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Comparative Tolerability of Pharmacological Treatments for Patent Ductus Arteriosus

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Abstract

The ductus arteriosus is a vascular channel which, although vital to the fetal circulation, rapidly becomes unnecessary and even deleterious after birth. As such, it is 'preprogrammed' to constrict within the first few hours of life. In infants born prematurely this natural closure is often delayed and/or ineffective. In this review, we summarise the current knowledge of the delicately orchestrated control of normal ductal closure, with emphasis on the role of various biochemical mediators.

The major focus of this review, however, is on pharmacological approaches designed to prevent and/or treat the persistently patent ductus arteriosus (PDA) which often fails to constrict spontaneously in the premature infant. The standard

treatment regimen is based on the administration of 3 doses of the nonselective cyclo-oxygenase inhibitor, indomethacin. We begin by examining, from the vantage point of the ductus, the use of this indomethacin as a tocolytic. It seems that antenatal administration of indomethacin can cause transient, reversible ductus constriction which renders the post-treatment ductus resistant to subsequent closure, both natural and therapeutic. We then review some of the pros and cons associated with the prophylactic administration of indomethacin. Although prophylactic indomethacin is aimed primarily at preventing intraventricular haemorrhages in premature neonates, it does tend to reduce the risk of PDA as well.

We then describe some novel therapeutic approaches to effect ductal closure with indomethacin, including the use of continuous infusions to minimise toxic vasoconstrictive phenomena and the use of prolonged maintenance dose to prevent PDA recurrences.

Finally we discuss some of the newer agents described more recently which play a role in closing the persistently patent ductus over the next decade. Most prominent of these is ibuprofen which some studies have shown to have less undesirable vasoconstrictive adverse effects. Studies which compare the use of ibuprofen to indomethacin are summarised.

1. Mechanisms Behind Persistent Patency of the Ductus Arteriosus (PDA)

The lungs of the fetus do not participate in gas exchange, and therefore the fetal circulation is endowed with a vascular channel that naturally enables blood flow to bypass the predominantly dormant pulmonary vasculature. Postnatally, as the lungs assume respiratory gas exchange functions, right ventricular output must be redirected to flow through the pulmonary vascular bed. To facilitate the redirection of blood, this vascular bypass – the ductus arteriosus – is physiologically programmed to constrict automatically once it is no longer needed. The ductus arteriosus is thus naturally transformed from being a vital component of the fetal circulation into an unnecessary and even deleterious appendage to the neonatal circulation.

Normal postnatal ductal constriction results from a complex interaction between the precipitous reversals of relative pulmonary and systemic vascular resistances, from sudden variations in the levels of prostaglandins and other biochemical mediators, and from rapid increases in oxygenation of the blood. However, when infants are born prematurely, the normal mechanisms of ductal closure do not always function effectively. Alterations in the normal physiological shifts of these parameters is likely to impede spontaneous ductal closure, resulting in clinical signs consistent with persistent patency of the ductus arteriosus (PDA).

Prostaglandins are potent vasoactive substances with extremely short half-lives. They are produced in exceedingly small quantities, and they have been found to be intimately involved in maintaining ductal patency *in utero*. Prostaglandin levels drop precipitously after birth, thereby facilitating spontaneous ductal constriction. Increased oxygen tension (PO_2) is also a potent stimulator of ductal closure after birth and, conversely, hypoxia can precipitate or sustain ductal dilation.

All of these systems are delicately intertwined with multiple potential sites of interaction both in the metabolic/pathophysiological sphere and in the clinical setting. For instance, clinically, the incidence of PDA is inversely related to gestational age, occurring in up to 40% of infants weighing <2000g at birth and in up to 80% of infants weighing <1200g at birth.[1,2] It is these same premature infants who also have respiratory distress syndrome, placing them at higher risk for hypoxia, a known contributor towards ductal patency in its own right. Furthermore, ductal sensitivity to hyp-

oxia is inversely related to gestational age,[3-6] rendering the premature ductus – already at high risk for persistent patency – more exquisitely sensitive to even mild degrees of hypoxia than the more mature ductus.

These premature infants also require higher levels of ventilatory assistance, leading to increased shear stress in the pulmonary tissue, which in turn can induce the release of prostacyclin. Prostacyclin is a potent prostanoid vasodilator that is instrumental in mediating the early postnatal drop in pulmonary vascular resistance, which is generally associated with increased ductal shunting.[7]

On another level, these infants tend to experience apnoea, which can lead to even further hypoxia. The increased endogenous prostaglandin (PG) E levels which contribute to ductal patency may well also be an aetiological factor in this apnoea, demonstrating another of the many cyclic physiological interactions.[8]

Infection also adversely influences PDA outcome by increasing the risk of failure of PDA closure and late ductal reopening. Increased levels of prostaglandins and tumour necrosis factor α (TNFα) in infants with infection may explain the poor outcome with regard to PDA. TNFα is an inflammatory cytokine. Its levels are increased in systemic infections, and it has been shown to be elevated in late (>8 days) PDA.[9] TNFα induces several other inflammatory factors in a complex cascade which, in turn, amplifies its biological effects. The list of TNFα-inducible factors is long and includes prostaglandins, endothelium-derived relaxing factor and reactive oxygen intermediates, all of which might adversely affect ductal closure.

Nitric oxide (NO) may also function as an endogenous dilator and regulator of ductal tone. At fetal PO_2, little NO is produced. Once exposed to the elevated neonatal PO_2, however, NO is produced within the ductus wall. Because the immature ductus is more sensitive to NO-induced vasodilation than the mature ductus, it may have more potent effects in the premature newborn. The left-to-right shunting of oxygenated blood, with its increased shear forces through the premature PDA, may shift the balance of vasodilators within the wall from one primarily controlled by prostaglandin to one that is strongly influenced by NO.[10]

The early regulation of ductal tension basically depends upon the balance between the many vasoconstricting and vasodilating factors at any given time. Ductal relaxation is facilitated by prostaglandins and NO, while vasoconstriction is promoted by increased PO_2. Should these regulatory mechanisms fail, and the ductus remains patent, further complications may evolve: respiratory distress can be exacerbated, and apnoeic episodes and pulmonary haemorrhage may develop. The pulmonary vasculature becomes exposed to increased pulmonary blood flow and to systemic blood pressures. Eventually, bronchopulmonary dysplasia, congestive heart failure and failure to thrive may ensue.

Even with small shunts, there is a redistribution of systemic blood flow, which can lead to impaired perfusion of various organ systems. Blood flow to the gastrointestinal tract, kidneys and even the brain is especially vulnerable to the effects of PDA, rendering the premature neonate with PDA more susceptible to necrotising enterocolitis, renal hypoperfusion and/or cerebral ischaemia. Therefore, intervention is generally recommended to close even small PDA.

In this review, we discuss the tolerability of several therapeutic approaches to closing the persistent PDA in the premature neonate, and the clinical ramifications of such treatments.

2. Prophylactic Indomethacin

Current pharmacological therapy for PDA generally involves the use of the cyclo-oxygenase (COX) inhibitor indomethacin. Over the years, indomethacin therapy has become accepted as being quite effective in the premature neonate and has been shown to be successful in mediating ductal closure in 70 to 90% of treated neonates. However, there is little consensus, clinically, over when and how to administer indomethacin therapy to achieve the best outcome possible.

2.1 Prenatal Prostaglandin Inhibition and the Ductus

Prostaglandins exert a potent effect on uterine smooth muscle. Thus, the therapeutic use of prostaglandin inhibition has been suggested for tocolysis. In 1974, Zuckerman et al.[11] reported an uncontrolled study of the treatment of premature labour with indomethacin, in which 80% of the 50 women who received treatment experienced a cessation of uterine contractions. However, even prior to the first formal study, there was cause for concern. In 1969, Arcilla et al.[12] reported a case of antenatal closure of the fetal ductus arteriosus following administration of indomethacin to a pregnant woman. In the study by Zuckerman et al.,[11] 1 infant was stillborn and 4 others died with no cause of death listed.

Indomethacin readily crosses the placenta and may inhibit fetal prostaglandin synthesis. As such, it can cause a multitude of adverse effects, the most common being *in utero* constriction of the ductus arteriosus. Fetal rat,[13] lamb,[14,15] guinea-pig[16] and human[17] studies have demonstrated ductal narrowing secondary to indomethacin administration. This effect is seen as early as 27 weeks' gestation[18] and increases with advancing gestation, peaking at 31 to 32 weeks.[19] Moise et al.[20] examined fetal ductal constriction by pulsed Doppler echocardiography in mothers given 25 to 50mg of oral indomethacin for ≤24 hours. Constriction of the ductus was detected in 7 of the 14 fetuses studied. Although this effect is generally transient, *in utero* constriction of the ductus arteriosus can lead to persistent pulmonary hypertension in the newborn,[17,21] *in utero* congestive heart failure or even fetal mortality.

While fetal ductal constriction may occur in as many as 60% of fetuses exposed to indomethacin *in utero* it is most interesting that, postnatally, these same infants experience a higher incidence of persistent PDA postnatally.[22-24] Hammerman et al.[25] and Norton et al.[22] have demonstrated that not only does prenatal indomethacin constitute a risk factor for the development of PDA, but it renders the PDA refractive to postnatal therapeutic indomethacin. This is the most significant risk factor in the development of therapeutic resistance – more significant than low birthweight, low gestational age at birth and prenatal exposure to corticosteroids.

Apparently, the ability of the ductus to actively contract is limited, reflecting early constriction–associated ischaemic damage to the inner muscle wall. Although this prenatal constriction is generally reversible after 24 hours, there is probably some residual damage to the muscle wall that prevents it from contracting as effectively in response to the normal postnatal increase in PO_2 and/or to postnatal indomethacin administration. Gittenberger-de Groot et al.[26] described cytolytic necrosis in the muscular media of the ductus following functional constriction, and preceding full anatomic closure. Ductal muscular necrosis has also been described in response to chronic hypoxia,[27] with similar histological changes observed in fetuses who experience retarded growth *in utero*.[28] All of these infants have a diminished capacity for subsequent ductal constriction, manifesting clinically as a loss of ductal responsiveness and decreased sensitivity to indomethacin.

While the main concern with *in utero* indomethacin administration remains its effect on the ductus arteriosus, it has also been associated with other vasoconstrictive phenomena. These effects are not directly relevant to the current review and, thus, they are not discussed here.

2.2 Prophylactic Postnatal Prostaglandin Inhibition

The administration of prophylactic postnatal indomethacin has been suggested to decrease the incidence of intraventricular haemorrhage in premature infants.[29] Nevertheless, recently published follow-up data have concluded that the use of prophylactic low dose indomethacin initiated in the first 24 hours of life to low birthweight infants does not affect subsequent long term neurodevelopmental outcome.[30,31] Most of these treatment protocols have been directed towards improving neuro-

logical outcome, and not towards ductal closure, and thus they are not relevant to this discussion.

Several studies have looked prospectively, in a randomised fashion, at the effect of prophylactic administration of indomethacin within the first 24 hours of life on PDA, and they have generally found it to decrease the subsequent incidence of left to right ductal shunting,[32-36] although at least 1 study[33] reported that the rate of ductus reopening remained unacceptably high in the most premature infants. In another recent study of note,[37] the incidence of PDA was compared between sequential eras with different treatment approaches – symptomatic versus prophylactic indomethacin therapy – and a better rate of initial ductal closure was noted when indomethacin therapy was initiated prophylactically by 15 hours of age. Although this study was neither prospective nor randomised, similar trends have been observed by others. In fact, calculations made by Fowlie[38] based on the Cochrane review of 1997[39] suggest that for every 100 infants with very low birthweight who receive prophylactic indomethacin, symptomatic PDA is prevented in 20 infants.

Whether this reduction in the incidence of subsequent PDA is sufficient to warrant a recommendation to prophylactically administer indomethacin to all premature neonates remains debatable, especially in view of the other vasoactive effects of prophylactic indomethacin. Yanowitz et al.[40] demonstrated that prophylactic indomethacin reduced cerebral and mesenteric blood flow velocity and increased cerebral vascular resistance relatively more so than mesenteric resistance. Furthermore, studies have demonstrated that despite fewer subsequent occurrences of PDA, there is no improvement in overall respiratory morbidity or mortality, and there does seem to be a trend towards an increased incidence of necrotising enterocolitis following prophylactic indomethacin therapy.[41,42]

In addition to the potentially adverse vasoconstrictive effects of indomethacin, there is also hypothetical concern about possible bleeding phenomena secondary to interference with platelet aggregation. This is of particular concern since the target patient population is already at increased risk for intraventricular haemorrhage with its potentially irreversible adverse effects. All relevant clinical studies have looked at the effect of indomethacin on the precipitation and/or extension of intracranial bleeding, and they have not shown any deleterious effect.[43,44] Again, the interaction is potentially complex as indomethacin also has vasoconstrictive effects that may even reduce intracranial bleeds. While there is at least 1 study showing a mild increase in gastrointestinal bleeding with the use of indomethacin,[45] this does not seem to be a major clinical concern. A recent Cochrane review[42] concluded that, 'there is no [clinical] evidence that haemostasis is disturbed', with the use of prophylactic indomethacin.

Table I summarises the advantages and disadvantages of the various indomethacin administration regimens.

3. Therapeutic Indomethacin

By definition, the prophylactic approach implies that neonates will receive treatment regardless of the pretreatment status of their ductus. However, if prophylactic treatment is not initiated, the clinicians' aim should be towards early therapeutic administration of indomethacin. This necessitates early diagnosis. PDA can be detected in the 'at-risk' premature neonate using an echocardiogram performed between 24 and 48 hours of age. Although treatment is most effective at this age, it is true that many of these infants will not become symptomatic if treatment is not given; perhaps leading to the unnecessary treatment of some infants. However, if treatment is limited to a high risk group, i.e. ventilated infants weighing <1500g with evidence of a patent ductus, it is more likely to be warranted. In fact in a meta-analysis of more than 25 randomised, controlled trials,[49] early symptomatic therapy (at 1 to 3 days of age), as compared with late symptomatic therapy (at 7 to 10 days of age), was found to reduce morbidity, decrease the need for subsequent surgical ductal ligation, reduce pulmonary morbidity and to be as-

Table I. Advantages and disadvantages of the standard indomethacin administration regimens

Type of administration	Clinical advantages	Clinical concerns
Antenatal	Inhibits premature labour	Premature (*in utero*) ductal closure
		Subsequent increased incidence of PDA
		Subsequent resistance of PDA to therapy
		Increased PVL
		Increased focal intestinal perforations
Postnatal prophylactic	Decreased IVH	No overall improvement in outcome
	Subsequent decreased incidence of PDA	Decreased cerebral and mesenteric blood flow
		Trend towards increased NEC
		Infants treated unnecessarily
Early therapeutic	Treat only those with PDA	
	Best response with earliest postnatal treatment	
bolus	More convenient	Decreased renal, cerebral and mesenteric blood flow
continuous	Virtually eliminates reductions in blood flow	No definitive study to prove efficacy equal to bolus
Prolonged administration	Possible reduction in ductal recurrence rate	Possible increase in NEC and oxygen requirement (Tammela et al.[46])
		Possible decrease in IVH (Rhodes et al.[47])
		Possible decreased rise in creatinine and urea (Rennie and Cooke[48])

IVH = intraventricular haemorrhage; **NEC** = necrotising enterocolitis; **PDA** = patency of the ductus arteriosus; **PVL** = periventricular leukomalacia.

sociated with a lower incidence of necrotising enterocolitis.

Classically, indomethacin has been administered as 3 separate doses at regular intervals over a 36-hour period. There are several dosage regimens outlined in the literature, all of which are reasonably similar. The following, suggested in a recent review by Clyman,[50] is typical of these protocols. An initial loading dose of 0.2 mg/kg is given intravenously. For infants either weighing >1250g or of >7 days of postnatal age, subsequent doses are also 0.2 mg/kg. However, for infants weighing <1250g and at <7 days of postnatal age, he recommends that the second and third doses be 0.1 mg/kg per dose.

3.1 Continuous Indomethacin

There is concern that the drop in dilator prostaglandin tone effected by indomethacin causes concurrent vasoconstriction of other vascular beds, most notably the cerebral, renal and mesenteric vasculature, which in turn can cause potentially toxic adverse effects. Indomethacin, as classically administered to premature neonates, causes reductions in cerebral blood flow (CBF)[51,52] and in CBF velocity[37,53-56] ranging from 25 to 60%. The effect of indomethacin under conditions of underlying decreased cerebral perfusion remains to be determined. The cerebral circulation of the premature neonate is known to be exquisitely sensitive to decreases in CBF which, in turn, may cause hypoperfusion and even precipitate ischaemic insults in the affected areas. Leffler et al.[57] demonstrated in newborn piglets that relatively small degrees of haemorrhagic hypotension, which alone are not severe enough to alter CBF or cerebral oxygen consumption, will produce a 40% decrease in CBF, a 40 to 60% decrease in cerebral oxygen consumption and coma in 75% of animals, when they occur in conjunction with indomethacin treatment. Thus, conditions such as periventricular leucomalacia have the potential to be exacerbated by indomethacin administration, although to date this has not been demonstrated clinically.

Slowing the indomethacin infusion rate to 20 to 30 minutes ameliorates, but does not totally eliminate, the indomethacin-mediated reduction in CBF velocity.[53,58-60] Hammerman et al.,[49] therefore, studied an even slower infusion rate, i.e. a continuous infusion of indomethacin. The results of this study, using the same total dose of indomethacin (17 μg/kg/h over 36 hours), indicate that, while rapid injection decreased CBF velocity in each of the infants who received it, continuous administration of the indomethacin virtually eliminated any drops in CBF velocity. Renal vasoconstriction, another well known adverse effect of indomethacin therapy, was also eliminated by continuous infusion. However, it must be remembered that, although it appears from this study that continuously infused indomethacin is equally efficacious in closing the ductus, the study lacked sufficient power to definitively prove comparable therapeutic efficacy.

In summary, continuous intravenous infusion of therapeutic indomethacin is clearly less toxic than bolus indomethacin and it should, therefore, be considered as a treatment alternative in the premature neonate with persistent PDA.

3.2 Prolonged Indomethacin

Although indomethacin is currently the best pharmacological treatment for PDA, the ductus subsequently reopens in 20 to 35% of those neonates who respond initially.[61] Late recurrences are associated with lower birthweights and earlier postnatal age at treatment. Normally, ductal closure occurs in 2 phases, initial vasoconstriction followed by anatomic closure. Until full anatomic closure is achieved, vasoconstriction is reversible and, thus, the infant remains at risk for recurrence. Conventional indomethacin therapy transiently suppresses dilator prostanoid production, facilitating ductal vasoconstriction but not always allowing sufficient time for anatomic ductal closure. Seyberth et al.[62] reported that 6 out of 17 infants who received indomethacin had a resurgence of PGE_2 production within 5 days of the completion of therapy. Reopening of the ductus has been associated with a resurgence in dilator prostanoid levels, which occurs as serum indomethacin-induced suppression of prostaglandin production wanes.[63]

It has been hypothesised, therefore, that sustaining the vasoconstriction phase via a more prolonged treatment plan would enable more effective development of anatomic closure, which would be irreversible and thereby prevent the recurrence of PDA. With this in mind, several investigators[46-48,64] have independently conducted randomised studies of conventional short term versus prolonged low dose maintenance indomethacin treatment. Two of these studies[48,64] demonstrated that a 5- to 7-day treatment protocol significantly minimised PDA recurrences and decreased the need for surgical ligations, with no increase in complications. One study[47] demonstrated no difference in the overall rate of ductus reopening, but found less intraventricular haemorrhage in the prolonged treatment group and no difference in necrotising enterocolitis, retinopathy of prematurity or death between the groups. Seyberth et al.[65] studied the renal effects of prolonged indomethacin therapy and found that prolonged indomethacin therapy for the prevention of PDA relapse constituted no further risk to kidney function after successful pharmacologically induced ductal constriction.

In apparent contrast to the above studies, Tammela et al.[46] also compared 2 indomethacin protocols – the standard 3 doses every 12 hours versus a prolonged protocol of 1 low dose given daily for 7 days. They found no difference in the success of treatment of haemodynamically significant PDA and they conclude that, 'a prolonged low dose indomethacin regimen offers no advantage compared with a standard dosage short course in the management of . . . PDA'. Although it is appropriate to conclude that the protocol they administered offered no advantage, their conclusion may be overstated. The basic difference between the therapeutic approach of the Tammela et al.[46] protocol, in which there was no clinical effect, and previous protocols, in which the number of PDA recurrences was reduced, was in the initial therapy. Hammerman et al.[64] felt that effective initial vasoconstric-

tion was basic to the treatment approach and, thus, all infants received the initial 3-dose course at 12-hour intervals. Only afterwards was the low dose maintenance protocol begun. The increased requirement for surgical ligation demonstrated in the Tammela et al.[46] study supports the observation that the initial closure was ineffective. In contrast, Tammela et al.[46] sought 'to . . . have fewer side effects, and a better outcome'. Consequently, they altered the initial therapy, giving the lower dose from the beginning in the prolonged treatment group. Possibly, by doing this, they never achieved effective initial closure and, thus, preventing reopening became a nonissue. Furthermore, the mild increases in oxygen requirement and necrotising enterocolitis in the prolonged therapy group in the study by Tammela et al.[46] may, in fact, be related either to the effects of more prolonged ductal shunting or to the prolonged indomethacin administration.

In summary, we think it appropriate to conclude that prolonged low dose indomethacin does not achieve better short or long term closure. However, a 3-dose course of the normal indomethacin dose (see section 3) followed by a prolonged maintenance phase of low dose indomethacin (0.1 mg/kg/day for 5 days) may be therapeutically advantageous in preventing recurrences of PDA. Figure I summarises our approach to the medical treatment of the premature neonate with PDA.

Some patients may respond to a third course at a higher dose, or to a more prolonged course; some may require surgery.

3.3 Concurrent Furosemide

Classical administration of indomethacin tends to be associated with a transient oliguria, which can be ameliorated with concomitant furosemide. However, furosemide has been shown to increase dilator prostaglandin production,[66] and thus it has the potential to antagonise the vasoconstrictor effect of indomethacin on the ductus, and even increase ductal dilatation. Consequently, furosemide may have conflicting physiological effects in the premature neonate with PDA. In 1998, a Cochrane review was initiated to assess the pros and cons of concurrent furosemide and indomethacin administration. They found only 3 studies that fulfilled their entry criteria, and there was substantial heterogeneity among these studies. However, while they did not find evidence that furosemide administration significantly increased the risk for failure of ductal closure, they also found insufficient evidence to support the administration of furosemide to premature infants receiving indomethacin for symptomatic PDA.[67]

3.4 Concurrent Dopamine

In 1984, Seri et al.[68] postulated that dopamine might be able to counteract the renal adverse effects of indomethacin. They randomised 15 infants to receive either indomethacin alone or indomethacin with dopamine. They found that dopamine reduced some of the renal adverse effects of indomethacin that were tubular in origin, but was not able to prevent the renal vasoconstrictive action that occurred following the inhibition of prostaglandin synthesis by indomethacin. Two subsequent studies[69,70] showed no reduction of the renal adverse effects of indomethacin with the addition of dopamine.

3.5 Mefenemic Acid

Mefenemic acid is an anthranilic acid derivative that both inhibits prostaglandin synthesis and reduces prostaglandin activity, possibly by blocking prostaglandin receptors.[71] However, it appears to be associated with more serious gastrointestinal adverse effects than some of the other nonsteroidal anti-inflammatory drugs. Sakhalkar and Merchant[72] administered mefenemic acid to 16 premature neonates with PDA, and they observed a closure rate of 93%. They compared this group with a retrospective group of controls who received indomethacin and had a closure rate of 70%. Although the methodological problems with such a study are obvious and numerous, mefenemic acid does appear to have some effect in closing the PDA and it may warrant additional research.

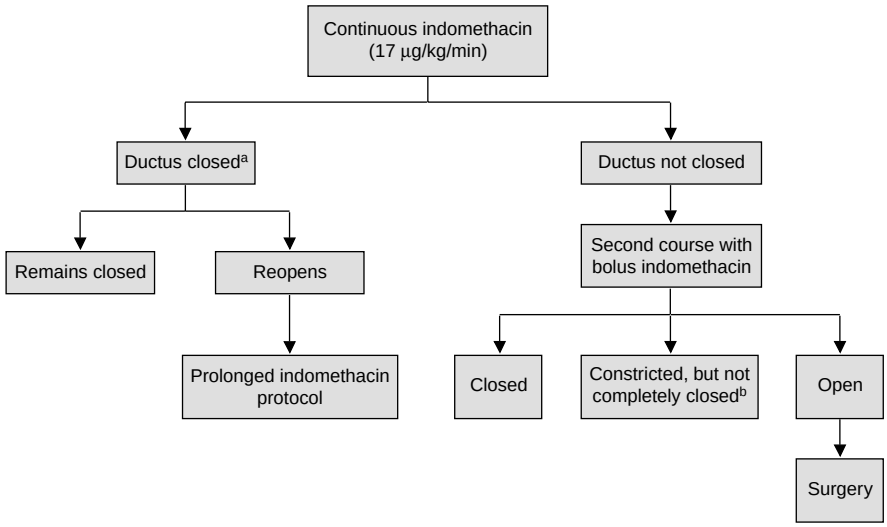

Fig. 1. Therapeutic use of indomethacin for patency of the ductus arteriosus: practical guidelines.
a Evaluate no sooner than 12 hours after the completion of therapy.
b Each patient must be individually evaluated. Some patients may respond to a third course at a higher dose, or to a more prolonged course; some may require surgery.

4. Potential Alternative to Indomethacin: Ibuprofen

Indomethacin, although therapeutically quite effective, is known to be associated with certain adverse effects, which are predominantly mediated by the vasoconstriction of other vascular beds – specifically, the cerebral, renal and intestinal vessels – critical to the well-being of the premature neonate. Ibuprofen is rapidly emerging as a potential alternative to indomethacin in the treatment of PDA.[73-75] It is the prototype phenylpropionate, another class of COX inhibitor. Ibuprofen appears to be effective in mediating ductal closure while possibly causing less vascular compromise.[75-77]

4.1 Intestinal Blood Flow

In 1 study of the comparative effects of ibuprofen and indomethacin on the regional circulation in dogs, indomethacin produced severe, acute mesenteric vasoconstriction while ibuprofen did not.[78] Grosfeld et al.,[79] in a study of bowel ischaemia in rats, noted that ibuprofen-treated animals had a significantly lower incidence of bowel necrosis compared with indomethacin-treated animals. In a recent study comparing the 2 treatments in preterm infants,[74] indomethacin was noted to cause a significant reduction in mesenteric and renal blood flow velocity 30 minutes after drug administration, which did not return to the pretreatment values by 120 minutes. Ibuprofen, in contrast, did not alter blood flow at 30 minutes after treatment; however, blood flow was increased by 120 minutes after treatment. It is not inherently clear whether acute increases in blood flow velocity might not be equally detrimental.

4.2 Renal Blood Flow

In a study in dogs,[78] both ibuprofen and indomethacin caused similar decreases in renal blood flow.[78] Speziale et al.[80] reported that both ibuprofen and indomethacin significantly increased renal vascular resistance in newborn piglets. Most recently, Chamaa et al.[81] demonstrated in newborn rabbits that intravenous ibuprofen caused a dose-dependent, significant reduction in urine vol-

ume, glomerular filtration rate and renal blood flow, with a fall in filtration fraction, together with a steep rise in renal vascular resistance and a decrease in urinary sodium excretion. They concluded that short term intravenous doses of ibuprofen are associated with significant renal haemodynamic and functional adverse effects, occurring with a similar incidence to those seen previously with indomethacin. In possible contrast to these animal studies is a recently published clinical study[75] which showed less oliguria in infants receiving ibuprofen than in those receiving indomethacin. Nevertheless, we must heed the warnings of the more sophisticated animal studies, that is that ibuprofen-induced renal adverse effects are of the same order of magnitude as those seen with indomethacin, at least until further clinical data are available.

4.3 Cerebral Blood Flow

The effect of ibuprofen on CBF reduction remains unclear. Some studies have shown no ibuprofen-mediated reduction of CBF.[80,82] One study actually demonstrated increased CBF following ibuprofen administration,[83] the implications of which are unknown. Another recent study documented a reduction in the release of the vasodilator PGE_2 from cerebral microvessels, implying a possible resulting cerebral vasoconstriction and, thereby, a reduction in CBF.[84]

In contrast, indomethacin, as classically administered to premature neonates, does in fact cause well-documented reductions in CBF[51,52] and in CBF velocity[37,53,55,56] ranging from 25 to 60%. The effect of indomethacin under conditions of underlying decreased cerebral perfusion remains to be determined.

4.4 Bilirubin

Cooper-Peel et al.[85] have raised questions concerning a possibly undesirable adverse effect of ibuprofen. They have demonstrated that at clinically appropriate ibuprofen concentrations the free fraction of bilirubin is increased by a factor of 4. Indomethacin was studied and showed no measurable displacement of bilirubin from albumin.[86] Ibuprofen may, thus, increase the risk of bilirubin encephalopathy when used in sick, premature infants.

A recent clinical study comparing these 2 treatment modalities was considered to be of sufficient importance to be rushed for rapid publication in the *New England Journal of Medicine*.[75] The study concluded that ibuprofen therapy on the third day of life was as efficacious as indomethacin in treating PDA, and was significantly less likely to induce oliguria. However, this study is far from the *sine qua non* of PDA therapy. First, the only outcome measure found to be significantly decreased was urine output, which was neither a very sensitive nor a very significant measure. There were no differences in the incidence of bronchopulmonary dysplasia, necrotising enterocolitis, neurological or other long term outcomes between the 2 treatment groups. An editorial accompanying this article[87] raised several additional caveats, including the fact

Table II. Advantages and disadvantages of ibuprofen therapy for patency of the ductus arteriosus (PDA)

Parameter	Advantages	Disadvantages
Therapeutic efficacy and availability	Appears to be as effective as indomethacin in closing PDA	No long term outcome studies
		No intravenous form universally commercially available
Effect on peripheral vascular beds	Probably less reduction in cerebral blood flow than indomethacin	Reduction of prostaglandin E_2 production from cerebral microvessels, implying possible cerebral vasoconstriction
	Less impairment of renal and gastrointestinal haemodynamics than indomethacin	
Bilirubin		Free bilirubin is increased by a factor of 4, possibly increasing the risk of bilirubin encephalopathy

that the infants in these trials were more mature (average gestational age of 28 weeks) than those who are at greatest risk for PDA and its associated complications (those born at 26 weeks or less). Whether these results apply to this very premature group remains to be tested. Similarly, the low frequency of gastrointestinal and intracranial complications in these more mature infants makes it impossible to draw any conclusion about safety issues regarding these organ systems in less mature infants.

In summary, although ibuprofen and indomethacin appear to be similarly effective in facilitating ductal closure, and although ibuprofen may be associated with fewer vasoconstrictive effects as compared with indomethacin, this has not yet been definitively proven to be clinically significant (table II). Moreover, studies of the long term outcome comparing indomethacin and ibuprofen treatment do not exist. Finally, from a technical standpoint, intravenous preparations of ibuprofen are not universally commercially available at this time.

4.5 Prophylactic Ibuprofen

A natural corollary of the indomethacin prophylaxis studies and the emergence of ibuprofen as an alternative to indomethacin has been a group of studies attempting to evaluate ibuprofen prophylaxis.

There have been studies to demonstrate its efficacy in achieving ductal closure when given prophylactically,[88] and to evaluate short term cerebral and renal blood flow velocity changes in infants undergoing prophylactic ibuprofen therapy.[89] In the latter study, infants were divided into 2 groups – those without PDA and those with PDA pretreatment. As the study was one of prophylaxis, both groups received treatment; however, the responses were different. In those without PDA, ibuprofen itself had no effect on blood flow velocities; however, in those with PDA, increased end-diastolic velocity and mean flow velocity were increased in both the cerebral and renal vessels post-treatment. The authors attributed these results to the haemodynamic effect of having closed the ductus rather than to a direct drug-mediated effect, and thus pronounced ibuprofen to be free of vascular adverse effects. Nevertheless, it must be remembered that the clinical situation will be analogous to the group with PDA in that patients embarking upon therapy will mainly be those with ductal patency at the onset.

5. Possible Future Treatments For PDA

5.1 Nitric Oxide Inhibitors

In addition to prostaglandins, the ductus arteriosus produces an NO-like vasodilator. Clyman et al.[10] noted that the relative importance of these 2 vasodilators, PGE_2 and NO, appears to change after birth, with NO becoming increasingly important with time. Among other predisposing factors, the flow of oxygenated arterial blood through the narrowed ductus lumen may stimulate increased NO production. As a result, drugs which interfere with NO synthesis could become useful therapeutic adjuncts in ductal closure, especially in situations where indomethacin has proven to be ineffective.

5.2 Selective Cyclo-Oxygenase Inhibitors

Two isoforms of COX have been described to coexist physiologically: COX-1, which is constitutively expressed; and COX-2, which is inducible. The constitutive COX-1 has been implicated in the production of the relatively small amounts of prostaglandins required for the mediation, modulation and maintenance of normal physiological functions, such as mediating normal platelet function and regulating renal blood flow. As such, the inhibition of COX-1 accounts for many of the adverse effects observed with nonselective COX inhibition. In contrast, basal COX-2 expression is low and tightly regulated, but with inflammation COX-2 is rapidly induced by cytokines, growth factors and bacterial endotoxin. Nonselective COX inhibitors are currently the clinical mainstay for the treatment of PDA, but at the same time they produce adverse effects associated with inhibition of COX-1 and the consequent suppression of the production of prostaglandins necessary for normal

cellular functions. Recently, new drugs have been designed with specific selectivities against the COX-1 and COX-2 isoforms, and the applicability of these novel compounds to the treatment of PDA must be considered.

Animal studies[90,91] have shown that while the fetal ductus arteriosus expresses virtually only COX-1, the ductus of the newborn produces both COX-1 and COX-2, with the latter contributing over 90% of local PGE_2 formation. Thus, in the newborn, while COX-1 remains the principal source of systemic circulating prostaglandins, COX-2 appears to be the main intrinsic source of prostaglandins produced by the ductus arteriosus of the newborn piglet, leading to early speculation that selective COX-2 blockers might be effective in closing the newborn ductus arteriosus.[90] This would be true provided that these intrinsically produced prostaglandins contribute more to ductal tone *in vivo* than do circulating prostaglandins derived from COX-1. If successful therapeutically, COX-2 inhibitors would be expected to produce fewer adverse effects than the general COX inhibitors. However, Guerguerian et al.[91] found that while selective COX-2 inhibitor treatment in the newborn pig did reduce local PGE_2 levels in the ductus arteriosus, it failed to affect ductal patency. In contrast, treatment with a selective COX-1 inhibitor did produce significant constriction of the ductus arteriosus. Thus, it appears that although the newborn ductus arteriosus, in contrast to that of the fetus, does express COX-2, it is the circulating prostaglandins that arise mostly from COX-1 which seem to exert the major control on ductal patency *in vivo*. Hence, the applicability of selective COX inhibitors to the treatment of PDA does not seem to be very promising at the moment.

5.3 Prostaglandin E_2 Receptor Manipulation

The vascular effects of prostaglandins are mediated by prostanoid receptors. Each receptor is named after the prostaglandin that is its most potent agonist, e.g. EP_2 receptors mediate the action of PGE_2.[92] EP receptors are further classified into 4 subtypes, and the distribution of receptor subtypes varies with developmental stages of the ductus arteriosus.[93] There are fewer EP_2 receptors, for example, in the newborn ductus than in that of the fetus, possibly accounting for the decreased responsiveness of the newborn ductus to PGE_2. A full description of the function of EP receptor subtypes and their distribution in the developing ductus arteriosus has yet to be substantiated for the human neonate. Potentially, manipulation of these receptors with agonists and antagonists may offer interesting avenues for future therapeutic investigations.

5.4 Combination Therapy

Finally, there remains the possibility of combined therapy. Preliminary studies of this sort have been performed by Clyman et al.,[94] in which 2 methods of closing the ductus were compared in premature baboons: indomethacin alone versus inhibition of both NO (with L-NG-nitro-L-arginine methyl ester) and prostaglandin production (with indomethacin). The combined approach achieved a higher degree of ductus closure. Furthermore, the animals treated with indomethacin alone did not develop significant hypoxia in the ductus and did not develop neointimal mounds on the ductus (thereby rendering them susceptible to later reopening). In contrast, animals in the combined treatment group developed a zone of intense hypoxia in the ductus muscle media, which was associated with development of a neointima composed of proliferating endothelial cells that completely occluded the lumen of the vessel.

6. Conclusion

Future studies will undoubtedly focus on the development of new receptor antagonists, on the role of other mediators, such as vascular endothelial growth factor, and their inhibitors in ductal patency. Furthermore, there will be a development of treatment 'cocktails', enabling a multipronged approach and, of course, a further fine-tuning of the current therapeutic regimens. Nevertheless, recently published follow-up data have concluded that the use of prophylactic low dose indomethacin

initiated in low birthweight infants in the first 24 hours of life is not associated with a subsequent adverse neurodevelopmental outcome.[30,31] Inevitably, the trip from the laboratory to the bedside must be an arduous and rigorous one.

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