Perinatal/Neonatal Case Presentation

Neonatal Acute Renal Failure Secondary to Maternal Exposure to Telmisartan, Angiotensin II Receptor Antagonist

Christine Pietrement, MD
Lilia Malot, MD
Brigitte Santerne, MD
Bernard Roussel, MD
Jacques Motte, MD
Patrice Morville, MD

Fetal and neonatal toxic effects of angiotensin II receptor antagonists have been described in animals and humans. Five cases of fetal or neonatal deaths have been reported following maternal use of sartans for hypertension. We report a case of neonatal transient renal failure following telmisartan therapy during pregnancy. This class of antihypertensive drugs should be avoided during pregnancy and breastfeeding.
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INTRODUCTION

The treatment of maternal hypertension by angiotensin-converting enzyme (ACE) inhibitors during pregnancy has been associated with fetal and neonatal mortality and morbidity.[1,2] A few cases in the literature report death in fetuses and in newborn infants associated with the maternal use of sartans. Sartans are a new class of antihypertension drugs that directly inhibit the type 1 subtype of angiotensin II receptors. We report a case with neonatal survival despite early neonatal failure.

CASE REPORT

In a 35-year-old hypertensive woman treated by telmisartan (40 mg/day), pregnancy on coil was recognized after 4 months and telmisartan was not discontinued. Pregnancy follow-up was normal until 33 weeks' gestation (GA) when oligohydramnios were noticed. Delivery by cesarean section occurred at 34 weeks GA due to pre-eclampsia. At birth, the baby — a 2.2 kg girl — presented no respiratory or cardiovascular distress. The Apgar score was 9–10–10 at 1, 5 and 10 minutes. During the first 48 hours, she received 60 cm^3/kg/day of premature formula. At day 2, urinary output was nil and renal function was assessed: serum creatinine concentration 4.3 mg/dl, blood urea 60 mg/dl, potassium 4.7 mmol/l. She was referred to a level III unit at day 2. She weighed 2.2 kg and her blood pressure was normal. Complete physical examination was normal. Renal Doppler and ultrasound examinations were normal. Furosemide did not increase urinary output. Oral formula intakes were limited to 60 cm^3/kg/day. Urine production started spontaneously on day 3 (0.3 cm^3/kg/h), increasing progressively, without polyuria. Proteinuria (0.6 g/l) and glycosuria with euglycemia led to the diagnosis of tubulopathy without hematuria, requiring bicarbonate and magnesium supplementation. The maximum serum creatinine level was 5.8 mg/dl at day 4. Telmisartan plasma level was assessed only on days 10 and 13, respectively at 20 and 13 ng/l. Renal function and tubulopathy progressively improved, with a serum creatinine concentration of 0.8 mG/dl at discharge day 18 and 0.55 mG/dl at 1.5 months. We conclude that the acute renal failure was secondary to telmisartan maternal exposure.

DISCUSSION

Telmisartan is a specific angiotensin II type 1 (AT1) receptor antagonist used for adult hypertension therapy. It is strongly bound to protein (more than 99.5%) and conjugated in the liver to an inactive acylglucuronide. Most of the drug is eliminated in the feces, via biliary excretion (>97%). As renal excretion does not contribute to the clearance of telmisartan, dose reduction is unnecessary in patients with renal disease. Telmisartan is not removed by dialysis. Studies during breast-feeding have not been performed. Telmisartan adult half-life is 20–24 hours. Clearance is expected to be slower in neonates because of liver immaturity, especially in premature infants. The approximate serum half-life using levels at days 10 and 13 indicated an estimate of 116 hours.

In rats, after intrauterine exposure to losartan, pups have a lower weight and higher mortality rate compared to non-exposed rats. Exposed newborn rats also present irreversible histological renal damages such as dilatation of the renal pelvis, edema of the renal papilla, medial hypertrophy of intracortical arterioles, chronic renal inflammation and irregular scarring of the renal parenchyma. The critical period for losartan-induced

Department of Pediatrics, American Memorial Hospital, Reims, France.

Address correspondence and reprint requests to Patrice Morville, MD, Service de Pédiatrie, American Memorial Hospital, 49 Rue Cognacq Jay, 51092 Reims Cedex, France.

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developmental toxicity is gestation day 15 through lactation day 20, while the critical period for losartan-induced renal lesions is gestation days 15–20.[3] As both fetal development of the renin–angiotensin system and the critical period for losartan-induced renal lesions take place approximately at gestation day 17, these data support the hypothesis that the observed adverse fetal and neonatal effects are pharmacologically mediated, presumably through the lack of AT1 subtype of angiotensin II receptor stimulation.[4]

Five cases of fetal deaths and one neonatal death at day 4, with persistent anuria, have recently been reported.[5–7] Each case was exposed during the first part of gestation. All cases presented severe oligohydramnios. Three fetuses had foot and face deformities of the oligohydramnios sequence, and skull bones were hypoplastic as in ACE inhibitor toxicity. Autopsies in these five cases demonstrated pulmonary hypoplasia in only one patient. The kidneys were enlarged with tubular dysgenesis, retraction of glomerular tufts and thickening of arteries. Our case and those in the literature suggest similar adverse effects of angiotensin-II-receptor inhibitor antagonists and ACE inhibitors. They include a spectrum of adverse effects from fetal death to transient renal failure. Our case, though presenting the longest exposure so far, exhibited the best outcome. Thus the duration does not seem to be a relevant prognostic criterion.

Warnings against the use of AT1 selective angiotensin receptor antagonists during pregnancy have been widely published.[8,9] In France, these recommendations are clearly spelt out in the Dictionnaire Vidal (French physician drug index),[10] and in the notices enclosed in the medication packaging. We emphasize the necessity for physicians to check possible adverse effects when prescribing drugs to pregnant women.

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