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Case Report

Angiotensin Converting Enzyme Inhibitor (ACEI)-Induced Acute Renal Failure in Premature Newborns with Congenital Heart Disease

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We report three cases of angiotensin converting enzyme inhibitor (ACEI) induced nephrotoxicity in preterm infants with congenital heart disease. Patients developed acute renal failure after starting captopril or enalapril at doses commonly prescribed for term neonates. There was no underlying renal disease found in these infants and the acute renal failure was reversible upon discontinuation of the ACEI. Conservative starting doses of ACEI should be used in patients with multiple risk factors for nephrotoxicity. A summary of previously reported ACEI induced renal failure in premature infants and congenital heart disease is included.

KEYWORDS captopril, congenital heart disease, enalapril

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INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEI) are used in a variety of pediatric cardiovascular conditions as an afterload reducer. During ACEI initiation, renal dysfunction can occur due to a drop in renal perfusion pressure and subsequent decrease in glomerular filtration. This is attributed to the drug's preferential vasodilation of the renal efferent arteriole, which impairs the kidney's ability to compensate for low perfusion states.[1] Diminished renal perfusion can occur at the local level (e.g., renal artery stenosis), or on a systemic level secondary to heart failure; these conditions increase reliance on angiotensin II mediated vasoconstriction and increase one's risk of ACEI induced renal toxicity.[1]

Neonates are highly dependent on the renin angiotensin aldosterone system (RAAS) for maintaining hemodynamic stability and therefore also vulnerable to ACEI associated toxicities. The importance of this system even before birth is highlighted in an experiment done in pregnant ewes that were given captopril.[2] A single infusion of captopril caused an immediate fall in arterial pressure, renal vascular resistance and subsequent decrease in urine output in the sheep fetus. Repeated administration of captopril resulted in anuria or low urine rates. Reversal of these adverse effects with an infusion of angiotensin II supported the role of the RAAS in the pathogenesis of nephrotoxicity. In humans, the deleterious effects of prenatal exposure to ACEI, including oligohydramnios, associated fetal abnormalities, hypotension and acute renal failure after birth, have been described in several case reports and one epidemiological study.[3-5]

According to one common drug reference, the starting dose of captopril varies up to 10 fold in the neonatal period and is dependent on gestational age. For enalapril, no explicit dosing is provided for prematurity.[6] Failure to appreciate these dosing nuances may increase a patient's risk for ACEI-associated adverse effects,

ABBREVIATIONS ACEI, angiotensin converting enzyme inhibitor; BUN, blood urea nitrogen; GFR, glomerular filtration rate; MAP, mean arterial pressures; RAAS, renin angiotensin aldosterone system

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particularly in those with multiple risk factors such as prematurity and low cardiac output. We report 3 unfortunate cases of acute renal failure in preterm infants with congenital heart disease likely precipitated by ACEI initiation at doses commonly recommended for full term infants.

CASE REPORTS

Case 1

A 1.42 kg, (height 42 cm) 30 week gestational age Caucasian female triplet is born via caesarian section due to hydrops and poor cardiac function secondary to her recipient status in "twin-twin" transfusion syndrome. The infant required intubation and ventilation in the delivery room and Apgar scores were 6 and 8. Echocardiography showed severely reduced biventricular function with a left ventricular ejection fraction of 15%. The infant was managed with fluid restriction, furosemide intravenously 2 mg/kg/day, milrinone 0.5 mcg/kg/min, and dobutamine 5 mcg/kg/min. Renal function showed a blood urea nitrogen (BUN) of 12 mg/dL, serum creatinine (Scr) of 0.59 mg/dL (normal reference range: 0.74-1.72 mg/dL,) glomerular filtration rate (GFR) 23 ml/min/1.73m^2, and urine output was 4.2 mL/kg/day. Blood pressure was in the normal range with mean arterial pressures (MAP) of 50.

By the 8th day of life the infant remained on mechanical ventilation with occasional low MAPsof 40 mmHg. Dobutamine had been discontinued and milrinone was continued at 0.5 mcg/kg/min. The ejection fraction remained at less than 20% by echocardiogram. Captopril dosing was initiated at 0.1 mg/kg/dose orally every 8 hours. Other potentially nephrotoxic agents administered included furosemide and one dose of gentamicin. Within 72 hours, 8 total doses of captopril had been given. Serum creatinine was noted to have increased from 0.59 mg/dL to 1.08 mg/dL (predicted GFR decreased from 23 to 12.6 mL/min/1.73m^2) (Figure 1A). Captopril was discontinued; however, renal function continued to worsen and hypotension to a nadir MAP of 33 mm Hg developed such that for several days the infant was oliguric despite therapy with furosemide, epinephrine and dopamine. Serum creatinine eventually peaked at 2.53 mg/dL (5 mL/min/1.73m^2) 4 days after captopril was discontinued. Concurrently the infant was diagnosed with necrotizing enterocolitis. Over the next 2 weeks hemodynamic status, ejection fraction, urine output, and serum creatinine normalized. Unfortunately head ultrasound and magnetic resonance imaging documented severe bilateral white matter necrosis. The infant died at 2 months of age while receiving paliative care.

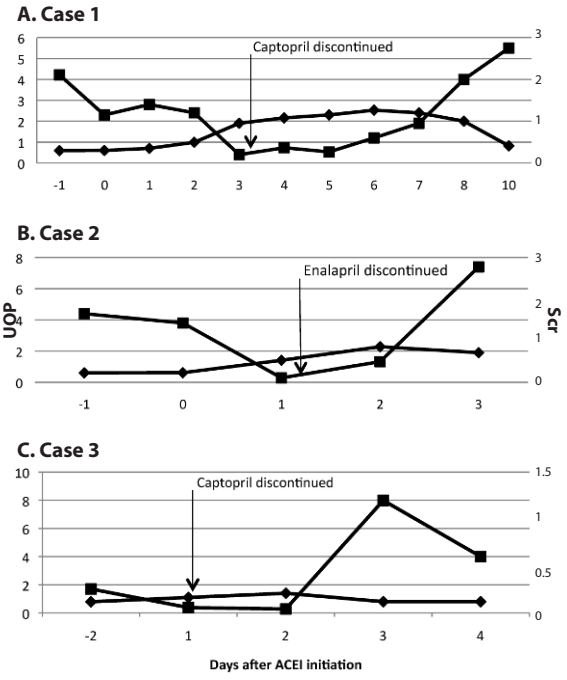

Figure 1. Serum creatinine and urine output in three patients during and after administration of an angiotensin converting enzyme inhibitor.
■ Urine Output (mL/kg/hr), ◆ Serum Creatinine (mg/dL)

Case 2

A 2.699 kg (height 48cm) 36 week gestational age Hispanic male infant was born following an uncomplicated pregnancy. The infant was vigorous in the delivery room; however, a grade 3 out of 6 harsh holosystolic murmur was noted at the left sternal border radiating widely throughout the precordium. There was normal S1 and a single S2. Echocardiogram revealed a large ventricular septal defect and type 2 truncus arteriosus. The truncal valve appeared to be trileaflet, but dysplastic with mild stenosis and regurgitation. Left ventricular function was normal. A chest x ray showed mild cardiomegaly and mildly increased pulmonary vascular markings. The patient was admitted to the neonatal intensive care unit for further evaluation and management.

At 24 hours of age heart rate was 145 beats per minute and MAP was 48 mmHg. There was mild

tachypnea with comfortable respirations and arterial oxygen saturation was 87% on room air. Urine output was 2.5 mL/kg/hr, BUN was 3.0 mg/dL and serum creatinine 0.6 mg/dL (normal reference: 0.81-1.63 mg/dL), GFR was 36 mL/min/1.73m^2. Oral feedings were well tolerated. Over the next three days the patient showed signs of pulmonary overcirculation with an oxygen saturation of 95% and pulmonary edema noted on chest x-ray. Furosemide orally 3 mg/kg/day and enalapril were added at a dose of 0.11 mg/kg/day divided twice daily. The patient was not on any other nephrotoxic agents.

The 24 hours after initial enalapril dosing, urine output decreased to1.3 mL/kg/hr and serum creatinine had increased to 1.4 mg/dL (GFR 15 mL/min/1.73m^2) (Figure 1B). Ultrasonography of kidneys showed normal renal parenchyma, and mild bilateral hydronephrosis. The enalapril was discontinued after a total of 3 doses; however, over the next 12-24 hours urine output was minimal, serum creatinine increased to 2.3 mg/dL (GFR 9 mL/min/1.73m^2), and the patient's level of illness increased. Mechanical ventilation was initiated. The infant developed hypotension (MAP=32 mm Hg) requiring dopamine (10 mcg/kg/min) and epinephrine (0.02 mcg/kg/min) infusions.

Surgical repair of the truncus arteriosus was delayed in hopes that renal function would improve with time off ACEI. Seventy two hours after discontinuing enalapril, urine output improved to 6.2 mL/kg/hour, BUN decreased to 29 mg/dL and serum creatinine decreased to 0.8 mg/dL. Surgical repair was performed on day of life 8. Post operatively the patient had no complications, normal renal function, and was discharged home on day of life 16.

Case 3

A 0.98 kg (height = 39 cm) 27 week gestational age Caucasian male infant was referred for management of a patent ductus arteriosus and moderate to large ventricular septal defect. The patient failed ibuprofen therapy (5 doses) and PDA ligation was performed on Day 10 of life with no complications. Three days later the patient was intubated for impending respiratory failure. Follow-up echocardiogram showed moderate perimembranous ventricular septal defect along with mild left atrial and ventricular dilation. At 3 weeks of age the infant remained on mechanical ventilation. Patient exhibited signs of congestive heart failure on x-ray including enlarged heart size and increased pulmonary markings despite furosemide and digoxin. BUN was 27 mg/dL, serum creatinine 0.72 mg/dL (normal reference: 0.58-0.89 mg/dL), GFR 17 mL/min/1.73m2, and urine output was 4.4 mL/kg/hr. Pulmonary edema was noted on chest x ray and the infant was moderately tachypneic, which led to the decision of starting captopril at 0.1 mg/kg/dose orally every 8 hours.

Within 1 hour of captopril dosing systolic blood presume decreased from 71 to 58 mmHg and continued to decline over 24 hours to a MAP nadir of 26 mmHg despite vasoactive support with dopamine. Urine output decreased to 1.7 mL/kg/hr and serum creatinine increased to 1.37 mg/dL (GFR 9.4 mL/min/1.73m^2) (Figure 1C). Captopril was discontinued after 3 doses, but urine output continued to decrease to less than 0.5 mL/kg/hr. Other potentially nephrotoxic agents included furosemide and one dose of vancomycin. A renal ultrasound showed no hydronephrosis and the kidneys and bladder were unremarkable with good vascular flow. Over the next several days the serum creatinine decreased. Due to ongoing medical complications the patient's serum creatinine continued to fluctuate, but eventually stabilized (0.2-0.3 mg/dL) two months after the initial insult. Unfortunately, the patient ultimately developed periventricular leukomalacia and was discharged for palliative care at 4 months of age.

DISCUSSION

Due to the strong temporal relationship between drug initiation, renal deterioration and reversibility of these conditions upon drug discontinuation, we believe our patients likely suffered from ACEI-induced nephrotoxicity. While the contribution of other risk factors such as borderline hypotension and concurrent use of other nephrotoxic agents cannot be ruled out, conditions that increase renal dependence on angiotensin mediated vasoconstriction (e.g., prematurity and congenital heart disease) likely increased susceptibility to ACEI related complications.

These cases illustrate the challenge of managing congestive heart failure in the preterm infant, beginning with selection of the initial ACEI dose.

Table 1. Case Reports of ACEI-induced Nephrotoxicity in Premature Neonates

Reference	Patient	Agent and Initial Dose	Outcome
Schilder[8]	25 wk premature infant. ACEI started for neonatal hypertension from thrombus in umbilical artery catheter.	enalapril 0.1 mg/kg	Anuria and renal failure after 1 dose; accompanied by dramatic drop in blood pressure 8 hrs. Renal function recovered over next couple of days.
Tack[9]	8 premature infants. All with bronchopulmonary dysplasia, 7 with ventricular hypertrophy. All had increased renin levels at baseline, normal renal function.	captopril 0.3 mg/kg	All 8 patients blood pressure dropped by an average of 37% within hrs of test dose. All experienced oliguria. 4 had severe hypotension and oliguria unresponsive to volume expansion, accompanied by change in neurological status.
Hymes[10]	33 wk premature infant. ACEI started for neonatal hypertension. Baseline BUN and Scr were elevated at 17 and1.2 mg dL, respectively.	captopril 0.3 mg/kg	Hypotension and oliguria after 1 dose. Captopril dose decreased and then gradually titrated. Scr continued to increase to 1.8 mg/dL but patient was treated through and eventually recovered normal renal function after 2 months.
Wood[11]	33 wk premature infant born with periductal coarctation, ventricular septal defect, and hypoplastic arch. ACEI started for afterload reduction after coarctation repair.	captopril 0.5 mg/kg	After receiving several doses of captopril, Scr increased from 0.5 to 2.3mg/dL, associated with oliguria, weight gain and hyperakalemia. Renal impairment returned to baseline one week after captopril was discontinued.

ACEI, angiotensin converting enzyme inhibitor; BUN, blood urea nitrogen; Scr, serum creatinine

Recommended starting doses of captopril during the newborn period range from 0.01 mg/kg/dose every 8 to 12 hours for "newborns or preterm infants," to 0.05-0.1 mg/kg/dose every 8 to 24 hours in "neonates." [6] Although two distinctive dosing schemes, which encompass a 10-fold range in dosing, are recommended during the neonatal period, the exact chronological age at which this transition should occur is unclear. Similarly, the commonly referenced starting dose listed for enalapril in the neonatal period is 0.04-0.1 mg/kg/dose every 24 hours with no distinction made between preterm and full term infants.[7] Prematurity is a well known risk factor for ACEI nephrotoxicty supported by several case reports compiled in Table 1.[8-11] In the case of these 3 patients, the selection of ACEI starting doses commonly used in full term neonates reflected a failure to appreciate the inherent nuances in age related dosing. The fact that three separate pediatric cardiologists initiated these therapies is a measure of the potential pervasiveness of this ambiguity.

Infants with congenital heart lesions can be at increased risk for renal dysfunction depending on their propensity towards low systemic output. This relationship has been shown by Harrison and colleagues, who noted that neonates with transposition of the great arteries and hypoplastic left heart syndrome exhibited functionally worse serum creatinine clearance than predicted by conventional measures.[12] Conditions that compromise determinants of stroke volume (preload, afterload, contractility) can activate the RAAS and potentially increase the risk of renal dysfunction during angiotensin converting enzyme inhibition. In infants with congenital heart disease, diminished preload often occur due to aggressive diuresis or pulmonary steal. We believe cases 2 and 3 with truncus arteriosus and ventricular defect respectively, may have been at high risk for pulmonary steal. In contrast, case 1, who presented with dilated cardiomyopathy, was susceptible to low cardiac output resulting from poor contractility. Table 2 summarizes other reports of ACEI-induced nephrotoxicity in patients with symptoms of congestive heart failure or left sided obstructive lesions.[11,13-17]

In general, the onset of renal dysfunction occurred within 24 to 72 hours after ACEI initiation while the duration was proportional to the length of ACEI use. The development of severe hypotension within several hours of starting ACEI may be the first warning signs of subsequent renal decline. Although hypotension in patient 3 occurred as early as one hour after the initial dose,

Table 2. Case Reports of ACEI Induced Nephrotoxicity Based on Cardiac Defect

Reference	Patient	Outcome
Left sided obstructive lesions		
Harrison[12]	33 wk neonate born with periductal coarctation, hypoplastic aortic arch, ventricular septal defect. Captopril initiated 1 month after surgery for persistent hypertension. Final dose 4.4 mg/kg/day	Scr increased from 0.5 to 2.3 mg/dL associated with oliguria, weight gain and hyperkalemia. Scr recovered to baseline within a week of discontinuing captopril
Maliheh[13]	Patient 1. full term infant with interrupted aortic arch. Captopril 0.5 mg/kg/day started for congestive heart failure symptoms.	Patient 1. Two days after captopril, pt became anuric and edematous. BUN and Scr was 14 and 2.4 mg/dL. Ultrasound of kidney and bladder normal. Renal function and urine output normalized 2 days after discontinuing captopril
	Patient 2. 36 wk infant with juxtaductal coarctation and ventricular septal defect. Discharged home with furosemide and captopril 0.5mg/kg/day	Patient 2. Readmitted to hospital on day of life 25. Hypotensive and anuric for 24 hours. BUN and Scr was 68/10.8 mg/dL. Ultrasound of kidney bladder normal. Renal function improved within 2 days after discontinuing captopril
Ventricular septal defect and/or congestive heart failure		
Dutta[14]	Full term baby boy with ventricular septal defect. Enalapril 0.1 mg/kg/day started for congestive heart failure along with diuretics and digoxin.	Three days after starting enalapril, developed oliguria. Enalapril immediately stopped however oliguria continued to worsen into anuria (BUN and Scr 130 and 4.6 mg/dL) Renal ultrasound normal. Three rounds of peritoneal dialysis were required to normalize renal function.
Krishna[15]	2 children with Down's syndrome, arterioventricular canal and congestive heart failure Patient 1. 5 yr old had undergone repair with residual heart failure. On digoxin. Started on enalapril 0.2 mg/kg/day and diuretic regimen.	Patient 1: BUN was elevated 3 weeks after starting enalapril. Developed digoxin toxicity two weeks later secondary to renal failure (BUN and Scr 91 and 3.2 mg/dL.)
	Patient 2. 5 mo old had undergone patent ductus arteriosus ligation and pulmonary artery banding. Started on captopril 0.17 mg/kg/day for signs of congestive heart failure.	Patient 2. 1 week after captopril, BUN 80 mg/dL and Scr 4.3 mg/dL. Biopsy revealed patchy nephrocalcinosis.
Leversha[16]	63 patients, median age 5.4 mo, enalapril started for heart failure (dose stratified by weight ranging from 0.1-2.5 mg/day)	Renal failure occurred in 8 patients within 5 days of starting enalapril. Renal failure may have contributed to early death in three infants with severe heart failure. Univariant analysis suggested young age, low weight and left to right shunt as risk factors for renal failure.
Gantenbein[17]	43 newborns and young infants who had undergone surgical correction of congenital heart disease. Median age 26 days. Captopril 0.05 mg/kg/dose started for heart failure and titrated	Renal impairment or failure occurred in 6 patients, at an average of 9 days after reaching the final dose. Low birth weight (< 500 gm) was a risk factor for renal failure. All side effects were fully reversible.

ACEI, angiotensin converting enzyme inhibitor; BUN blood urea nitrogen; Scr, serum creatinine

pharmacokinetic studies suggest that extended monitoring of vital signs may be necessary due to prolonged clearance in neonates, especially those with congestive heart failure. There is a paucity of ACEI pharmacokinetic data in neonates. In a study by Nakamura and colleagues, three infants less than 20 days old given enalapril show a delayed peak concentration and decline of the active metabolite enalaprilat compared to children, resulting in an average half life of

10.3 hours compared to 2.07 hours in infants.[18] Enalapril's onset of action is 1 to 2 hours and its duration of action ranges from 8 to 24 hours. In contrast, captopril's onset of action is 15 minutes. Although peak effects can be seen in 30 minutes, infants with congestive heart failure may see a delay of up to 90 minutes.[19] Captopril's duration of action is usually 2-6 hours, but may be significantly longer. Based on theoretical pharmacokinetic principles, our institution strongly encourages the initial selection of a shorter acting agent such as captopril to minimize any lingering hemodynamic effects should they occur.

Based on our observations, premature neonates at risk for low cardiac output secondary to congenital heart disease may be particularly susceptible to ACEI-induced nephrotoxicity. The necessity for initiating ACEIs in this high risk population should be carefully evaluated. During drug initiation and titration, hemodynamic instability and changes in urine output may be the earliest predictors of renal dysfunction. Serum creatinine should be measured daily. Prompt discontinuation of ACEIs and hemodynamic intervention are necessary to reverse the course of renal injury. Until more pharmacokinetic studies in premature neonates are performed, the selection of a shorter acting ACEI like captopril at conservative starting doses of 0.01 mg/kg/dose every 12 hours, may be especially critical in preventing acute nephrotoxicity.

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