Captopril induced reversible acute renal failure in a premature neonate with double outlet right ventricle and congestive heart failure

Lin-Hua Tan, Li-Zhong Du, Michael R. Carr, Julia K. Kuzin, Brady S. Moffett, Anthony C. Chang
Houston, USA

Background: **Captopril is well tolerated in most patients. There is no report of acute deterioration in renal function after administration of captopril in neonates with congestive heart failure secondary to congenital heart defects with large left-to-right shunts.**

Methods: **We report a premature neonate with double outlet right ventricle and congestive heart failure who developed acute renal failure after administration of captopril at a low dose of 0.1 mg/kg per 8 hours.**

Results: **On the third day after captopril therapy, the levels of serum creatinine and blood urea nitrogen increased to 2.6 mg/dl and 73 mg/dl respectively, and hyperkalemia appeared. Captopril was discontinued immediately. On the fourth day, the infant developed oliguria which persisted for 24 hours and resolved on the fifth day when the serum potassium normalized to 4.5 mmol/L. The level of serum creatinine peaked at 3.9 mg/dL on the sixth day and gradually decreased to normal on the ninth day after administration of captopril. The captopril-induced acute renal failure resolved completely after cessation of the drug.**

Conclusions: **Attention should be given to captopril therapy in premature neonates with congestive heart failure secondary to congenital heart disease with large left-to-right shunts. Routine hemodynamic examination and biochemical monitoring are suggested before and during captopril therapy.**

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Introduction

Congestive heart failure (CHF) in early infancy is frequently related to high pulmonary blood flow and volume overload in the presence of congenital heart disease (CHD) with large left-to-right shunts. In such patients, captopril, an angiotensin converting enzyme (ACE) inhibitor, is a rational drug choice for treatment.[1] Captopril is well tolerated in most patients. However, uncommon adverse effects such as acute renal failure (ARF) have been reported in pediatric patients with hypertension.[2] To the present, there is no report of acute deterioration in renal function after administration of captopril in neonates with CHF secondary to CHD with large left-to-right shunts. We report a premature neonate with CHF secondary to double outlet right ventricle (DORV) and large left-to-right shunt developed ARF while receiving a low dose of captopril.

Case report

A 1600 g male infant was born via spontaneous vaginal delivery at 34 weeks gestation after an uneventful pregnancy. Apgar score was 9 both at 1 and 5 minutes. Shortly after birth, he was diagnosed with a tracheoesophageal cleft as well as DORV without chromosomal abnormality detected. He underwent placement of a gastrostomy tube and fundoplication at an outside institution. The infant was then transferred to our neonatal intensive care unit for further care at 18 days of life with a body weight of 2160 g. An echocardiogram revealed DORV with a subaortic ventricular septal defect,

Author Affiliations: Department of Surgical Intensive Care Unit, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310003 China (Tan LH, Du LZ); The Lillie Frank Abercrombie Section of Cardiology, Department of Pediatrics, Texas Children's Hospital, Baylor College of Medicine, 6621 Fannin, MC 19345-C, Houston, TX 77030 USA (Carr MR, Kuzin JK); Pediatric Cardiology, Department of Pharmacy, Texas Children's Hospital, 6621 Fannin, Houston, TX 77030 USA (Moffett BS); CHOC Heart Institute, Children's Hospital of Orange County, 455 S. Main Street Orange, CA 92868 USA (Chang AC)

Corresponding Author: Anthony C. Chang, MD, MBA, MPH, CHOC Heart Institute, Children's Hospital of Orange County, 455 S. Main Street Orange, CA 92868 USA (Tel: 714-532-7576; Fax: 714-289-4962; Email: achang@choc.org)

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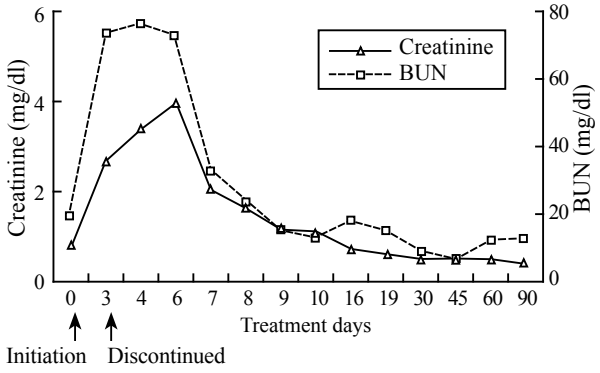
mild subvalvular and valvular pulmonary stenosis with a peak velocity of 2.1 m/sec and moderate right ventricular dilation. An electrocardiogram demonstrated right ventricular hypertrophy. A chest roentgenogram revealed mild to moderate cardiomegaly and increased pulmonary vascularity, consistent with excessive pulmonary blood flow. With the underlying cardiac structural abnormality and the above findings, the patient was diagnosed with CHF and pulmonary over-circulation secondary to DORV with large left-to-right shunt.

He was initially treated with intravenous furosemide (1 mg/kg per dose, every 8 hours). However, CHF persisted, evidenced by clinical symptoms and elevated plasma B-type natriuretic peptide (848 pg/ml, normal <100 pg/ml). Three days later, captopril was instituted at a low dose of 0.1 mg/kg, per 8 hours. Prior to starting captopril, renal function was normal with serum creatinine of 0.8 mg/dl (normal range, 0.2-1.2 mg/dl) and blood urea nitrogen (BUN) of 19 mg/dl (normal range, 8-28 mg/dl). Fig. shows the changes of serum creatinine and BUN associated with blood pressure and urine output before and after captopril therapy. The patient was not found to have a significant reduction in blood pressure on the first day after administration of captopril (from 72/30 mmHg to 82/50 mmHg). Blood pressure of the patient ranged from 50/25 mmHg to 62/27 mmHg during maintenance therapy. On the third day after captopril therapy, serum creatinine and BUN levels increased to 2.6 mg/dl and 73 mg/dl respectively, while hyperkalemia appeared (serum potassium 6.9 mmol/L) despite normal urine output at that time. Hyperkalemia was treated by intravenous administration of calcium gluconate and hypertonic dextrose/insulin infusion.



Days after treatment	0	1	2	3	4	5	6	7	8
Blood pressure (mmHg)	82/50	72/30	50/25	55/22	65/30	75/43	72/42	70/38	65/42
Urine output (mL/kg/h)	3.2	4.1	5.2	2.8	0.16	3.0	1.2	2.2	2.3

Fig. Changes of serum creatinine and blood urea nitrogen (BUN) associated with blood pressure and urine output before and after captopril therapy in a premature neonate with double outlet right ventricle and congestive heart failure.

There was no evidence of eosinophilia, eosinophiluria, skin rash, neutropenia or proteinuria. Serum electrolyte analysis was normal prior to this episode of ARF. During this interval, the infant did not receive any nephrotoxic medication. There was no evidence suggesting a secondary etiology for renal deterioration such as sepsis or renal venous or arterial thrombosis.

ARF was found to be related to the administration of captopril. Both captopril and furosemide were discontinued immediately. The infant developed oliguria with continued hyperkalemia (serum potassium, 7.0-7.3 mmol/L) on the fourth day after captopril therapy. Oliguria persisted for 24 hours and resolved on the fifth day when the level of serum potassium returned to 4.5 mmol/L. The level of serum creatinine continued to go upward and peaked at 3.9 mg/dl on the sixth day after administration of captopril. Then, the levels of serum creatinine and BUN showed a downward tendency and normalized to 1.1 mg/dl and 15 mg/dl respectively on the ninth day after captopril treatment.

The patient remained hemodynamically stable without cardiac arrhythmias during the episode of acute renal insufficiency.

Discussion

The present case demonstrated an acute decrease in renal function while receiving a low dose of captopril in a premature neonate with CHF secondary to CHD with large left-to-right shunt. The captopril-induced ARF resolved completely shortly after cessation of the drug. ACE inhibitors result in significant vascular relaxation, reduction of afterload, and improvement of cardiac output. Fetal renal function is characterized by a low glomerular filtration rate (GFR). After birth, GFR rises very rapidly because of an increase in mean arterial blood pressure and glomerular hydraulic pressure, a sharp fall in renal vascular resistance, as well as an increase in the glomerular filtration area.[3] But the GFR of the newborn is still very low, both in absolute and corrected terms for adult body surface area. This is a unique situation confined to the newborn and explains the vulnerability of renal function in early extrauterine life. One of the mechanisms for maintaining adequate GFR in face of a low neonatal mean arterial blood pressure is postglomerular, efferent arteriolar vasoconstriction, which is mainly dependent on angiotensin II. This results in a higher sensitivity of neonates to the administration of ACE inhibitors compared with adults.[4]

Different mechanisms have been postulated for the development of the captopril-induced ARF. Scammell et al[5] demonstrated that there was a significant fall in blood pressure at 90 minutes after the first dose of captopril in infants who had CHD with left-to-right

shunts and increased pulmonary blood flow. Al Shohaib et al[6] demonstrated that decreased renal function paralleled captopril-induced hypotension. Captopril inhibits angiotensin II-mediated renal efferent arteriolar vasoconstriction and reduces intra-glomerular capillary pressure and subsequently GFR when renal perfusion pressure is reduced.[7] Captopril was reported to stimulate immunoallergic interstitial nephritis, which is occasionally accompanied by fever, skin rashes and/or eosinophilia.[8] Rarely, the etiology for renal dysfunction was determined to be captopril-induced nephrotoxicity.[9]

In our case, disruption of the autoregulation of glomerular filtration at the lower renal perfusion pressure resulting from ACE inhibition rather than drug toxicity or immunoallergic interstitial nephritis seems to be the most likely mechanism for captopril-induced reversible ARF. In this patient, none of the potentially nephrotoxic drugs were used during captopril therapy. There were no signs of interstitial nephritis such as eosinophilia, eosinophiluria, skin rash, neutropenia or proteinuria. In addition, neither decrease in body weight to suggest volume depletion nor changes of clinical symptoms or other laboratory parameters to suggest septicemia or other overwhelming systemic illness were observed as an etiology for the deterioration of renal function.

The large left-to-right shunt from the cardiac lesion in this case resulted in an increased Qp/Qs ratio, decreased systemic blood flow and renal hypoperfusion. The administration of captopril reduced the patient's pulmonary vascular resistance (PVR) and systemic vascular resistance, especially PVR, and led to a further increased Qp/Qs, causing decreased renal perfusion and acute renal failure. The levels of ACE were found to be negatively correlated with birth weight and gestational age.[10] Thus, premature infants with low birth weight are more liable to develop ARF after therapy with ACE inhibitors. At last the concomitant use of diuretics and captopril may have compromised renal perfusion by increasing renin activity which results in greater dependence on angiotensin II-mediated efferent arteriolar vasoconstriction for filtration.[11] Under these circumstances, blockade of the renin-angiotensin system may result in not only unloading of the heart but also unloading of the kidney and subsequently decreased GFR.

Renal function needs to be evaluated carefully before and during captopril administration. There may be impaired GFR even when serum creatinine and urine output are normal in neonates.[12] The risk of inducing functional renal impairment and symptomatic hypotension is dose-dependent, and small doses should be given especially at the beginning of ACE inhibitor therapy.

In conclusion, ACE inhibitor therapy should be considered in the etiology of any change in renal function. Attention should be given to captopril therapy in premature neonates with CHF secondary to CHD with large left-to-right shunts, particularly if used concomitantly with diuretics. Routine hemodynamic examination and biochemical monitoring are suggested before and during captopril therapy.

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