

RENAL FAILURE AND PERSISTENT HYPERTENSION IN A CHILD PRENATALLY EXPOSED TO LOSARTAN

Cinzia AURITI, Fiammetta PIERSIGILLI, Gabriella MARROCCO,
Mary HAYWOOD LOMBARDI, Andrea DOTTA

Department of Neonatology
Bambino Gesù Children's Hospital IRCCS
Rome, Italy

Corresponding author:

Cinzia Auriti
Department of Neonatology
Sub Intensive Care Unit
Bambino Gesù Children's Hospital IRCCS
Piazza S. Onofrio 4 - 00165
Rome, Italy
cinzia.auriti@opbg.net
c.auriti@agtgroup.it
Tel.: + 39 066 8592 346
Fax.: + 39 066 8592 832

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E-mail for permission to publish:
paediatrictoday@ukctuzla.ba

Objective – To underline the fetal kidney toxicity of losartan, an angiotensin receptor blocker (ARB), administered to a woman during pregnancy. **Case report** – We describe a male infant, prenatally exposed to losartan from week 32 of gestation, born at term by cesarean section due to maternal hypertension and oligohydramnios. The baby was admitted to the NICU of our hospital for anuria; he required peritoneal dialysis and survived the neonatal period. Presently, the child is 24 months old and is affected by severe chronic renal failure, failure to thrive and persistent hypertension. **Conclusions** – Although ARBs are recommended as first line antihypertensive agents, their administration should be avoided during pregnancy, especially from the second trimester onward. Most fetuses, affected by ARB toxicity, progress to death. The few that survive show serious outcomes. If a pregnant woman is under antihypertensive treatment with ARB, this has to be discontinued and replaced as soon as possible, and especially within the second trimester of pregnancy. Obstetricians should also be alerted of the potential risks of ARB administration beyond the first trimester of gestation.

Key words: Angiotensin receptor blockers ■ Neonatal renal failure ■ Angiotensin converting enzyme inhibitors.

Introduction

The renin-angiotensin system (RAS) plays an important role in the regulation of the cardiovascular system and the homeostasis of body fluids. In addition to these physiological functions, RAS has other biological effects, such as cellular proliferation in the fetal kidney. Angiotensin II promotes cellular growth via angiotensin II type 1 receptor (AT1 receptor). This function is essential for the development of the kidney, especially in later

fetal life. Drugs that have inhibitory activity on RAS may reduce nephron endowment, seriously impeding the normal development of the kidneys, and predispose to renal failure and hypertension in adulthood. Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptors blockers (ARBs) control hypertension by interrupting the production or action of angiotensin II, the major end-product of RAS. ARBs, as well as ACE-Is, are currently recommended as first line antihypertensive agents (1). Nevertheless, research

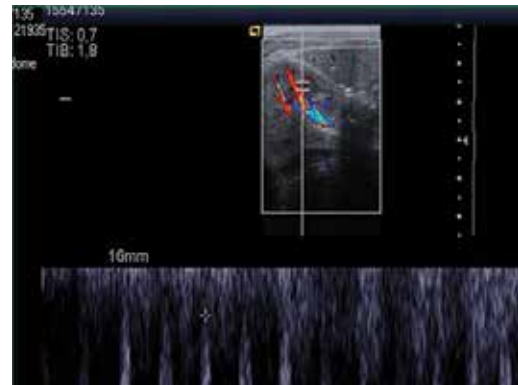
carried out on animals and observations in humans recommend that their administration should be avoided in women during pregnancy. Many authors have described the association between maternal treatment with ARBs in pregnancy, fetal renal failure and oligohydramnios, resulting in severe oligo-anuria, pulmonary hypoplasia, and congenital abnormalities of the skeleton and skull in the newborn (2-6). We report a case of adverse neonatal outcomes in a hypertensive pregnant woman exposed to losartan in the last trimester of gestation.

Case report

A 2320 g male infant, born at 38 weeks of gestational age by cesarean section due to maternal hypertension and oligohydramnios, was admitted to our NICU on the second day of life (DOL) for acute renal failure. Pregnancy was complicated by maternal hypertension treated initially with alpha-methyldopa 250 mg twice daily, progressively increased to 750 mg twice daily. Due to insufficient control of hypertension, losartan 50 mg twice daily was added at week 32 of gestation. At 36 weeks a fetal ultrasound revealed oligohydramnios.

At birth, the newborn was in good health condition, with Apgar scores 8 and 9 at 1 and 5 minutes, respectively, and he was admitted to the nursery. At 48 hours of life the baby was still anuric and showed elevated levels of serum creatinine (5.6 mg/dl), blood urea nitrogen (BUN 25 mg/dl) and potassium (7 mEq/l). Therefore, he was referred to our NICU. A renal ultrasound revealed bilateral renal length of 4.5 cm and parenchymal thickness of 9 mm, increased cortical echogenicity and decreased corticomedullary differentiation. Despite an initial improvement in urine output, after Albumin 5% and Furosemide administration, the renal function worsened (creatinine 6.7 mg/dl, BUN 35 mg/dl, potassium 7 mEq/l), requiring peritoneal dialysis

by DOL 7. Creatinine improved to 2.5 mg/dl, BUN to 13 mg/dl and potassium to 4.8 mEq/l; however, on DOL 11, the baby developed *Pseudomonas aeruginosa* peritonitis that required antibiotic therapy. On DOL 20, oral nifedipine was initiated for hypertension, (SBP 110-135, DBP 70-90 mmHg), and Doppler ultrasound showed increased renal artery resistance (Resistive Index 0.9-1) (Fig. 1).



Color version available online.

Fig. 1 Doppler ultrasound exam of the kidney at day of life 20 shows increased renal artery resistance and a decreased representation of intraparenchymal flow signals. On color Doppler the intraparenchymal resistive index ranges between 0.9 and 1 (normal values 0.6 ± 0.01) (12), especially in the sub capsular region of the kidney.

Dialysis was stopped on DOL 27. An X-ray of the skull, upper and lower limbs excluded abnormalities; the echocardiography was normal. Upon discharge, on DOL 65, the baby was clinically stable under therapy, with feeding difficulties and tendency to vomit. Growth assessment showed weight 3.480 g, height 50 cm and head circumference 35 cm. All measurements were below the 3th percentile. SBP was 80 and DBP 42 mmHg (mean 64 mmHg). Laboratory tests, showed moderate anemia (Hb 8.8 g/dl, RBC $3.430.000/\text{mm}^3$, WBC $14.870/\text{mm}^3$, Plts $552.000/\text{mm}^3$), a creatinine level of 1.81 mg/dl (range 0.2-0.8), BUN 14 mg/dl (range 5-18), sodium 141mEq/l (range 136-145),

potassium 5.97 mEq/l (range 3.5-5.1), calcium 10.6 mg/dl (range 8-10.5), phosphorus 7 mg/dl (range 3-6). The arterial blood gas analysis showed pH 7.37 (range 7.32-7.48), pCO₂ 37.5 mmHg (range 32-48), pO₂ 92.2 mmHg, HCO₃ 21.6 mmol/l (range 19-27), Bases excess -3.2 mmol/l (range -2/+3). Urine had a specific gravity of 1005. Urinalysis reflected increased protein excretion: 29 mg/dl (range 0-15) with protein/creatinine ratio of 4.14 (range 0-0.15) and loss of bicarbonates. Therefore, the baby was discharged with ongoing therapy with amlodipine 0.3 mg twice/day, as well as calcitriol 0.25 micrograms three times/day, kayexalate 3 g by rectal route three times/day, and salts supplementation (NaHCO₃ 3 mEq six times/day, Calcium carbonate 50 mg six times/day), SC erythropoietin 1000 IU three times/week.

At follow-up, performed at 12 months of age, the baby still showed persistent hypertension, despite therapy with amlodipine, the antihypertensive therapy was replaced with carvedilol 0.6 mg twice/day and nifedipine 1 drop in case of arterial systolic pressure >100 mmHg. Renal ultrasound performed at the same time showed right renal length of 4.3 cm, with a parenchymal thickness of 8 mm and left renal length of 4.6 cm with a parenchymal thickness of 9.5 mm, as well as increased cortical echogenicity and decreased corticomedullary differentiation.

Presently, the child is 24 months old, at the 3rd centile for weight (12.5 kg) and height (83 cm) and, presents severe feeding difficulties, for which he is under rehabilitation treatment. His chronic renal failure is severe, with salt wasting and hypertension. Renal ultrasound shows bilateral reduction of renal size. Blood laboratory exams show serum creatinine 2.54 mg/dl, BUN 31 mg/dl potassium 4.24 mEq/l, sodium 140 mEq/l, calcium 11 mg/dl. Blood gas analysis shows pH 7.40, HCO₃ 28 mmol/l, bases excess -3.2 mmol/l. The child requires oral salts supplementation,

NaCL 4 mEq and NaHCO₃ 6 mEq, three times/day, calcitriol 0.25 micrograms/day, allopurinol 25 mg once/day, and antihypertensive therapy with ramipril (Triatec Aventis Pharma ®) 0.25 mg two times/day. His BP under antihypertensive therapy is 83/52.

Discussion

ARBs and ACE inhibitors alter the renin-angiotensin aldosterone system, which plays a central role in renal cellular proliferation during fetal life (7). In fact, angiotensin receptors AT1 and AT2 are expressed from the 24th day of gestation. AT1 receptors mediate the effects of angiotensin II on cell growth by inducing the secretion of the Tissue Growth Factor-beta 1 (8). AT2 receptors are expressed in the undifferentiated mesenchymal tissue and are responsible for the regulation of renal tubular development; their activation may influence proximal tubule sodium reabsorption (9). ARBs and ACE inhibitors administered to rats during fetal life can induce renal histological abnormalities, such as papillary atrophy, tubulo-interstitial fibrosis and tubular atrophy, resulting in suppression of fetal renal function and subsequently leading to oligo- or anhydramnios. Finally, fetal hypotension, resulting from maternal treatment with AT1 antagonist receptors and/or ACE inhibitors, may cause fetal renal hypoperfusion, leading to decreased glomerular filtration pressure, oligo-anuria and consequent oligohydramnios. Most fetuses affected by ARBs toxicity progress to death (2). The compression of the fetal chest wall, the restriction of the fetal breathing movements, and the decrease in the intrapulmonary pressure all together probably play a significant role, because oligohydramnios is responsible for severe pulmonary hypoplasia, especially if it is severe and prolonged over. Deformities of limbs, joint contractures and skull bone hypoplasia have also been described after pre-

natal exposure to ARBs. The mechanism by which maternal treatment with ARBs cause hypoplasia of the fetal skull bones is not yet clear, but a combination of oligohydramnios and fetal hypotension with poor peripheral perfusion of superficial tissues may be involved (5). If the fetal exposure is of limited duration, renal injury may be reversible, and discontinuation of therapy results in restoration of an adequate amniotic fluid volume (10). Nevertheless, if such babies survive the neonatal period, they will later suffer from salt wasting, nephrogenic diabetes insipidus and failure to thrive (3). Not only experimental studies, but also case reports have shown that prenatally exposed children may develop hypertension later in life, even in the absence of neonatal problems. The blockade of the RAS with sartans in normal rats for the first 12 days after birth (the latter portion of nephrogenesis) leads to a reduced number of nephrons and hypertension in adulthood (11). Nevertheless, the information on long-term outcome in children is limited because very few infants with ACE inhibitors and ARB fetopathy survive.

In the case we reported, the fetus was exposed to 100 mg/day losartan in the last six weeks of gestation, when nephrogenesis is in progress. As a consequence of the maternal treatment, the baby developed severely impaired renal function during fetal life and just after birth, but survived. To date, the child is affected by chronic kidney failure, severe growth retardation, chronic hypertension, thus requiring regular therapy.

Conclusion

ARB administration during pregnancy is associated with severe adverse effects on the fetal development, especially on the development of kidneys. If a pregnant woman is under antihypertensive treatment with ARBs, this has to be discontinued and replaced as

soon as possible and, certainly within the second trimester of pregnancy. Obstetricians should also be aware of the potential risks of ARB administration throughout gestation, as this antihypertensive treatment must be replaced by drugs with less toxicity to the fetus, as soon as pregnancy is confirmed. Obstetricians have also be alerted that in cases of oligo or anhydramnios they should ask the patient for her drug history regarding recent ARB exposure as a potential cause. Finally pregnant women who have been treated with these agents during the second or third trimester of pregnancy should be referred to tertiary care centers for delivery.

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Conflict of interest: The authors declare that they have no conflict of interest.

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