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Indomethacin Treatment of Patent Ductus Arteriosus in Premature Infants

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Abstract

Shortly after birth, physiological processes usually effect prompt functional closure of the ductus arteriosus. With increasing prematurity there is an increased likelihood of the ductus arteriosus remaining patent. To overcome the undesirable effects of left to right shunting of blood through the patent ductus arteriosus (PDA), closure by surgical ligation and medical treatment have become established practice. Since the mid-1970s, indomethacin, an inhibitor of prostaglandin synthesis, has been used to promote closure of a PDA. Despite longstanding use and numerous clinical trials, the optimal management remains unclear. This overview covers the pharmacology of indomethacin in the neonate and its use for treating PDA in the premature infant.

Key words: Indomethacin – Ductus arteriosus, patent – Infant, premature

Introduction

In fetal circulation the ductus arteriosus channels blood from the pulmonary artery directly into the descending aorta. This enables about 90% of right ventricular output to bypass the unexpanded lungs. At birth, functional closure of this channel redirects blood flow to the pulmonary vascular bed and allows the lungs to start effective respiratory gas exchange. Closure involves interaction of oxygen, prostaglandins, nitric oxide and the unique musculature of the ductus arteriosus[1–3]. In healthy term babies, ducts are functionally closed in 20% on day 1, 82% by day 2, 96% by day 3 and 100% by day 4[4].

These mechanisms do not always occur promptly in premature infants. A patent ductus arteriosus (PDA) is found in about 40% of infants of < 1000 g birthweight on day 3[5], and, in infants of < 28 weeks' gestation, spontaneous closure by day 5 occurs in only 27%[6]. Left to right shunting of blood through a haemodynamically significant PDA increases pulmonary blood flow and cardiac workload, and reduces renal and gastrointestinal blood flow. A PDA has been thought to increase the severity of respiratory distress[7,8] and the risk of bronchopulmonary dysplasia[9].

Surgical ligation and medical drugs, most commonly indomethacin, are used to treat infants with a haemodynamically significant PDA. Pharmacological closure of a PDA in premature infants was first reported in 1976[10,11] and subsequent studies show it to be effective in about 80% of treated infants[12]. Indomethacin has

also been used to prevent a symptomatic PDA developing in at-risk infants[13]. However, despite over 30 years of various approaches, the optimum regimen for the management of PDA in prematurity has still not been unequivocally established.

Pharmacology of Indomethacin

Indomethacin is a methylated indole derivative and a non-selective potent inhibitor of the prostaglandin-forming cyclo-oxygenase. It is highly bound to serum proteins. Metabolism via *O*-methylation, deacylation and conjugation to inactive metabolites allows for elimination via the biliary route; < 10% is excreted unchanged in the urine[3].

Intravenous indomethacin in adults has a plasma half-life of 2.6–11.2 h and a plasma clearance of 44–109 ml/kg/h[14,15]. Defining pharmacokinetic parameters in the neonate is hampered by the many physiological changes occurring after birth. Despite their limitations, pharmacokinetic studies that have been attempted do give some insight. With oral administration, absorption of indomethacin is incomplete and variable[16]. For intravenous indomethacin, studies have used different doses (0.2, 0.25 and 0.3 mg/kg) but all show large inter-individual variations and important differences compared with the adult data: plasma half-life ($t_{1/2}$: 11–36 h) is much longer and the clearance rate (7–16 ml/kg/h) much less[17–20]. There are also large inter-individual variations in the apparent volume of distribution, and the duct being open or closed may in part contribute to this[19]. Increasing postnatal age, not gestational age, is an important determinant of increasing indomethacin clearance and volume of distribution. A study of the population pharmacokinetic parameters of indomethacin found similar results[21].

The relationship between the plasma concentration of indomethacin and the desired effect of ductal closure is controversial. In some studies plasma concentration has not correlated with efficacy[12,22,23]. In contrast, others have found a relationship[19,21,24–28]. Various effective concentrations are suggested: 1 mg/l 10 h post-dose[24]; 0.5 mg/l 8 h post-dose[25]; and 0.25 mg/l over a three-day course[27]. From population pharmacokinetic data, the mean serum concentration at PDA closure was 1.43 mg/l[21]. Furthermore, low plasma levels of indomethacin, short $t_{1/2}$ and more efficient clearance, are associated with unsuccessful indomethacin infusions[19].

Surgical Treatment

From the early 1970s surgical ligation has been used in premature neonates with a PDA, but, with increasing use of indomethacin surgery, is more often reserved for infants with contraindications to, or failure of, medical treatment. The National Collaborative Study suggested surgery as a backup treatment[12]. However, some reports recommend surgery as the first-line approach in extremely low-birth-weight infants. The perioperative complications associated with surgery include hypertension, pneumothorax, chylothorax, ductal tear, minor wound infections and vocal cord paralysis. Morbidity rates reported are 1–16% and mortality 0–10%[29–32]. In experienced centres with low morbidity and mortality, surgery may be an appropriate alternative in extremely low-birth-weight infants where indomethacin has a high failure rate and significant adverse effects.

Medical Treatment

Timing of Treatment

With respect to timing, medical treatment may be prophylactic (usually within 24 hours of birth), early (2–3 days) or late (8–10 days). Clyman[33] identified four general treatment strategies that have been studied with respect to timing:

Late symptomatic vs. no backup.
Late symptomatic vs. later backup.
Early symptomatic vs. late symptomatic.
Prophylactic vs. early symptomatic.

The only study of Strategy 1 was too small to draw firm conclusions, but ductal closure did appear associated with reduced mechanical ventilation, necrotising enterocolitis (NEC) and retinopathy of prematurity (ROP)[34]. In the other studies, a backup treatment (indomethacin or ligation) was available. From meta-analysis of the studies available in 1996[33], the group receiving early symptomatic treatment with indomethacin had a reduction in bronchopulmonary dysplasia (OR = 0.39, CI 0.21–0.76; $p < 0.005$), need for mechanical ventilation ($p < 0.005$) and NEC (OR = 0.24; CI = 0.06–0.96; $p < 0.05$) compared with late symptomatic treatment. Prophylactic treatment did not have any advantage in long-term pulmonary outcomes or NEC compared with early symptomatic treatment; however, the incidence of grade 3 and 4 intraventricular haemorrhage (IVH) was reduced (OR = 0.51; CI = 0.28–0.95; $p < 0.05$). In another systematic review and meta-analysis, Fowlie[35] found evidence that prophylactic indomethacin reduced the incidence of symptomatic PDA (estimate of risk difference –0.217; CI –0.275, –0.160) and the incidence of grades 3 and 4 IVH (estimate of risk difference

–0.039; CI –0.066, –0.011). However, mortality and other morbidity was not significantly affected.

The benefit of prophylactic indomethacin in reducing the incidence of IVH may be independent of its effect on a PDA. There is evidence of low-dose prophylactic indomethacin reducing IVH[36]. More recently it has been suggested that prophylaxis may also reduce the incidence of periventricular leukomalacia (PVL)[6].

Length of Treatment

A commonly used course of indomethacin is three doses. The National Collaborative Study used three doses at 12-hourly intervals: 0.2 mg/kg for infants in the first 2–7 days and 0.2 mg/kg followed by 0.25 mg/kg for the second and third dose for infants > 8 days. The initial response rate of duct closure (about 80%) and subsequent reopening in responders (about 30%) was broadly in keeping with the many previous studies[12]. To improve sustained closure rates, prolonged courses of indomethacin have been suggested as an alternative[24,37,38].

Using indomethacin level monitoring to individually tailor doses it was suggested that maintaining a plasma level of 0.5 mg/l for a week would be effective in maintaining duct closure[24]. In a study of 39 low-birth-weight babies with a PDA, after three doses of indomethacin at 0.2 mg/kg, babies were randomised to placebo or 0.2 mg/kg/day for five days[37]. The maintenance regimen reduced the PDA recurrence rate and the need for surgical ligation. In a study of 121 babies, where PDA detection and follow-up was clinical, 0.1 mg/kg/day for six days was compared with three doses of 0.2 mg/kg 12-hourly[38]. For the prolonged course, the initial response rate was better (90% vs. 77%) and of the responders the relapse rate (21% vs. 40%) was lower.

Other studies have not confirmed the advantages of a prolonged course. In a study of 70 low-birth-weight infants, randomisation was to just two doses of 0.15 mg/kg 12 hours apart or a maintenance regimen of 0.1 mg/kg/day for five days after the initial doses[39]. The initial closure rate appeared better in the maintenance group but overall the incidence of reopening was not different. More recently short versus prolonged indomethacin therapy was compared in 61 preterm infants with a PDA, confirmed on echocardiography[40]. Those receiving a short course had a shorter duration of oxygen supplementation and less frequent symptoms of NEC, but sustained closure rates (74% vs. 60%), mortality and other neonatal morbidity rates were similar. It was concluded that a prolonged course offered no advantages over a standard course in preterm infants with a haemodynamically significant PDA.

Table 1. Indomethacin for closure of PDA-licensed recommendations (from ABP1 Compendium of Data Sheets and Summaries of Product Characteristics 1999–2000)

Age at first dose	Intravenous dose (microgram/kg)		
	1st dose	2nd dose	3rd dose
< 48 hours	200	100	100
2–7 days	200	200	200
> 7days	200	250	250

In the absence of a clear benefit for prolonged courses, the current licensed therapy (shown in Table 1) is three intravenous doses given at 12–24-hour intervals.

Other Effects of Indomethacin

As a non-specific prostaglandin synthesis inhibitor, indomethacin would be expected to have a spectrum of systemic effects, and these have been confirmed in clinical studies.

Cerebral

Doppler ultrasound and near infrared spectroscopy (NIRS) have been used to study the effects of indomethacin on cerebral haemodynamics. Doppler ultrasound shows significant reductions in cerebral blood flow velocities of 20–40% within minutes of the injection that persist for one to two hours[41–44]. However, infusion over 20 minutes did not result in significant changes[43] and a slow continuous infusion effectively closed a PDA without decreasing cerebral blood flow velocities[45]. NIRS shows substantial reductions in cerebral blood flow, cerebral oxygen delivery, cerebral blood volume and cerebral blood volume reactivity[46–48]. The underlying mechanism of these changes is unclear and they are not seen with another prostaglandin inhibitor, ibuprofen[47,48], raising the possibility of a mechanism other than prostaglandin synthesis inhibition. The alteration of cerebral haemodynamics in infants already vulnerable to cerebral hypoperfusion remains an area of concern.

There is evidence that early use of indomethacin may protect against IVH[36,49,50] and PVL[6]. Meta-analysis of trials using indomethacin prophylaxis[35] suggests the incidence of severe IVH is reduced by about 40% (estimate of risk difference –0.039; CI –0.066, –0.011). Furthermore, data from the Multicentre Randomised Indomethacin IVH Prevention Trial showed no adverse neuro-

developmental effects at 4.5 years in those who had received early low-dose indomethacin compared with those who had received placebo[51]. In this the study, the cerebral palsy rate was the same in both groups (7%) but the proportion of children with no, or minor, developmental handicap was smaller in the indomethacin group.

Renal

Both a PDA and indomethacin treatment can alter renal function[3]. Indomethacin can result in oliguria, increased serum blood urea nitrogen and creatinine, decreased glomerular filtration rate and serum electrolyte imbalance. The renal dysfunction associated with indomethacin can in part be explained by a reduction in renal blood flow and perfusion[52–53]. Associated changes also include a decrease in plasma renin activity and a rise in arginine vasopressin[54].

These effects are usually transitory without resulting in prolonged renal dysfunction[55]. Infants receiving frusemide with indomethacin have higher urine output, glomerular filtration rates and fractional excretion of sodium[56]. However, studies of frusemide in indomethacin-treated infants have been small with methodological limitations. Meta-analysis of these highlighted dehydration as a contraindication to frusemide use and concluded that the risk–benefit ratio could only be assessed by a large randomised trial[57]. Dopamine does not reduce the renal side-effects of indomethacin[58].

Gastrointestinal

Bowel perforation and necrotising enterocolitis are reported in infants with a PDA who are treated with indomethacin[59]; isolated perforation without NEC is also well described[60].

Doppler studies show a pronounced and sustained fall in the velocity of the superior mesenteric artery shortly after administration of indomethacin[61,62]; this is less and later if the indomethacin is given by infusion rather than as a bolus[62]. The further reduction in flow to an already compromised vascular bed helps explain some of the observed gastrointestinal effects. The mechanism remains unclear and it has been suggested may be independent of its effect on prostaglandins[62].

Despite the potential for adverse effects on the GI tract, early use of indomethacin may reduce the incidence of NEC overall[33]. Meta-analysis of studies of prophylactic indomethacin found the effect of indomethacin on the incidence of NEC did not reach statistical significance, although there is, perhaps, a trend towards increased risk[13].

Haematological

Indomethacin may interfere with platelet function and result in impaired haemostasis[63]. Although reduced platelet counts after treatment are reported with prophylactic indomethacin[36], there does not appear to be a significant difference between treatment and placebo groups[35].

Alternative Prostaglandin Inhibitors

Because of the side-effects of indomethacin, alternative prostaglandin inhibitors have been tried: aspirin, mefenamic acid, ethamsylate, sulidinac and ibuprofen[10,64–68]. Ibuprofen appears to offer effective closure of the PDA without notable early adverse effects[67,68]. Furthermore, it seems to have less effect on cerebral, mesenteric and renal haemodynamics[48,69]. A recent study of ibuprofen used on the third day of life concluded it was as efficacious as indomethacin for treatment of a PDA and less likely to induce oliguria[70]. Long-term follow-up studies will be required to determine the precise role of ibuprofen in treating PDA.

Conclusion

For over 30 years closure of the ductus arteriosus in premature infants has been pursued by surgical and pharmacological means. From this accumulated experience, what conclusions can be drawn?

A PDA is common in premature infants with RDS and is present in 40% of infants < 1000 g on day 3. Persistent large left to right shunting is undesirable. Interventions to promote PDA closure need to be carefully considered as it will close spontaneously in many infants. Pharmacotherapy is the first-line approach in most cases, but for very low-birth-weight infants, surgery is predictable, and, in experienced centres, has low morbidity and mortality[29–32]. Indomethacin is effective and the most commonly used drug treatment, but controversy still surrounds optimum timing and dosing strategies. Early treatment in the first 2–4 days, before clinical evidence of a large shunt with congestive heart failure develops, reduces pulmonary morbidity and NEC compared with late (8–10 days) treatment[33]. Prophylactic indomethacin exposes all infants to its wide range of potential adverse effects and does not appear to have benefit in terms of mortality and pulmonary morbidity compared with early symptomatic treatment[33,35]. However, prophylaxis does result in a higher rate of permanent ductal closure[6], appears to have a benefit of protecting against severe IVH and, at

present, there is no long-term evidence of harm[13,51]. The standard course is three doses at 12-hour intervals, but evidence is conflicting on whether a prolonged course has additional benefit. Pharmacological closure of a PDA without side-effects remains a challenge, although recent studies of ibuprofen[47,48,67–70] show some promising new developments.

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