CASE REPORT

Neonatal acute kidney injury following Valsartan exposure in utero: report of two cases

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Abstract

Background: Maternal sartan intake during pregnancy has been associated with several fetal/neonatal complications related to disturbed renal development.

Description of cases: We present two cases of neonatal acute kidney injury (AKI) following valsartan administration during pregnancy and provide evidence for the use of novel AKI biomarkers in these neonates. The first case was a female neonate, delivered at 32+4 weeks of gestation after maternal valsartan intake from 24 to 32 gestational weeks. In the second case, ultrasound examination revealed a growth-restricted fetus with severe oligohydramnios following maternal valsartan intake during the first 29 gestational weeks. In the absence of any improvement in amniotic fluid, the neonate was born at 31+5 weeks. In both cases, AKI was documented after birth, but renal function progressively recovered. Urine cystatin-C and neutrophil gelatinase-associated lipocalin were found abnormally increased during the first week of life.

Conclusion: Sartan use during pregnancy is associated with the development of neonatal AKI. Novel urine biomarkers may be used to document renal injury. Hippokratia 2016, 20(1): 73-75

Keywords: Valsartan, pregnancy, neonate, cystatin-C, neutrophil gelatinase-associated lipocalin

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Introduction

Sartans are angiotensin (AT) II receptor antagonists (ARAs) that inhibit the binding of angiotensin II to AT1 receptors[1]. Several reports have described fetal complications due to maternal sartan intake during pregnancy[2,3], and this class of drugs has been assigned to pregnancy category D by the FDA. Fetal side-effects of sartans range from transient oligohydramnios and intrauterine growth restriction to renal failure and prolonged anhydramnios with its sequelae including skeletal deformities, pulmonary hypoplasia, and fetal-perinatal death[2-6]. Herein, we report two cases of infants developing acute kidney injury (AKI) after exposure to valsartan, as documented by serum creatinine and the use of novel AKI biomarkers such as urine cystatin-C and neutrophil gelatinase-associated lipocalin (NGAL)

Case 1

A female neonate weighing 1,660 g was delivered by cesarean section at 32+4 weeks to a G2 P1 mother who had been receiving valsartan (160 mg/day) for the preceding two months prior to delivery due to gestational hypertension; maternal systolic/diastolic blood pressure at the

Table 1. Serial measurements of serum creatinine and urine biomarkers in two neonates with neonatal acute kidney injury following valsartan administration during pregnancy.

		Day of life						
Biomarker	**Case**	**1**	**2**	**5**	**7**	**10**	**15**	**18**
Creatinine (mg/dL)	1	0.8	2.6	5.3	3.94	2.7	1.3	0.9
	2	0.9	-	1.58	1.45	-	-	0.5
Cystatin-C (ng/mL)	1	406.4	430.4	-	232	-	-	-
	2	472.2	-	-	461.6	-	-	-
NGAL (ng/mL)	1	21.58	20.65	-	22.97	-	-	-
	2	20.7	-	-	20.18	-	-	-

NGAL: Neutrophil gelatinase-associated lipocalin, - : measurement was not performed.

day of delivery was 128/79 mmHg. The second-trimester ultrasound scan was normal, whereas growth scan during the third trimester detected intrauterine growth restriction and oligohydramnios. The neonate only required routine care at birth (Apgar scores 7 and 8 at 1 and 5 min, respectively) and no congenital abnormalities were noticed at clinical examination. However, the neonate manifested anuria and increasing serum creatinine reaching maximal value on the 5th day of life (5.31 mg/dL) (Table 1). Ultrasound examination on the second day of life showed hyperechoic kidneys. AKI was conservatively managed, whereas renal function progressively recovered as proved by the normalization of diuresis and the decrease in serum creatinine to normal by the 20th day of life. The infant was discharged home on the 41st day of life.

Case 2

A woman with chronic hypertension received valsartan plus hydrochlorothiazide up to the 29th week of gestation without being aware of her pregnancy. Ultrasound examination at 29 weeks revealed a small for gestational age fetus and severe oligohydramnios (amniotic fluid index: 2 cm). Of note, fetal kidneys had normal size, structure, and echogenicity. Antenatal corticosteroids were given, and the fetus was followed-up for potential resumption of the renal function. In the absence of any improvement in amniotic fluid volume, a cesarean section was performed at 31+5 weeks. Maternal systolic/diastolic blood pressure at birth was 137/83 mmHg. A female infant weighing 1,610 g was delivered and the Apgar scores were 6 and 9 at 1 and 5 min, respectively. Renal ultrasound showed hyperechoic kidneys and loss of the corticomedullary differentiation. Diuresis was unaffected postnatally, and maximal serum creatinine (1.72 mg/dL) was observed on the forth day of life (Table 1).

In both cases, urine cystatin-C and NGAL were assessed during the 1st week of life using enzyme-linked immunosorbent assays (Quantikine® Human Cystatin-C, Quantikine® Human Lipocalin-2/NGAL, R&D Systems Europe, Inc., Abingdon, UK). Based on the results of studies published previously by our group of investigators[7,8], levels of cystatin-C and NGAL during the first days of life were abnormally increased (Table 1). Obviously, no statistics could be calculated, given the extremely small number of neonates.

Discussion

Although sartans do not directly cause major malformations to the fetus[3,9], the continuation of their use during the second and third trimester may cause fetal renal impairment. Depending on the extent of kidney injury, clinical manifestations vary from transient oligohydramnios to prolonged anhydramnios[6]. Fetal hyperechogenic kidneys indicating serious renal disease[10] have been reported following maternal ARA administration[1,4]. Interestingly, oligohydramnios may be reversed if treatment is discontinued[6,11]. As this was not observed in our cases, and given the intrauterine growth restriction, the fetuses were delivered prematurely.

In both cases reported herein, AKI was conservatively managed, and renal function recovered within the first month of life. This fact indicates a possibly good outcome (at least in the short-term) even after prolonged exposure to these agents. Similar outcome has been reported in other case series as well[2]. Re-evaluation of the renal function in both infants was not made possible as they were lost to routine follow-up.

We used novel biomarkers of AKI in addition to serum creatinine, which is considered to be the gold standard for the detection of kidney injury in clinical practice[12]. Urine and blood cystatin-C and NGAL have been evaluated with promising results in various disease states and age groups including neonates[7,8,12], but their diagnostic accuracy and clinical utility have not yet been clearly defined. Both cases presented in this study had abnormally increased levels of these AKI indicators in the urine. There is only one study by Hünseller et al, in which cystatin-C levels (apparently in the blood) were reported in three neonates[4]. Our study is the first to report on NGAL in the urine of neonates suffering kidney damage associated with maternal valsartan intake, providing further evidence for the use of the novel AKI biomarkers in neonates.

In conclusion, we present two cases of neonatal AKI following a prolonged sartan administration during pregnancy. Although the renal outcome of our patients was favorable postnatally, physicians must be aware that the use of all agents interfering with the renin-angiotensin system should be absolutely avoided during pregnancy, as clearly stated by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC)[13]. The novel AKI markers may be used to assess sartan induced AKI, but their diagnostic and prognostic value should be confirmed in the context of larger studies.

Conflict of interest

Authors declare no conflict of interest

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