

PERSISTENT PULMONARY HYPERTENSION AFTER MATERNAL NAPROXEN INGESTION IN A TERM NEWBORN: A CASE REPORT

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ABSTRACT

Constricting effect of indomethacin on the ductus arteriosus of the fetus is well known. The fetal effects of other nonsteroid anti-inflammatory drugs (NSAIDs) like naproxen are not well reported. We report here a case of a 3790-g term neonate who developed persistent pulmonary hypertension after birth with a closed ductus arteriosus. The mother admitted to taking naproxen sodium immediately prior to the birth of the infant. The course of illness was progressively better on conservative management. Like indomethacin, other NSAIDs can also cause premature closure of fetal ductus arteriosus, pulmonary hypertension, and life-threatening problems to the neonate. Patient education regarding over-the-counter pain medication during pregnancy should be emphasized.

Keywords: NSAID; ductus arteriosus; prenatal

Nonsteroidal anti-inflammatory drugs (NSAIDs) taken early in pregnancy are not teratogenic, but taken later in pregnancy they are known to have cardiopulmonary, renal, hematological, and gastrointestinal effects in the fetus.¹ The prostaglandin-inhibiting action of NSAID may constrict the fetal ductus arteriosus. Indomethacin used for tocolysis may have such an effect when used in pregnancy after 32 gestational weeks.² We report a case of maternal ingestion of naproxen, a few days before the delivery of a term infant, whose ductus arteriosus apparently constricted in utero, and who was admitted to the neonatal intensive care unit (NICU) with primary pulmonary hypertension.

CASE REPORT

A 3790-g term Black male infant was born at 39 and 4/7 weeks of gestation to a 21-year-old Gravida 2, para 1 female by spontaneous vaginal delivery. There was maternal fever at the time of delivery. Maternal HIV screen was positive but Western blot was negative. She denied using drugs, smoking, or alcohol intake during pregnancy. She reported taking two tablets of Aleve® (naproxen sodium 220 mg) twice a day over the 4 days preceding birth of the infant.

The baby was born with a lusty cry, Apgar scores of 9 at 1 min and 9 at 5 min and he was sent to the

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Well Baby Nursery. At approximately 2 hr postnatal age, the infant was transferred to the NICU due to tachypnea and hypoglycemia (serum glucose 22 mg/dL). Initial saturation by pulse oximeter reading was 75% on an FiO_2 of 0.4 in a hood. Oxygen saturation only increased to 84% when the FiO_2 was elevated to 1.0 in the oxygen hood. An arterial blood gas obtained at that time revealed pH 7.33, PO_2 43, PCO_2 47, and BE -0.6 . The infant was cyanotic and a grade III/VI systolic murmur was heard over the left lower sternal margin.

Chest X ray showed cardiomegaly. An echocardiogram at 4 postnatal hr revealed a dilated and hypertrophied right ventricle (RV), and a thickened pulmonary valve. Color doppler indicated a predominant right to left shunt through the Patent Foramen Orale (PFO) and tricuspid regurgitation with a maximum velocity of 4.5m/sec, thus predicting right ventricular systolic pressure of approximately 100 mmHg (systemic pressure was 75 systolic). There was no evidence of a patent ductus arteriosus. The coronary arteries were dilated; flow was increased. There was no gradient across the pulmonary valve. At this point the differential diagnosis was primary pulmonary hypertension due to premature closure of the ductus arteriosus, or pulmonary atresia with intact ventricular septum and possible coronary fistulae. A trial of prostaglandin E_1 (PGE_1) to reopen the ductus caused a rapid deterioration in preductal and postductal saturation to 40%. PGE_1 infusion was stopped within 20 min. Antibiotic therapy was continued. FiO_2 was maintained at 0.4 by hood.

Overnight the infant's oxygen saturation steadily improved. About 24 hr after birth the peripheral oxygen saturation on pulse oximeter was over 90%. An echocardiogram was repeated at this time. It revealed hypertrophy of the RV, and normal mobility of pulmonary valves. Color doppler demonstrated a bi-directional flow at the atrial level still more right to left, and moderate tricuspid regurgitation at maximum velocity of 3.4 m/sec, thus predicting RV systolic pressure of 60 mmHg (systemic systolic pressure was 77 mmHg). There was no evidence of a patent ductus arteriosus, and the impression was that the primary pulmonary hypertension was in resolution and supplemental oxygen was maintained. The initial septic work-up was negative and antibiotics were discontinued after 24 hr. The infant's oxygen requirement regressed over the next 24 hr and his peripheral oxygen saturation was 100% on room air by pulse oxymetry. An echocardiogram on the sixth postnatal day

showed a normal pulmonary valve with RV pressure of 60 mmHg, and a PFO with a bi-directional shunt. The infant was discharged home with the mother for follow-up in the cardiology clinic. At 6-week follow-up the infant was acyanotic and doing well clinically. At 5 month follow-up an echocardiogram demonstrated closure of the atrial communication and mild right ventricular hypertrophy. The right ventricular systolic pressure as estimated by the tricuspid regurgitation flow velocity was 30 mmHg (less than a third of the systemic systolic pressure).

DISCUSSION

The sequence of events suggests that closure of the ductus arteriosus occurred in utero. The fetal ductus arteriosus allows equalization of pulmonary and systemic pressures. Narrowing of the ductus arteriosus in utero impedes right ventricular outflow.³ With narrowing or complete closure of the ductus arteriosus in utero, RV pressure increases and exceeds systemic levels. Closure of the ductus causes transient pulmonary hyperperfusion and the pulmonary arterioles are exposed to suprasystemic pressures from the time of ductal closure until birth. This causes smooth-muscle hypertrophy in acinar pulmonary arteries⁴ and pulmonary hypertension ensues.^{5,6} The direct constriction of the pulmonary vessels secondary to the action of prostaglandin synthetase inhibiting drugs could lead to increased muscle development. After birth, as pulmonary vascular resistance falls, RV pressure decreases. Several cases in the literature, and studies on animal models, have shown that indomethacin given late in pregnancy may activate closure of the ductus arteriosus in utero, causing persistent pulmonary hypertension.^{2,7-9} The fetal impact of prostaglandin inhibitors in closure of the ductus is well known.¹⁰ The desaturation event coinciding with the start of PGE_1 infusion may have resulted from systemic vasodilation and an increase of right to left shunt away from high pulmonary resistance due to excessive smooth muscle induced by fetal constriction of the ductus.¹¹

This infant's mother reported intake of Aleve® (naproxen sodium) during the 4 days prior to the delivery. Naproxen sodium is an NSAID that inhibits cyclo-oxygenase and production of prostaglandins. Like indomethacin, it causes ductal closure in utero. Momma et al,¹² in animal studies, have demonstrated the constricting effects of all acidic

NSAIDs, including naproxen, on the fetal ductus arteriosus of full-term pregnant rats. We do not have evidence of naproxen in the infant's or mother's blood, but the time of self-medication, and the cardiovascular events that followed birth, strongly suggest that naproxen was responsible for the transient cardiovascular dysfunction suffered by the infant. Excessive use of over-the-counter NSAIDs may also cause adverse effects on the pregnant mother who can have excessive intrapartum and postpartum bleeding.¹ This case illustrates a real need for patient education regarding the significance of self-medication with ductus-closing preparations, particularly NSAIDs.

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