

## CURRENT TOPIC

## Patent ductus arteriosus in the newborn

Nick Archer

Patent ductus arteriosus (PDA) may occur as an isolated structural congenital heart lesion and in such circumstances most of the affected individuals are born at term and are unlikely to have symptoms in the newborn period, indeed many will not be detected until well beyond this time. A patent ductus may be part of a more complex cardiac abnormality and presentation will then be determined by the overall haemodynamic derangement. Some babies with structural heart diseases will present or become much sicker when a normal ductus closes, usually in the first or second week after birth although sometimes later. Most of these infants will be term and present either with collapse and heart failure (in duct dependent systemic circulation) or with the appearance of or worsening of cyanosis and the consequences of severe hypoxaemia (in duct dependent pulmonary circulation). Such babies can be confused with non-cardiac conditions and can usually be resuscitated and stabilised with the use of prostaglandin E<sub>1</sub> or E<sub>2</sub>. Detailed consideration of this area is outside the scope of this paper, which is to address the more common problem presented by delayed closure of the ductus arteriosus in the preterm infant. PDA is a common accompaniment of prematurity, although most evidence suggests that preterm infants without respiratory distress syndrome close their ductus arteriosus in the same timescale as term infants.<sup>1,2</sup> It is clear that infants with respiratory distress syndrome do have delayed closure of the ductus<sup>3</sup> and a good review of the pathogenesis of this disturbance of the physiology of the ductus arteriosus appeared in this journal over a decade ago.<sup>4</sup> Delayed closure of the ductus causing clinical problems occurs with increasing frequency with decreasing birth weight and over 40% of babies of less than 1000 g at birth had symptoms attributable to PDA in one large study,<sup>5</sup> although more recently a lower figure of 20% has been reported.<sup>6</sup> Some of these differences may be attributable to definition of symptomatic PDA (sPDA) and others to management details such as fluid regimens. The natural history of PDA in the preterm infant with respiratory distress syndrome and otherwise structurally normal cardiovascular systems is of spontaneous closure,<sup>7</sup> if the infant survives acute respiratory distress syndrome and all its sequelae, many of which are at least in part caused or exacerbated by PDA. Many preterm babies receiving intensive care are under the care of

paediatricians without on site paediatric cardiology or echocardiography expertise and the vast majority of problems both diagnostic and management relating to PDA must be dealt with under these conditions.

**Prevention**

Dexamethasone given to women in preterm labour to reduce the severity of respiratory distress syndrome also reduces the incidence of sPDA,<sup>8</sup> interestingly there is also some anecdotal evidence that PDA may close in response to dexamethasone given to babies developing chronic lung disease after respiratory distress syndrome.<sup>9</sup> Postnatal attempts to prevent respiratory distress syndrome by administration of artificial surfactant are now standard practice, there is no evidence that this reduces the occurrence of sPDA, indeed there is a little evidence that the opposite has been the case.<sup>10</sup> It has long been known that cautious fluid regimens in respiratory distress syndrome are associated with less sPDA than liberal ones.<sup>11</sup> Intakes greater than 140 ml/kg/24 hours by the end of the first week in babies with respiratory distress syndrome are generally inadvisable and much more restricted amounts are appropriate in the first few days of life. The use of plasma expanders for hypotension is also an area of concern in that hypotension may be a sign of poor cardiac function rather than of inadequate circulating volume, it may even be evidence of a significant PDA.<sup>12</sup> Thus plasma infusion may not only be inappropriate but may also predispose to the development of sPDA. Repeated infusions should not be used to raise blood pressure without a trial of inotrope (usually dopamine) unless echocardiographic assessment of ventricular function<sup>13</sup> and ductal patency are available.

Prophylactic use of indomethacin<sup>14</sup> and surgery<sup>15</sup> have been advocated. Fears about the safety of indomethacin make such use seem unwise even if a clear long term benefit had been demonstrated, which it has not.<sup>14,16,17</sup> Prophylactic surgery presents logistic problems and the only clear benefit demonstrated is a reduction in necrotising enterocolitis but not in improved morbidity in other areas nor in reduction in mortality.<sup>15</sup> In either case prospective identification of infants with a high probability of sPDA would be essential and is not reliably possible, thus any prophylactic intervention would end up being administered

Department of  
Paediatrics, John  
Radcliffe Hospital,  
Headington, Oxford  
OX3 9DU

Correspondence to:  
Dr Archer.

to a considerable number of babies who did not actually need it.

### Clinical picture

The most common clinical situation in which sPDA features is the preterm infant being ventilated for respiratory distress syndrome who does not show the anticipated improvement after 3–4 days or who having done so then deteriorates. When there are an active praecordium, hepatomegaly, bounding pulses, and a murmur in the pulmonary area extending from systole into diastole the diagnosis is easy. In such circumstances the heart size on radiography may have increased; even over-inflation of lung fields and carbon dioxide retention with their effect on palpable liver size and pulse characteristics respectively should not confuse the diagnosis. When the murmur is only systolic the position is harder, although in the presence of an active praecordium and bounding pulses a high degree of confidence in the diagnosis is possible if the clinical problem is a failing to improve or of deteriorating oxygen requirement and ventilator dependency. A murmur may be absent<sup>5</sup> but if all clinical signs are looked for regularly this will only rarely result in serious delay in making the diagnosis.<sup>18</sup> There are situations other than heart failure and respiratory distress syndrome in which PDA must also be considered as a possible contributor to problems for the preterm infant, these particularly include necrotising enterocolitis and recurrent apnoea. If there is serious consideration that there may be structural congenital heart disease careful physical examination, including upper and lower limb blood pressures, detailed review of the chest x ray film and electrocardiography (ECG) may help clarify this. In other circumstances an ECG is not required in diagnosing or managing sPDA. Echocardiography is strongly recommended if doubt about the contribution of PDA to the overall picture exists and is essential if important structural heart disease is suspected or surgery for PDA is to be performed. Ultrasound is not necessary in the majority of decisions required concerning PDA in preterm infants. Thus details of echocardiographic assessment are not within the scope of this article but have been well described.<sup>19 20</sup>

### Treatment

Treatment should be started as soon as sPDA is strongly suspected, often as early as the third or fourth day and frequently before the end of the first week of life. Fluid restriction, diuretics, correction of anaemia, and ensuring optimal oxygenation are the initial manoeuvres. If parenteral diuretic is required, frusemide (0.5 to 1 mg/kg/dose) can be used but regular maintenance with chlorothiazide (10–20 mg/kg/dose) twice daily gastrically is probably preferable to regular frusemide as there are both theoretical grounds and clinical evidence that frusemide promotes ductal patency by stimulating renal prostaglandin E<sub>2</sub> production.<sup>21</sup> Potassium concentrations need

watching and supplements or a potassium sparing diuretic are likely to be needed. Digoxin may well have a small beneficial effect<sup>22</sup> but generally is not recommended because of the short timescale over which improvement is sought, its marginal benefit, and the risks of toxicity.<sup>23</sup>

If marked improvement is not seen in 24–48 hours the next stage is the use of the prostaglandin synthetase inhibitor, indomethacin. In a national collaborative study in the USA, indomethacin closed the ductus in approximately 80% of infants under 1750 g birth weight if given within 14 days of birth with a spontaneous closure rate of only 28%.<sup>24</sup> These figures relate to administration of indomethacin at the same time as instituting medical treatment; closure rate was lower if medical treatment had failed before indomethacin was given but so was recurrence rate giving an overall success rate for either approach of 70%. Information on efficacy after 14 days of age is less detailed but the drug should still be tried. Recurrence rates in the collaborative study were up to 26% but many babies in whom recurrence occurs will respond to a further course of indomethacin and will not require any additional treatment.

Indomethacin is usually given intravenously at a dose of 0.2 mg/kg repeated twice with eight or 12 hours between each dose. Relative contraindications include a bleeding tendency, particularly thrombocytopenia (less than  $50 \times 10^9/l$ ) as the drug interferes with platelet function and significant renal dysfunction as demonstrated by markedly raised or rising blood urea or creatinine concentrations. Hyperbilirubinaemia was at one time considered a contraindication to the use of indomethacin but is now generally not considered to be so as the drug appears not to displace bilirubin from albumin.<sup>25</sup> Definite necrotising enterocolitis is also a contraindication in view of the clinical association of indomethacin administration with necrotising enterocolitis, gastric haemorrhage, and perforation and because of the effect of the drug on gut blood flow velocity.<sup>26</sup> Indomethacin administration causes a transient fall in glomerular filtration rate and urine output with a resultant increase in serum creatinine concentration.<sup>27</sup> Reduction in administered fluid by about 20% for the duration of a course of treatment is wise and hyponatraemia and hyperkalaemia need to be watched for. Major or sustained renal dysfunction is very uncommon. When it was demonstrated that injected indomethacin increased blood pressure<sup>28</sup> and reduced cerebral blood flow velocity,<sup>28 29</sup> administration over 30 minutes was advocated as these effects were not then noted.<sup>30</sup> More recently infrared spectroscopy has demonstrated the effects of the drug in reducing cerebral blood volume and oxygen content irrespective of the speed of administration.<sup>31</sup>

In an attempt to reduce recurrence prolonged use of indomethacin<sup>32</sup> has been tried and more attractively prolonged low dose administration has been investigated.<sup>33</sup> The use of 0.1 mg/kg/dose daily for six days showed

as good a response or marginally better than the standard regimen with a lower recurrence rate (21% as opposed to 40%) and less elevation of serum creatinine. Cerebral haemodynamics were not examined closely in this study. Currently three doses eight or 12 hours apart given over 30 minutes seems a reasonable suggestion. If a relative contraindication exists, the smaller dose daily for six days could be used instead, although gastrointestinal side effects have not been shown to be less on this regimen and there is the uncertainty about prolonged adverse effects on cerebral blood flow and oxygen delivery. The concerns about cerebral oxygen delivery underline the importance of maintaining optimal arterial blood oxygen content while indomethacin is being used. Plasma concentrations of the drug have not been convincingly shown to be of practical help in management, although their use has been advocated.<sup>34</sup> If a course of indomethacin succeeds but is followed by a recurrence of sPDA a further course can be given. If a repeat course fails, a clear contraindication exists, or a significant side effect occurs surgery should be proceeded to without delay.

Surgical closure of sPDA in the preterm infant requires definitive diagnosis by echocardiography and can be achieved with a low operative morbidity and mortality.<sup>35</sup> Exact arrangements for surgery will depend on local conditions and can involve either a day trip to the surgical centre<sup>36</sup> or transfer to the neonatal unit of the surgical centre where surgery can be carried out without further moving to an operating theatre.<sup>37</sup> In some circumstances it may even be preferable for the surgical team to travel to the baby, in this event as in the day attendance at a surgical centre it is important for the referring unit to be aware of the potential postoperative complications and to be able to manage them. Transfer for admission to the neonatal unit of the surgical centre does allow full assessment of the infant there and may allow surgery to be avoided if other factors contributing to the clinical picture are identified and dealt with. Outcome after surgery is related to many factors and infants are not necessarily rapidly weaned from ventilation. The major effects of tying a ductus on cerebral haemodynamics<sup>38</sup> have not been shown to be clinically disadvantageous, although detailed studies are few.<sup>39</sup>

### Conclusion

Early clinical recognition of sPDA is usually possible if a high index of suspicion is present. Comprehensive echocardiographic skills if available are helpful but are not essential except if structural heart disease is suspected or surgery contemplated. Fluid restriction and diuretics should be given a 1–2 day trial and then indomethacin used. A repeat course of indomethacin to relapsed responders is appropriate. Surgery should be proceeded to in those who fail to respond, who relapse a second time, and those in whom a strong contraindication to or side effect of indomethacin is detected.

This approach means that surgical ligation if needed is likely to be within three weeks of birth in the vast majority of babies and under two weeks in a significant number. Babies with clear signs of PDA but in whom heart failure is well controlled, so that ventilation is not required and growth can be established, can be managed conservatively. If the ductus persists beyond 3 months with this approach criteria for surgery are the same as for those in babies born at term.

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