Hypertension in a preterm after indomethacin use for patent ductus arteriosus

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(Received: December 25, 2019 Accepted: March 18, 2020)

Abstract
Non-steroidal anti-inflammatory drugs have been associated with hypertension in adults. We report an infant who developed hypertension after indomethacin use for patent ductus arteriosus. The patient was delivered at 31 weeks’ gestation. Patent ductus arteriosus was detected on day 2. Indomethacin was given intravenously from day 2 to day 6. The ductus arteriosus was closed on day 7. On day 8, urine output decreased and serum creatinine increased. With fluid restriction, however, body weight remained the same from day 7 to day 14. Blood pressure increased to 82/41 mmHg on day 13 and became 90/58 mmHg on day 14 despite an increase in urine output. Cardiac ultrasonography suggested high afterload. With the use of nitroglycerin, blood pressure normalized on day 17. While non-steroidal anti-inflammatory drug-induced hypertension in adults has been ascribed to renal vasoconstriction and resultant sodium retention, the major cause of hypertension in our case was thought to be high afterload due to increased peripheral vascular resistance presumably secondary to decreased synthesis of prostaglandin I₂.

Introduction
Hypertension is a known complication of non-steroidal anti-inflammatory drugs (NSAIDs) in adults¹. However, it has rarely been reported in children. In a retrospective study of neonates diagnosed with hypertension, indomethacin treatment for patent ductus arteriosus (PDA) was described to be associated with the development of hypertension². It is reported that medical PDA closure is usually associated with an increase in systemic blood pressure³. The clinical course and laboratory findings of such cases, however, have not been described. We report a preterm infant who developed hypertension after the administration of indomethacin for PDA. Although our case had preceding acute kidney injury (AKI) due to indomethacin, hypertension developed after urine output started to increase. While NSAID-induced hypertension in adults has been ascribed to renal vasoconstriction and subsequent sodium retention⁴, the major mechanism of hypertension in our case was thought to be high afterload due to increased vascular resistance, presumably induced by the inhibition of vascular prostaglandin I₂ (PGI₂) synthesis.

Case Report
The patient was delivered at 31 weeks’ gestation via caesarean section for placenta previa. Apgar score was 6 and 7 at 1 and 5 min, respectively. Birth weight was 1676 g. He was intubated and treated with surfactant for respiratory distress syndrome. He was extubated on day 1, when PDA was detected. The clinical course is depicted in Fig. 1. Heart murmur, hyperactive precordium and bounding peripheral pulses became evident on day 2. Indomethacin 0.2 mg/g/dose was given intravenously from day 2 to day 4. On day 5, the ductus arteriosus was still patent. Since urine output was maintained (2.4 ml/kg/hr) and the elevation of serum creatinine was moderate (from 0.62 mg/dl on day 0 to 1.05 mg/dl on day 5), indomethacin was readministered on day 5 and 6. On day 7,
Hypertension developed after urine output started to increase with a decrease in serum creatinine and body weight. IVH, intraventricular hemorrhage.

the ductus arteriosus was closed. On day 8, urine output decreased to 0.8 ml/kg/hr and fluid was restricted to 60 ml/kg/day. Urine output started to increase on day 9. Serum creatinine decreased to 0.91 mg/dl on day 13. Body weight did not change from day 7 to day 13. Blood pressure was 62/26 on day 7 and did not change until day 12. On day 13, blood pressure increased to 82/41 mmHg and became 90/58 mmHg on day 14 despite a decrease in body weight. At that time, body temperature was 36.8°C, heart rate 140 beats per min, respirations 45 per min. The physical examination was unremarkable. Edema was not detected. The white blood cell count was 16,250/µl, the red cell count 4,370,000/µl, hematocrit 39.2%, hemoglobin 14.6 g/L, and platelet count 179,000/µl. Blood urea nitrogen was 2.5 mg/dl, creatinine 0.41 mg/dl, calcium 9.2 mg/dl, phosphorus 3.8 mg/dl, sodium 130 mmol/L, potassium 4.3 mmol/L, chloride 101 mmol/L, uric acid 1.0 mg/dl, TP 4.7 g/dl, albumin 3.0 g/dl, glucose 135 mg/dl, NT-pro BNP 18210 pg/dl (reference range<2086), plasma renin activity 1.1 ng/ml/hr (reference range 7.4±3.74, mean±SD), aldosterone 38.2 ng/dl (reference range 52.19±23.49, mean±SD). The venous gas showed pH 7.288, pCO2 32.3 mmHg, bicarbonate 16.3 mmol/L, and anion gap 5.7 mmol/L. Urinalysis revealed pH 6.0, negative protein, glucose 3+, and negative blood. Urine sodium was 107 mmol/L, potassium 15 mmol/L, and chloride 84 mmol/L. The urine anion gap was 38 mmol/L, fractional excretion of sodium (FENa) 7.3%, tubular reabsorption of phosphate 61.5%, and fractional excretion of uric acid (FEUA) 64.1%. Cardiac ultrasonography showed mean velocity of circumferential fiber shortening of 0.6 circ/s and end-systolic wall stress of 119.3 g/cm² indicating after load mismatch. Ultrasonography of the brain revealed no intraventricular hemorrhage. Nitroglycerin and sodium bicarbonate infusion was started. On day 15, ultrasonography revealed left grade 1 intraventricular hemorrhage. The venous pH and bicarbonate concentration normalised on day 16, and sodium bicarbonate was discontinued on day 16. Blood pressure also normalized and nitroglycerin was discontinued on day 17.

**Discussion**

We described a preterm infant with transient hypertension after the use of indomethacin for PDA. Our hypothesis for the mechanism of his hypertension is depicted in **Fig. 2**. Sodium retention due to decreased renal prostaglandin E2 synthesis, as has been described in adults with NSAID-induced hypertension, was thought to be one of the causes of hypertension in our patient. Reduced glomerular filtration rate due to the use of indomethacin resulted in the state of AKI. Body weight, although did not increase before and during hypertension, decreased with the resolution of hypertension suggesting fluid overload despite sodium and fluid restriction. Hypertension, however, became severe after urine output started to increase in association with a decrease in serum creatinine and body weight. The major mechanism of hypertension in this case, therefore, is thought to be high afterload, as evidenced by cardiac ultrasonographic findings. The high afterload is presumably due to increase in peripheral vascular resistance caused by decreased PGI2 synthesis secondary to indomethacin (**Fig. 2**). Intraventricular hemorrhage is known to cause hypertension5. In our patient, however, intraventricular hemorrhage occurred after hypertension developed. Therefore it is probably the result rather than the cause of hypertension.

NSAID-induced hypertension is generally considered to result from reduction in PGE2 synthesis8 (**Fig. 2**). PGE2, a vasodilator, dilate pre-glomerular afferent arterioles. It increases renal blood flow inducing an increase in urinary sodium excretion. Reduction in PGE2 synthesis by NSAIDs, therefore, causes sodium retention both by directly affecting tubules and indirectly by reducing GFR7. PGI2, on the other hand, promotes vascular smooth muscle cell vasodilatation. Reduction in PGI therefore leads to high afterload9.
Hypertension due to decreased PGI2 biosynthesis is a well-known cause of preeclampsia.\(^9\)\(^10\).

In our patient, hypertension persisted for approximately one week after the last indomethacin administration. Indomethacin’s half-life is reported to be ~20 hrs in neonates, and renal clearance contributes to 15 to 20% of indomethacin elimination.\(^11\) It is reasonable, therefore, to assume that the half-life becomes longer with renal dysfunction. Moreover, a previous study demonstrated that daily indomethacin administration increases the serum concentration.\(^12\) We injected indomethacin for 5 consecutive days. The cumulative effect may explain the sustained hypertension. Lastly, toxicity of indomethacin is reported to be related to sustained tissue concentrations rather than serum levels.\(^12\).

An alternative explanation for the long duration of action of indomethacin is that gene polymorphisms for drug metabolizing enzymes. CYP2C9 catalyzes the biotransformation of indomethacin to its inactive metabolite O-desmethylinindomethacin.\(^13\) CYP2C9 polymorphisms has been shown to result in individual variation of the half-life of indomethacin.\(^12\).

Plasma renin activity and aldosterone were suppressed in our patient, which was thought to reflect the increased body fluid volume despite fluid restriction. Alternatively but not mutually exclusively, suppressed renin could be due to the inhibition of PGE2 synthesis. PGE2 in macula densa cells has been shown to release renin from juxtaglomerular cells through EP4 receptor.\(^14\)

Neonatal hypertension is an uncommon but important complication in intensive care units. In a retrospective review, antenatal steroid administration, maternal hypertension, umbilical arterial catheterization, postnatal AKI, PDA, indomethacin use, and chronic lung disease were associated with the development of neonatal hypertension.\(^15\) The mechanism of hypertension associated with PDA was postulated to be due either to thromboembolism of renal artery or indomethacin treatment.\(^15\). In our patient, indomethacin-induced PGI2 synthesis inhibition may be the major cause of hypertension since it developed after the recovery of AKI.

**Conclusion**

In summary, we report a preterm infant with transient hypertension after the use of indomethacin for patent ductus arteriosus. Unlike NSAID-induced hypertension in adults, decreased PGI2 synthesis may be the major cause. Although relatively unknown compared to AKI, hypertension can occur after the use of indomethacin for PDA in a preterm newborn.

**Compliance with ethical standards**

**Conflict of Interest**

The authors have declared that no conflict of interest exists.

This article does not contain any studies with animals performed by any authors.

Informed consent was obtained from the parents of the patient.

**Financial Disclosures**

No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

**References**

1) Morrison A, Ramey DR, van Adelsberg J, Watson DJ: Systematic review of trials of the effect of continued use of oral non-selective NSAIDs on blood pressure and hypertension. Curr Med Res Opin 2007; 23: 2395–2404.
2) Seliem WA, Falk MC, Shadbolt B, Kent AL: Antenatal and postnatal risk factors for neonatal hypertension and infant follow-up. Pediatr Nephrol 2007; 22: 2081–2087.
3) Evans N, Iyer P: Change in blood pressure after treatment of patent ductus arteriosus with indomethacin. Arch Dis Child 1993; 68: 584–587.
4) White WB: Cardiovascular effects of the cyclooxygenase inhibitors.
5) Fodstad H, Kelly PJ, Buchfelder M: History of the cushing reflex. Neurosurgery 2006; 59: 1132–1137; discussion 1137.
6) Kawada N, Moriyma T, Kitamura H, Yamamoto R, Furumatsu Y, Matsui I, Takabatake Y, Nagasawa Y, Imai E, Wilcox CS, Rakugi H, Isaka Y: Towards developing new strategies to reduce the adverse side-effects of nonsteroidal anti-inflammatory drugs. Clin Exp Nephrol 2012; 16: 25–29.
7) Yang T, Du Y: Distinct roles of central and peripheral prostaglandin E2 and EP subtypes in blood pressure regulation. Am J Hypertens 2012; 25: 1042–1049.
8) Fetalvero KM, Martin KA, Hwa J: Cardioprotective prostacyclin signaling in vascular smooth muscle. Prostaglandins Other Lipid Mediat 2007; 82: 109–118.
9) Wang YP, Walsh SW, Guo JD, Zhang JY: The imbalance between thromboxane and prostacyclin in preeclampsia is associated with an imbalance between lipid peroxides and vitamin E in maternal blood. Am J Obstet Gynecol 1991; 165: 1695–1700.
10) Crews JK, Herrington JN, Granger JP, Khalil RA: Decreased endothelium-dependent vascular relaxation during reduction of uterine perfusion pressure in pregnant rat. Hypertension 2000; 35: 367–372.
11) Alcorn J, McNamara PJ: Ontogeny of hepatic and renal systemic clearance pathways in infants: part I. Clin Pharmacokinet 2002; 41: 959–998.
12) Emori HW, Paulus H, Bluestone R, Champion GD, Pearson C: Indomethacin serum concentrations in man. Effects of dosage, food, and antacid. Ann Rheum Dis 1976; 35: 333–338.
13) Shah M, Xu M, Shah P, Wang X, Clark SM, Costantin M, West HA, Nanovskaya TN, Ahmed MS, Abdel-Rahman SZ, Venkataramanan R, Caritis SN, Hankins GDV, Ryting E: Effect of CYP2C9 polymorphisms on the pharmacokinetics of indomethacin during pregnancy. Eur J Drug Metab Pharmacokinet 2019; 44: 83–89.
14) Facemire CS, Nguyen M, Jania L, Beierwaltes WH, Kim HS, Koller BH, Coffman TM: A major role for the EP4 receptor in regulation of renin. Am J Physiol Renal Physiol 2011; 301: F1035–1041.
15) Flynn JT: Hypertension in the neonatal period. Curr Opin Pediatr 2012; 24: 197–204.