with indomethacin in sPDA. (1) Extremely preterm infants are less likely to respond to indomethacin. (2) Success is more likely if the drug is administered early, before 10 days of age. (3) Dosage of 0.3 mg/kg repeated in 24 hours is safe and causes no untoward side effects. (4) Increasing dosage will not increase success rate. (5) Bleeding tendency, hyperbilirubinaemia, and renal dysfunction are contraindications to its use. (6) Urinary output must be carefully monitored. (7) Long-term prognosis is still to be ascertained after clinical trials with this drug. (8) Indomethacin is effective in closing the ductus and a useful alternative to surgical ligation. (9) If it fails surgery should follow.

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