Neonatal Anuria by ACE Inhibitors during Pregnancy

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Dear Sir,

Angiotensin-converting enzyme inhibitors (ACE-I) are effective hypotensive drugs and extensively used for the treatment of hypertension [1]. They affect both the angiotensin/aldosterone and bradykinin/prosta-glandin systems inhibiting the conversion of angiotensin I to angiotensin II, increasing circulating bradykinin levels and directly stimulating prostaglandin synthesis. These drugs are able to cross the human placenta [2, 3] and their use during pregnancy has been associated with fetal injury [4-7].

We report a case of neonatal anuria in an infant of a woman treated with ACE-I in the third trimester of pregnancy for hypertensive gestosis. This was a 36-week, 2,000 g male infant born of a 33-year-old second gravida, by cesarean section for severe oligo-hydramnios. Apgar score was 5 and 7 at 1 and 5 min respectively. The infant had growth restriction (-2 SD), hypocalvaria, profound hypotension and renal failure with no urine output.

The kidneys were of normal size on renal ultrasound and the infant had no renal vaso-constriction on duplex Doppler scanning, no abnormalities of the urinary tract on the voiding cystourethrogram, no retroperitone-al/intra-abdominal masses on the abdominal computed tomography, and no cardiac dysfunctions on Doppler echocardiography. There was no history of maternal infections, but the mother had been treated for hypertensive gestosis from the 7th month of pregnancy with ACE-I (enalapril 20 mg/day) to the time of delivery.

On day 3 of life, the infant was started on peritoneal dialysis. ACE activity and enalaprilat level were measured in the serum of the infant. Before dialysis, the ACE level was 7.4 $\mu\text{m}/\text{ml}$ (normal 20/30). After peritoneal dialysis was started the ACE level in the serum rose to 20.5 $\mu\text{mol}/\text{ml}$. The enalaprilat level in the serum was 6.92 $\mu\text{g}/\text{ml}$, while that in the dialysate was 3.3 $\mu\text{g}/\text{ml}$. After 4 days of peritoneal dialysis the blood pressure returned to within normal limits for age. The urine output appeared on day 7 of life initially limited to 0.2 ml/kg/h, but gradually increased to 2.5 ml/kg/h. The peritoneal dialysis was interrupted on day 20 of life; a chronic renal failure remained.

Renal scanning with 99mTc-DTPA, 123I-hippuran showed: DTP A clearance 34 ml/ min/1.73 m² (normal for age 123 ± 16); hip-puran clearance 36 ml/min/1.73 m² (normal for age 650 ± 10).

At 8 months, due to worsening of renal function, peritoneal dialysis was re-started; actually the infant is awaiting renal transplantation. The child has a normal development, but he is still -2 SD below the growth curve. During these months considerable expansion of the calvarial bones was evident, with gradual closing of the fontanelles.

We consider the severe renal failure with no urine output of the infant with normal-size kidney on renal ultrasound and with low ACE activity in the serum was due to enalapril being able to cross the human placenta and cause fetal injury. In the fetus exists a condition of low renal perfusion and the angiotensin II-mediated arterial resistance is essential to the maintenance of glomerular filtration and production of urine. The suppression in the fetus of angiotensin II, by ACE-I, with the activation of bradykinin/ prostaglandin system, compromised the glomerular filtration rate, caused profound hypotension, severe hypoperfusion of the kidneys with intrinsic renal damage confined primarily to the renal tubules and extensive subsequently to other segments of the nephron. Angiotensin II is also a renal growth factor and chronic ACE inhibition results in glomerular growth retardation [8].

If the drug is administered during the second and third trimesters of pregnancy, it is estimated that 25% of infants will die and the remnants will be affected by ACE-I fetopathy [9] characterized by hypotension, oligohydramnios, renal failure, growth restriction and hypocalvaria, secondary to poor perfusion of plate-like bone structure in the skull. The kidneys have normal size with tubular necrosis and tubular dysplasia on renal histopathology.

Respiratory complications have also been found in 14% of new-borns and included respiratory distress syndrome, lung hypoplasia and apnea [7].

The strategy to prevent ACE fetopathy is to aggressively educate physicians and the public that these drugs should not be used during the second and third trimesters of pregnancy. ACE-I have indeed a deleterious effect on fetal development that occurred later in gestation. There has been no absolute proof that first-trimester exposure has adverse fetal effects; however, in some cases, bony malformations, limb contractures, facial abnormalities and lung hypoplasia have been associated with exposure to ACE-I throughout early pregnancy [7].

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