
Selected Summaries

Ibuprofen vs Indomethacin for Treatment of PDA in Preterm Infants

[Overmeire BV, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with Ibuprofen. Arch Dis Child 1997; 76: F179-F184].

Currently, Indomethacin is the only nonsteroidal anti-inflammatory drug (NSAID) used for the treatment of a hemodynamically significant patent ductus arteriosus (PDA) in preterm neonates. Authors evaluated the efficiency and side effects of ibuprofen for the early treatment of patent ductus arteriosus (PDA) and compared it with that of indomethacin.

Forty preterm infants (<33 weeks) with respiratory distress syndrome (RDS) and echocardiographically confirmed PDA were randomly assigned at days 2 and 3 of life to receive either intravenous indomethacin in a dose of 0.2 mg/kg for three doses at 12 hourly intervals, or intravenous ibuprofen 10 mg/kg followed by two more doses of 5 mg/kg administered at 24 and 48 hours after the first dose. All the neonates were being mechanically ventilated and received surfactant replacement therapy according to a strict protocol. Preterms with intraventricular hemorrhage, clinical bleeding tendency, thrombocytopenia (platelets < 60,000/mm³), oliguria (urine output < 1 ml/kg/h), uremia (blood urea nitrogen > 14 mmol/L, serum creatinine > 140 mmol/L) and severe hyperbilirubinemia requiring exchange transfusion were excluded from the study.

Patients in the two groups were

matched for their birth weight, gestation, maternal medication, type and duration of ventilatory support, oxygen requirement, size of the shunt and age at treatment. PDA closed in 15/20 patients in indomethacin group (75%) and 16/20 patients in ibuprofen group (80%). Seven patients (three indomethacin, four ibuprofen) required a second course of indomethacin. The duct had to be ligated in 5 cases (3 in indomethacin and 2 in ibuprofen group). The urine output and other renal parameters were steadier in the ibuprofen group. No other side effects of ibuprofen were noticed. It was concluded that ibuprofen treatment seems to be as efficient as indomethacin in closing PDA on the third day of life with fewer side effects in preterms with respiratory distress syndrome.

Comments

A hemodynamically significant PDA in a preterm neonate may lead to an increased risk for intraventricular cerebral hemorrhage, enterocolitis, bronchopulmonary dysplasia and death(1). Indomethacin, a methylated indole derivative and a potent inhibitor of the prostaglandin forming cyclo-oxygenase, is being used for more than one and half decade for medical closure of patent ductus arteriosus in preterms(2). Though highly effective (closure rate, 70%), it is fraught with the risk of poor perfusion to vital organs, hemorrhages, altered platelet function and renal failure(3). The risk of ischemic injury after indomethacin has led to recent research for alternative drugs for use in newborns. Strategies to replace indomethacin with an equally efficacious but safer alternative using frusemide, dopamine, mefenemic acid

and aspirin have not been so far successful(4).

Ibuprofen, a propionic acid derivative NSAID has been shown to close PDA in animals without producing a hemodynamic abnormality(5) Phase I trial with ibuprofen in newborns has been shown to decrease prostaglandin levels and reduce the incidence of PDA and severity of respiratory distress(2) The present study, however, takes the lead in assessing the comparative efficacy of indomethacin versus ibuprofen in treatment of sick preterms with PDA in a prospective randomized way and has been able to establish role of ibuprofen in closure of PDA with additional advantage of fewer side effects as compared to indomethacin.

The study fails to explain the differences in renal side effects of the two drugs Both the drugs inhibit the cyclo-oxygenase system in the neonatal kidneys to same extent *in vitro*(6) Little is known about the expression of isozymes in neonatal renal tissue A plausible explanation is that due to different pharmacokinetic characteristic of the neonate, serum indomethacin concentration remains high enough to influence both ductus and kidneys Another reason may be that indomethacin acts in part through mechanisms other than inhibition of prostaglandin synthesis.

In contrast to indomethacin, ibuprofen does not affect basal cerebral blood flow, cerebral metabolic rate or intestinal and renal hemodynamics even during increased positive pressure ventilation On the contrary, ibuprofen may enhance cerebral blood flow autoregulation and protect the neurological function following oxidative stress(2) Due to increase in cerebral blood flow autoregulation, one may also expect a reduction in the incidence of Intraventricular hemorrhage (IVH) in preterm infants

The efficacy of ibuprofen in preventing IVH still remains to be established.

In view of non-availability of parenteral ibuprofen in India and promising results with oral indomethacin in ductus closure, it would be interesting to find out whether ibuprofen given per orally serves the same purpose or not when given intravenously.

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