Don’t discard your indomethacin yet

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The beneficial effects of surgical intervention to close the ductus arteriosus in premature infants with significant left-to-right shunting through this vessel were demonstrated over 20 y ago (1). About the same time, Heymann et al. (2) and Friedman et al. (3) demonstrated that closure of the ductus could be achieved pharmacologically using the cyclooxygenase inhibitor indomethacin. The efficacy of indomethacin in this context was substantiated by a large multicenter randomized clinical trial that led its investigators to recommend indomethacin as the preferable treatment for infants with symptomatic PDA, reserving surgical ligation as back-up treatment for indomethacin failure (4).

Indomethacin has also been shown to be effective in the prevention of symptomatic PDA when given within 24 h after birth (5). In a review of 9 controlled trials, prophylactic indomethacin was found to reduce the incidence of symptomatic PDA from 40% to 6% among newborn premature infants who weighed less than 1500 g at birth (6). Studies have also shown that prophylactic indomethacin reduces the need for surgical ligation (7) and may reduce the incidence of severe intraventricular hemorrhage (8).

In spite of the beneficial effects of indomethacin in both the treatment and prevention of symptomatic PDA, there are numerous adverse effects of this drug that compete with its overall effectiveness. Reduced renal function manifest by decreased urine output, decreased serum sodium, and increased serum creatinine is frequently observed following indomethacin administration (9). When indomethacin treatment fails to achieve ductus closure, renal dysfunction may become markedly aggravated when the adverse effects of indomethacin are combined with decreased renal blood flow due to the ductus steal of left ventricular output. Other adverse effects include decreased cerebral (10) and mesenteric (11) blood flow velocity, gastrointestinal perforation (12), decreased cardiac function (13), impaired surfactant release from type II cells (14), and decreased platelet function (4).

Paradoxically, the most problematic complication of indomethacin is delayed permanent ductus closure (the ligated ductus rarely reopens). Failure to achieve permanent ductus closure with indomethacin is especially common in extremely immature infants who are less than 28 weeks gestational age. Narayanan et al. (7) reported that 41% of infants treated with indomethacin for symptomatic PDA and 21% of infants given prophylactic indomethacin required eventual ductus ligation. Arguably, the added morbidity related to delayed closure and the surgical procedure is at least comparable to, if not greater than the indomethacin-associated morbidity related to changes in cerebrovascular and renal function that are usually transient.

Recent studies have indicated that another non-steroidal anti-inflammatory drug, ibuprofen, may be an effective alternative to indomethacin without many of the side effects of this drug (15–19). The report by Dani et al. elsewhere in this journal (20) confirm the efficacy of intravenous ibuprofen in both the prevention and treatment of symptomatic PDA in newborn premature infants. On the third day after birth, only 8% of 40 infants who had received ibuprofen beginning within 24 h following delivery had a significant PDA compared with 53% of 40 infants in the control group. Ibuprofen treatment of infants in the control group who developed a significant PDA by 3 d after birth resulted in ductus closure in 90% (19/21). Only two infants from the prophylactic group and one infant from the control group who had been treated with ibuprofen developed recurrent ductus patency. None required surgical ligation. The design of this study did not permit assessment of side effects normally associated with indomethacin. However, no significant changes in renal function were seen following ibuprofen when used either prophylactically or as treatment for PDA.

The study by Dani et al. has several limitations. Since the mean birthweights of the study groups were over 1200 g, the results may not apply to extremely immature infants 24–26 wk gestational age in whom indomethacin failure and indomethacin-associated renal failure are such vexing problems. The number of patients enrolled in the study was sufficient to establish efficacy of ibuprofen to prevent symptomatic PDA. However, a much larger trial would be required to enroll the hundreds of patients necessary to detect differences between the prophylactic and rescue groups in regard to adverse outcomes such as need for ductus ligation and the incidence IVH. Nor can inferences be made about the relative safety of ibuprofen compared to indomethacin, since this study did not include an indomethacin group.

The main limitation on the usefulness of indomethacin is not the effect of this drug on renal function and cerebrovascular function, but the poor success rate of this drug in achieving permanent ductus closure in very immature infants. The efficacy of ibuprofen in regard to avoiding the need for eventual ligation of the ductus in extremely immature infants has not yet been adequately addressed. Published studies to date have not included sufficient numbers of patients who are less than 28 wk gestational age to draw valid conclusions in this regard.
However, based on work by the Clyman group implicating the involvement of endogenous nitric oxide in ductus patency (20, 21), one would not expect that the use of a different cyclooxygenase inhibitor is likely to decrease the number of indomethacin failures.

Nevertheless, this study and others on the same subject provide good evidence that ibuprofen may be preferable to indomethacin in the prevention and treatment of symptomatic PDA. However, before the use of ibuprofen can be accepted as the standard of care for this condition, a sufficiently large multicenter trial is needed to establish an acceptable equivalence between the drugs in regard to efficacy. Even though ibuprofen appears to be relatively free of the cerebrovascular and renal effects of indomethacin, it is important to establish that failure to achieve permanent closure is no worse with ibuprofen than with indomethacin.

When renal insufficiency accompanies a failed attempt to close the ductus using indomethacin, some physicians might be tempted to use ibuprofen in a repeated attempt to achieve pharmacologic induction of ductus closure. The safety and efficacy of ibuprofen in this clinical context have not been demonstrated. In addition, a failed repeated attempt at pharmacological closure would further compromise the patient’s clinical status by postponing definitive closure by surgical ligation.

At the present time, the intravenous preparation of ibuprofen is unavailable in the United States. The bioavailability of oral ibuprofen in the newborn premature infant is unknown. Oral ibuprofen should not be used as a substitute for intravenous indomethacin in the management of symptomatic PDA, either as primary treatment or prophylaxis, or as a backup drug when additional treatment with indomethacin is contraindicated by renal failure.

References


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