case report

Severe neonatal pulmonary hypertension secondary to antenatal maternal diclofenac ingestion reversed by inhaled nitric oxide and oral sildenafil

Ali Mersal, Ihab Attali, Abdulaziz Alkhotani

From the Department of Pediatrics, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

Correspondence and reprint requests: Ali Mersal, MD · Department of Pediatrics · King Faisal Specialist Hospital and Research Center · MBC 58-J · P.O. Box 40047 · Jeddah 21499 · Saudi Arabia · Tel: +966-2-607-0532 · Fax: +966-2-667-7777 ext. 3508 · alimersal@dr.com · Accepted for publication March 2007

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The nonsteroidal anti-inflammatory drugs (NSAID), which act as inhibitors of prostaglandin synthesis, are widely used in clinical practice as tocolytic agents.¹ Administration of these agents in pregnancy, however, carries a potential risk to the fetus. Indomethacin can cause premature closure of the ductus arteriosus,¹ which may lead to serious fetal and neonatal complications including oligohydramnios, hyperbilirubinemia, pulmonary hypertension, necrotizing enterocolitis and intraventricular hemorrhage.^{2,3} Diclofenac (*Voltaren*), closely related to indomethacin, is one of the group used to treat pain and fever, and it may cause the same fetal and neonatal complications.

CASE

A 37-year-old Saudi woman had an uneventful pregnancy until 38 weeks gestation when she was operated on for thrombosed hemorrhoids. She was given diclofenac sodium for pain, 50 mg orally three times a day. After 3 days she noticed decreased fetal movement. Subsequently, oligohydramnios and fetal distress developed, which led to cesarean section. The baby weighed 2900g. Soon after birth the baby developed severe respiratory distress and cyanosis. After a trial of aggressive ventilation for severe hypoxemia at the referring hospital, she showed no improvement. Oxygen saturation was 60% on FiO₂ of 100% and her oxygen index (OI) was 40. She was resuscitated and transferred to our institution at 20 hours of age. An echocardiogram done at the referral hospital and repeated in our center revealed right ventricular hypertrophy, moderate tricuspid regurgitation, closed ductus arteriosus and severe pulmonary hypertension. A high frequency oscillatory ventilator (HFOV), dopamine, dobutamine and milrinone all failed to improve oxygen saturation.

Inhaled nitric oxide (iNO) at 20 ppm also resulted in no improvement. After 2 days, sildenafil was added as adjunctive therapy at 0.15 mg orally every eight hours. Within 24 hours oxygen saturation improved to 88% and the OI declined to 15 (Figure 1). iNO was weaned and then completely discontinued. Sildenafil was given for 2 weeks. The baby was discharged in excellent condition at 3 weeks of age. Two weeks later, the echocardiogram was normal.

DISCUSSION

The pathophysiology leading to pulmonary hypertension in our patient is most likely related to NSAID exposure in late gestation. The patency of the ductus arteriosus is maintained in utero with dilatatory prostaglandins such as (prostaglandin E). Closure of the fetal ductus arteriosus in utero can be either spontaneous or due to pharmacological agents such as NSAIDs.⁴ It usually begins with progressive constriction of the vessel walls, which initially leads to very high flow velocities from the pulmonary trunk towards the descending aorta.⁵ In cases with severe constriction or closure, the ductus arteriosus can no longer function as a conduit of right ventricular flow into the descending aorta. More blood is directed to the pulmonary arteries, which leads to pulmonary hypertension.¹ Although most studies involved indomethacin in animal models, Mommas et al,⁶ who studied the effect of various NSAIDs on the ductus of fetal rats, demonstrated that diclofenac exerts an equally severe constrictive action as indomethacin. Thus, fetal exposure in late gestation provides the likely explanation for increased susceptibility to irreversible ductal constriction followed by severe pulmonary hypertension in our patient. Zenker et al reported a similar case where he used iNO alone. It required 22 days

Figure 1. Average oxygen index and oxygen saturation in the neonate over first 2 weeks of life.

for pulmonary hypertension to be controlled and the patient subsequently developed papillary muscle necrosis.⁶ Our patient was perfectly healthy at discharge and at follow up in 4 weeks.

Our experience replicates those reported by Kandavello et al and Atz et al, where sildenafil had an augmentation effect and prevented a rebound pulmonary hypertension or hypertensive crisis during weaning of nitric oxide. The addition of sildenafil led to a shorter duration of therapy and minimized the possible damaging effects of pulmonary hypertension and its

complications.^{7,8}

When pulmonary hypertension occurs, early transfer to a tertiary care center with the availability of nitric oxide should take place as soon as possible. In severe cases with pulmonary hypertension with suboptimal response to iNO, adjunctive therapy with sildenafil should be considered. Our experience and that of others^{8,9} should be confirmed by randomized double blind controlled studies to prove the safety and efficacy of sildenafil in neonates. Pregnant women should be instructed not to use NSAIDs during pregnancy.

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