INDOMETHACIN THERAPY IN THE NEWBORN

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Indomethacin is a widely used non-steroidal anti-inflammatory agent. Its activity as a prostaglandin synthetase inhibitor has brought it into prominence in neonatal medicine and resulted in its use in a number of diseases. This communication will highlight the various aspects of its use in the neonate.

Clinical Pharmacology

Chemically it is a methylated indole derivative with a structural formula as shown in *Fig. 1.* It is completely absorbed after oral administration with peak plasma concentration occurring after 3 hours. It has high plasma protein binding, nearly 90% gets bound to plasma protein and tissues. The half life of the drug depends on gestation and in preterms less than 32 weeks gestation it is much longer than in term infants(1). The half life of the drug also varies with postnatal age and is about 3 times higher on day 1 than on day 8(2,3). This, however, is of no clinical importance because the response of the ductus and the side effects of indomethacin do not correlate with the peak concentration of the drug(4). Indomethacin undergoes demethylation (50% of the drug), microsomal glucuronidation, and n-deacylation in the liver and is excreted into the bile and feces, with 10-20% of the drug excreted unchanged in the urine(1).

Pharmacological Actions

Indomethacin acts by inhibiting the cyclo-oxygenase pathway of arachidonic acid metabolism. As shown in *Fig. 2,* cyclo-

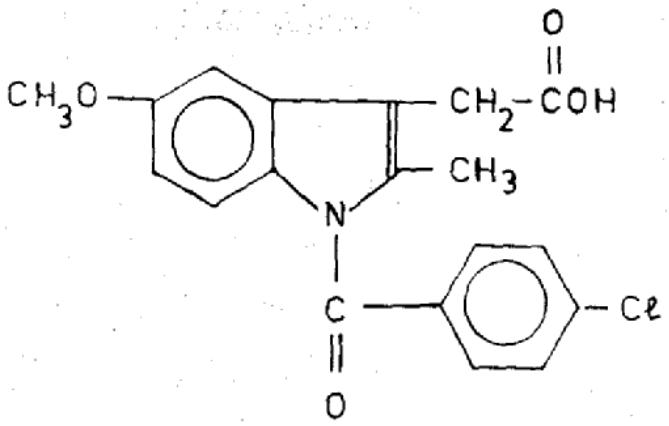

Fig. 1. Structural formula of indomethacin.

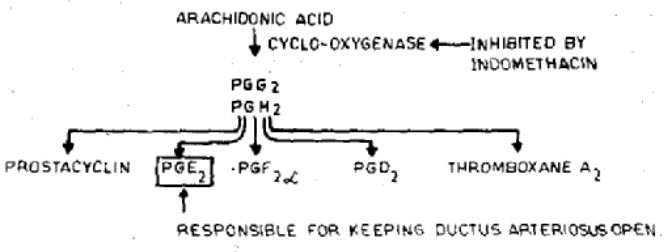

Fig. 2. Metabolism of arachidonic acid to prostaglandin and related compounds.

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Received for publication February 8, 1990; Accepted April 16, 1990

oxygenase converts arachidonic acid into unstable cyclic endoperoxide intermediary prostaglandin G_2 (PGG_2). This is then converted to any of the other prostaglandins or thromboxane by a number of enzymatic or spontaneous steps(5). By blocking cyclo-oxygenase, indomethacin thus non-specifically blocks prostaglandin and thromboxane production. This accounts for its pharmacological actions as well as side effects.

Clinical Uses

Pharmacological Closure of Patent Ductus Arteriosus (PDA)

The single most important role of indomethacin lies in its ability to inhibit prostaglandin E_2 (PGE_2) production, thereby inducing the closure of the ductus arteriosus in a preterm infant. During fetal life patency of the ductus arteriosus appears to be maintained by low oxygen tension and endogenously produced prostaglandins, specifically prostaglandin E_2(6,7). PGE_2 is also presumably responsible for keeping the ductus open postnatally. Levels of this prostaglandin have been found high in preterm infants with patent ductus arteriosus (PDA)(8).

Friedman *et al.*(9) were the first to demonstrate the efficacy of indomethacin in the treatment of PDA. Subsequently, Gersony *et al.*(4) in a large multicentric trial conclusively established the role of indomethacin in treatment of hemodynamically significant PDA. They showed that indomethacin given concurrently with fluid restriction and diuretics caused closure of PDA in 79% of the infants compared to 25% in the placebo treated group. Based on these observations, Barst and Gersony(5) have recommended administration of three doses of indomethacin orally or intravenously to preterm infants with hemodynamically significant PDA.

Studies from our own conuntry(10,11) have also shown similar results with closure rates of 60-75% with orally administered indomethacin. Oral or intravenous administration of the drug is followed by rapid clinical improvement and the physical and radiological signs disappear within 24-72 hours(5). The efficacy of pharmacological closure is comparable to surgical ligation in its ability to prevent complications associated with PDA(4). Prolonging the duration of therapy by increasing the number of doses does not influence either the closure rate or the rate of reopening of the ductus, but does delay the reopening(12).

While the role of indomethacin in treating symptomatic PDA is now well established, it is not so with asymptomatic PDA. Based on the fact that indomethacin becomes less efficacious in inducing ductal closure with increasing postnatal age, some authors(13-15) have advocated administering the drug early and prophylactically to infants with birth weights less than 1500 g. However, this has not been considered justifiable because only 30% of infants with birth weight greater than 1000 g who have an asymptomatic murmur will subsequently develop a major shunt(16). In contrast, infants weighing less than 1000 g at birth are at a high risk (80%) for developing large ductal shunts and appear to benefit from treatment(17). The consensus of opinion, however, still does not favour prophylactic treatment of PDA(5).

Indomethacin therapy for PDA is also associated with decreased incidence of pneumothorax(4) and possibly bronchopulmonary dysplasia(18).

Indomethacin in Prevention of Intraventricular Hemorrhage

Recent studies(13,18) have suggested that indomethacin reduced the incidence of intraventricular hemorrhage (IVH) in very low birth weight infants. Rennie *et al.*(14) however, reported no reduction in intraventricular hemorrhage in those infants who had been treated with indomethacin. Interestingly Setzer *et al.*(19) reported that infants treated with indomethacin had no difference in IVH, but on follow up had lesser motor disabilities though neurodevelopment scores were the same. Role of indomethacin in prevention of IVH is thus not well established(20).

Other Uses

Indomethacin has also been used for the treatment of preterm infants with Bartter like syndrome(21). It has been used in small doses to treat Bartter's syndrome(22) and nephrogenic diabetes insipidus(23).

Antental Administration

Indomethacin had earlier been used for inhibiting premature onset of labor with devastating results. It causes intrauterine constriction of ductus(24) resulting in heart failure, or persistent pulmonary hypertension(25).

Dosage and Formulation

Following the results of the National Collaborative Study(4) the preferred mode of therapy for a patent ductus arteriosus is three doses of indomethacin (0.2 mg/kg/dose) given at 12 hourly intervals either concurrently or after 24 to 48 hours of fluid restriction and diuretics. However, in neonates above 8 days of age, a dose of 0.25 mg/kg has been recommended(26).

The intravenous formulation of the drug is not available in our country and we have to resort to the oral form. The drug is marketed as a 25 mg capsule, and requires reconstitution into small satchets containing 0.2 mg of the drug in lactose as a diluent. This formulation can be administered through the Ryles tube whenever required according to the dosing regimen described above.

Side Effects

The chief side effect of indomethacin is on renal function. Indomethacin may cause a significant reduction in urine output (50% or more), decreased natriuresis, decreased creatinine clearance and fluid retention manifesting as increased body weight(27). Fortunately, these are transient and resolve when indomethacin therapy is stopped. It causes platelet dysfunction and predisposes to bleeding diathesis. It has been reported to cause gastrointestinal perforation(28). The drug binds to plasma albumin and may displace bilirubin predisposing to bilirubin encephalopathy.

We have been using the drug in our nursery over the last 5 years and have not seen any major adverse effect till date(10).

Drug Interactions

In view of its effect on renal functions, drugs that rely on renal functions, for clearance, should be administered in lower dosage. Digoxin dosage should be reduced by 50% if indomethacin has to be given concomitantly(29). Indomethacin also antagonises the antihypertensive effect of beta-adrenergic blocking agents and thiazides by unknown mechanisms(1).

In conclusion, we feel indomethacin is a powerful tool in the armamentarium of the

neonatologist and if used judiciously can be of immense use in pharmacological closure of the ductus. This is especially so in our country where facilities for neonatal cardiothoracic surgery are still not widely available.

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NOTES AND NEWS

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The first volume of this new series edited by Suraj Gupte was released at the inaugural ceremony of the National Conference of Pediatrics held at Hyderabad from January 24-27, 1991. It carries 26 chapters from as many eminent contributors drawn from around the world. The topics covered include "Growth Monitoring", "Elite Child", "Immunology of Malnutrition", "Bone-Marrow Transplantation", "AIDS", "IUGR", "Adolescent Health", *etc*. The book is modestly priced at Rs. 125. It is also available through the Editor, "Gupte House", 60, Lower Gumat, Jammu-180 001.