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ORIGINAL ARTICLE

Indomethacin Therapy in Premature Infants with Patent Ductus Arteriosus

by

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Abstract

Indomethacin has been shown to be effective in closing patent ductus arteriosus (PDA) in premature infants. Indomethacin administration decreased the need for assisted ventilation and surgical closure of PDA. Six premature neonates with birth weight less than 2500 gm diagnosed clinically as PDA were given indomethacin. The drug was given as a single dose by mouth or nasogastric tube in 2 or 3 consecutive days. The dose in the first two days was 0.1 mg/kg BW and the last dose (if necessary) was 0.3 mg/kg. BW. Closure of PDA was observed in all six cases. This experience in the use of indomethacin in PDA indicates a need for a further study on the effect of indomethacin in PDA.

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Introduction

The ductus arteriosus (ductus Botalli) is a large channel connecting the pulmonary trunk with the descending aorta during fetal life. It is a unique structure in that it is widely patent in the fetus, but it is capable of complete closure by contriction of its muscular wall within a few hours after birth. Closure of the ductus arteriosus occurs in two stages. Initial functional closure is brought about by contraction of the smooth muscle in the wall of the vessel. Following this, permanent closure is produced by destruction of the endothelium, proliferation of the subintimal layers, followed by connective tissue formation and eventual sealing of the lumen. It's patency after birth may result in cardiac decompensation and on the other hand, may provide the only life sustaining conduit to preserve systemic or pulmonary arterial blood flow in the presence of associated cardiac malformations. Patent ductus arteriosus has a high degree of association with respiratory distress syndrome (RDS) and with prematurity.

Many studies have shown the importance of an increase in oxygen tension as a stimulus for the muscular closure of the ductus arteriosus (Kovalvik, 1963; Heymann and Rudolph, 1975). Other factors such as hemodynamic changes in the pulmonary and systemic circulations, and release of vasoactive substances (such as histamine, acetylcholine, bradykinin, and endogenous catecholamines) may possibly contribute to the closure of the ductus arteriosus under physiologic conditions (Noel and Cassin, 1976). Fliedmann et al. (1976) and Heymann et al. (1976) reported successfull pharmacologic PDA closure using indomethacin, a known inhibitor of prostaglandin synthesis.

The following report is our preliminary experience in the use of indomethacin in 6 premature infants with PDA.

Materials and methods

Preterm infants admitted in the Department of Child Health, Cipto Mangunkusumo General Hospital with the diagnosis of PDA were given indomethacin. PDA was diagnosed on the basis of a continuous murmur, heard best in the left subclavicular area.

All patients had chest rontgenograms and ECGs and most had phonocardiograms before receiving treatment with indomethacin. Patient initially received single dose of 0.1 mg/kg/day for 2 consecutive days and if the ductus remained open the last dose of 0.3 mg/kg was given in the third day. Indomethacin was given at the time the diagnosis of PDA was made, and these were in the range of 14 to 23 days of age. Five patients received 3 doses and one patient received 2 doses of indomethacin. Indomethacin was prepared by suspending the content of a 25 mg capsule in normal saline. The drug was given orally or via nasogastric tube. Evaluation of the result of therapy was made cli-

nically by the disappearance of the murmur, and whenever possible by phonocardiogram.

Results

In all six patients closure of the ductus arteriosus was observed within 2 days (1 patient), 3 days (4 patients) and 8 days (1 patient). Clinically there was improvement in the general condition with the disappearance of respiratory distress. One patient died at the age of 33 days due to gastroenteritis and dehydration. No side effect of indomethacin therapy was observed (table 1).

Discussion

Patent ductus arteriosus (PDA) has a high degree of association with respiratory distress syndrome (RDS) and with prematurity. The incidence of PDA murmur in low birth weight infants was 21%, as reported by Siassi et al. (1976).

PDA may result in cardiac decompensation and respiratory distress syndrome. A large proportion, particularly the most immature infants are unresponsive to fluid restriction and the administration of digitalis and diuretics, and require surgical ligation.

Since inhibitors of arachidonic acid metabolism (such as acetyl salicylic acid or indomethacin) constrict the ductus arteriosus in premature infants (Friedmann et al, 1976; Heymann et al, 1976), lambs (Heymaan and Rudolph, 1976), and rabbits (Sharpe et al, 1975), the products of arachidonic acid metabolism have been implicated in the regulation of patency of the ductus arteriosus. Some studies have confirmed the initial observation of indomethacin associated PDA closure (Mernit et al., 1978; Holliday et al., 1977), whereas others have reported significantly less impressive PDA responses to indomethacin administrations (Neal et al. 1977; Cooke and Pickkering, 1979; Ivey et al. 1979).

Arachidonic acid relaxes oxygen-constricted ductus arteriosus rings, this relaxations is significantly greater in rings from immature animals than from those near term (Heymann et al., 1976). This effect is completely blocked by indomethacin, which implies that arachidonic acid does not act directly on muscle cells but through its intra-murall conversion to some vasoactive product.

It has been shown that indomethacin has a greater effect on the immature than on the mature ductus arteriosus, and this gestational age related difference in effectiveness of indomethacin on ductus arteriosus reflects a change in the sensitivity of the vessel to or a change in the synthesis and degradation of locally produced prostaglandins during development (Ronald et al., 1981). PGE2 appears to be the major prostaglandin released by the ductus arteriosus (Clyman, 1980).

It is likely that PGE2 plays a hormonal role in the fetus and that it is involved in the circulatory control and particularly in maintaining the ductus arteriosus in a dilated state during normal fetal life (Clyman and Heymann, 1981).

At birth, the pulmonary blood flow change from only 7 per cent of combined left and right ventricular output in the fetus to 100 per cent of the cardiac output in the neonate. This allow effective removal of circulatory PGE2 and thus enable the ductus arteriosus to constrict (Clyman and Heymann, 1981). In clinical situations in which pulmonary blood flow is likely to be reduced, the increased circulating plasma concentrations of PGE2 may contribute to the pathogenesis of persistent patent ductus arteriosus by exerting an additional vasodilatory effect on the ductus (Clyman and Heymann, 1981).

Infusion of PGE2 have been used in variety of congenital malformations in which it is critical to maintain the ductus arteriosus in a state as dilated as possible. Conversely, indomethacin has been used to constrict a persistently patent ductus arteriosus in infants in whom left to right shunting through the ductus has resulted in adverse hemodynamic effects.

The mean plasma half life of indomethacin ranged flom 11 to 90 hours, significantly prolonged when compared to the adult. The half life was related to the maturity of the infant, the mean half life was 17.2 hours in infants under 32 weeks gestation and 12.5 hours in those over 32 weeks gestation (Clyman and Heymann, 1981).

Clyman and Heymann (1981) recommended an initial dose of 0.2 mg per kg by orogastric tube, a second similar dose may be administered 12 to 24 hours later and occasionally a third dose is given 24 hours after that.

The effect of indomethacin therapy on the closure of patent ductus arteriosus in neonates or animals may be influenced by gestational age (Neal et al., 1977), birth weight (Cooke and Pickering, 1979; Ivey et al., 1979), postnatal age (Holliday, 1979), route of administration (Bhat et al., 1979). Most authors reported insignificant complication in the use of indomethacin.

In our initial trial in the use of indomethacin, we have observed the closure of ductus in all our patients. It is worth noted here that ECG findings showed right ventricular hypertrophy (RVH) in all patients and right atrial hypertrophy (RAH) in 3 patients (see table 1). Generally an infant with large left to right shunt will result in left ventricular hypertrophy (LVH). The presence of RVH and RAH may be due to the high resistency in the pulmonary circulation.

It is therefore possible that the patency of ductus arteriosus in our patients was due primarily to hypoxia as the result of pulmonary insufficiency. It is no doubt that there might be spontaneous closure of the ductus arteriosus among our patients. It is therefore necessary to assess the benefit of indomethacin therapy in PDA by a controlled study.

TABLE 1 : *Clinical data and result of indomethacin therapy on premature infant with PDA.*

Patient	Sex/Age	Birth weight	Diagnosis	Chest X ray	ECG	Phonocardiogram	Dosis of Indomethacin	Outcome
1	D, female 20 days	1470 gm	RDS, Hyperbilirubinemia PDA	X ray picture of RDS	RAH RVH	continuous murmur (+)	3 dosis	Murmur still persent at age 23 days, gone at age 28 days.
2	H, female 19 days	1650 gm	Hyperbilirubinemia, sepsis, PDA	Mild cardiomegaly, normal PVM	RVH	continuous murmur (+)	3 dosis	Murmur gone at age 22 days Phonocardiogram : murmur (—)
3	RW, male 20 days	1900 gm	RDS, Failure to thrive, PDA	Cardiomegaly	RVH	not done	3 dosis	Murmur gone at age 23 days, Phonocardiogram : murmur (—)
4	M, female 23 days	1550 gm	Hyperbilirubinemia, Sepsis, gastroenteritis, PDA	Normal	RVH RAH	not done	2 dosis	Murmur gone at age 25 days, Phonocardiogram : murmur (—) Died due to gastroenteritis dehydration at age 33 days.
5	S, male 17 days	1750 gm	RDS, Hyperbilirubinemia, PDA	Cardiomegaly	RAH RVH	continuous murmur (+)	3 dosis	Murmur gone at age 20 days, Phonocardiogram : murmur (—)
6	N, male 14 days	1900 gm	RDS, Hyperbilirubinemia, PDA	Cardiomegaly	RVH	not done	3 dosis	Murmur gone at age 17 days, Phonocardiogram : murmur (—)

Note : RDS = Respiratory Distress Syndrome
RAH = Right Atrial Hypertrophy
RVH = Right Ventricular Hypertrophy
CTR = Cardio Thoracis Ratio
PVM = Pulmonary Vascular Markings.

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