# Fetal Exposure to Lisinopril: Neonatal Manifestations and Management

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The use of angiotensin-converting enzyme (ACE) inhibitors in pregnancy has been associated with neonatal morbidity and mortality. The mechanism of renal dysfunction likely is related to fetal hypotension and prolonged decreased glomerular filtration. Six of 14 previously published cases of neonatal renal failure after maternal ACE inhibitor therapy resulted in death. Eight infants survived after peritoneal dialysis, some with residual renal impairment. Serum lisinopril levels and ACE activity in our patient indicate that during the anuric state the drug has an extremely prolonged half-life, and that it is removed by peritoneal dialysis. In view of this prolonged half-life and the drug's continued suppression of ACE activity and renal function, we recommend institution of early dialysis in infants with renal failure after maternal therapy with lisinopril.
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Angiotensin-converting enzyme (ACE) inhibitors are commonly used in the treatment of essential and renovascular hypertension. Although not recommended, they are sometimes used in pregnant women to treat severe hypertension particularly when the risk of maternal morbidity is high. Numerous cases of neonatal morbidity and mortality have been reported in offspring of women who received these drugs during pregnancy. Both fatal anuria and reversible acute renal failure have been reported in infants exposed to enalapril or captopril in utero.[1–11]

Although ACE inhibitors are not thought to be teratogenic in animals, the frequency of stillbirths is increased in pregnant animals exposed to them.[12, 13] Little information is available about the use of lisinopril in pregnancy. We cared for a premature infant with chronic renal failure who was exposed to lisinopril in utero throughout pregnancy. The teratologic aspects of this case were reported previously.[9]

## Case Report

A 1.48-kg boy was born to an 18-year-old woman at 33 weeks' gestation by cesarean section due to premature onset of labor and breech

presentation. The pregnancy was complicated by long-standing maternal hypertension treated with lisinopril (Zestril) 10 mg/day. The infant's Apgar scores were 4 and 7 at 1 and 5 minutes, respectively. He required mechanical ventilatory support and had a course consistent with moderate respiratory distress syndrome (RDS). In addition to prematurity, the physical examination was remarkable for a markedly hypoplastic skull.

Throughout the first 8 days of life the baby remained anuric despite several fluid boluses and furosemide administration. Dopamine was started for hypotension. On day 9 of life the infant was transferred to the University of Michigan for further evaluation and treatment. At the time of transfer, his blood urea nitrogen was 27 mg/dl (9.64 mmol/L) and serum creatinine was 7.0 mg/dl (619 μmol/L).

Further evaluation included renal ultrasonography, which showed normal renal architecture and size, and documented blood flow to both kidneys by Doppler examination. The femoral arteries were patent. Echocardiogram revealed a small patent ductus arteriosus. Cranial ultrasound was normal. The infant was diagnosed as having acute renal failure due to in utero exposure to an ACE inhibitor. This diagnosis was supported by hypoplasia of the skull, which has been associated with ACE inhibitors.[4, 5, 8, 9, 14]

Peritoneal dialysis was begun on day 9 of life. Due to technical problems, it was unsuccessful until day 10. The first urine output was on day 12 at 0.23 ml/kg/hour and slowly increased over the next 10 days.

**Table 1. Clinical and Laboratory Changes During Peritoneal Dialysis**

| Age (days) | Urine (ml/kg/hr) | ACE (nmol/ml/min) | PRA (ng/ml/hr) | Lisinopril | |
|---|---|---|---|---|---|
| | | | | Serum (ng/ml) | Dialysate (ng/ml) |
| 12 | 0.23 | 7.9 | — | 7.0[a] | — |
| 16 | 0.32 | 7.4 | — | 6.3 | 3.3 |
| 17 | 0.30 | — | — | — | 2.1 |
| 21 | 0.39 | — | — | — | 0.6 |
| 30 | 0.56 | 19.5 | — | — | — |
| 37 | 1.3 | 22.0 | 19.2 | — | — |
| 38 | 2.6 | — | — | 0.7[b] | — |
| 45 | 1.24 | — | 1.0 | — | — |

Continuous peritoneal dialysis began on day 12 of life.
Normal ACE 20–50 nmol/ml/min, normal PRA 0.5–3.5 ng/ml/hr.
[a]Lisinopril concentration before effective dialysis.
[b]Lisinopril concentration before administration of enalapril.

Initially, ACE activity was low (Table 1) and increased over the next 3 weeks as serum lisinopril concentrations decreased. After 4 weeks of dialysis plasma renin activity (PRA) was markedly elevated at 19.2 ng/ml/hour (normal range 0.5–3.5 ng/ml/hr) and the serum lisinopril concentration was negligible (0.7 ng/ml). The infant was very hypertensive during this time. His clinical response to hydralazine and propranolol to control hypertension was minimal, and prolonged use of nitroprusside was required. At this time it was decided to administer an ACE inhibitor based on the hypothesis that there may have been hyperplasia of the juxtaglomerular apparatus producing the high renin activity.[6] No further drug levels were measured after this time.

The infant responded well to enalapril 0.04 mg/kg every 6 hours intravenously. Four days later his renin value dropped to 1.0 ng/ml/hour. His blood pressure was controlled, and his urine output at this time was approximately 1.3 ml/kg/hour.

At 11 weeks, an open renal biopsy showed extensive atrophy and loss of tubules associated with interstitial fibrosis. Some tubules were dilated with cellular debris. The brush border of the proximal tubular epithelium did not stain with para-aminosalicylic acid (PAS). The extensive tubular atrophy and interstitial fibrosis was interpreted to be a result of previous tubular injury and interstitial nephritis possibly secondary to a nephrotoxic agent. No hypertrophy of the juxtaglomerular apparatus was seen.

Adequate renal function did not return. The infant was discharged from the hospital at 10 months of age on continuous peritoneal dialysis for severe renal failure. He received a renal transplant at approximately 22 months that is functioning well. He appears cognitively normal, but has suffered from malabsorption and severe failure to thrive, and remains small for his age.

## Discussion

This case illustrates neonatal anuria due to in utero exposure to lisinopril, a newer ACE inhibitor. Numerous reports of fetal and neonatal morbidity and mortality after the use of these drugs during pregnancy can be found in the literature.[1-11] There are also reports of pregnant women receiving ACE inhibitors with no obvious ill effects on pregnancy outcome,[11, 15, 16] suggesting that several factors such as the timing or duration of exposure, particularly during the second and third trimesters, may be crucial. Consequently, the frequency of fetal exposure and the likelihood of subsequent neonatal morbidity is unknown, but both are undoubtedly underreported in the literature. Pregnancies without untoward neonatal events would be less likely to be reported, and very premature infants who die soon after birth with RDS, refractory hypotension, and short-term anuria are not likely to be recognized as suffering from the effects of fetal ACE inhibitor exposure. In addition, the relative risks of neonatal renal failure after exposure to different ACE inhibitors are unknown.

The typical characteristics of fetal exposure reported with captopril and enalapril include renal dysfunction with severe oliguria or anuria in the absence of a history suggestive of asphyxia at birth,[1-11] normal-size kidneys without hydronephrosis,[3-6, 8, 9] variable but often intractable hypotension,[1, 3-5, 7-9] and osseous cranial hypoplasia.[4, 5, 8, 9, 14] Patent ductus arteriosus and/or pulmonary hypoplasia also were present in many of the patients, but they are commonly related to prematurity or oligohydramnios and are thus not easily attributable to exposure to ACE inhibitors. Features seen in our patient were severe renal failure at birth without antecedent asphyxia, normal-size kidneys, hypotension, and cranial hypoplasia.

Possible mechanisms by which the agents might

cause renal injury are speculative. Data from animal studies indicate that glomerular filtration is controlled, at least partially, through the renin-angiotensin system. Blockage of angiotensin II in dogs during renal artery hypotension results in a marked decrease in glomerular filtration rate (GFR) and filtration fraction despite well-maintained renal blood flow.[17] This mechanism is thought to be involved in the transient renal impairment observed in humans with renal artery stenosis during treatment with captopril.[18] A similar mechanism may be operative in fetuses exposed to the agents. The combination of fetal hypotension[19] and loss of a functional renin-angiotensin system results in a marked fall in GFR.[17] Over a prolonged period, the lack of GFR would likely impair renal tubular development. The findings in our patient with extreme paucity of tubules are consistent with this mechanism, as are the simultaneous changes in urine output as ACE activity increased.

Calvarial hypoplasia, a very uncommon congenital abnormality that has been reported in connection with fetal exposure to ACE inhibitors,[4, 5, 8, 9, 14] is also postulated to be related to fetal hypotension. Decreased fetal blood pressure associated with increased uterine pressure directly on the developing bones of the skull due to prolonged oligohydramnios may impair cranial ossification.[9]

Treatment of neonates with renal failure at birth after in utero exposure to ACE inhibitors has been varied. Although many of the infants were premature and suffered from other problems likely to complicate the clinical course, the presence of anuria was an ominous finding. Despite dialysis, deaths occurred due to persistent renal failure, although survivors had eventual return of variable degrees of renal function.[1–11]

Continued suppression of ACE activity and elevation of plasma renin activity were documented 3 days after birth in a newborn whose mother took enalapril.[6] The ACE activity increased and enalapril plasma concentrations decreased with 1 week of dialysis. In our patient, serum lisinopril concentration 12 days after birth, prior to the onset of effective dialysis, was 7.0 ng/ml and ACE activity was suppressed at 7.9 nmol/ml/minute, indicating minimal or no excretion of the drug over a prolonged period. This is consistent with lisinopril not undergoing any measurable metabolism.[20] In this infant, it was effectively removed by peritoneal dialysis, as shown by its decreasing serum levels and its presence in the dialysate. It is likely that hemodialysis would be more effective in removing circulating ACE inhibitor in the face of hypotension; however, the attendant risks involved with hemodialysis, including rapid fluid shifts and the need for systemic heparin therapy, especially when the patient is a premature infant at risk of intraventricular hemorrhage, must

also be considered.

Lisinopril is a water-soluble, small-molecular-weight compound (mw 441.53 daltons). The peak serum concentration of a single dose is linearly related to the amount given. About 30% of the drug is recovered unchanged from urine and about 70% appears in feces. There appears to be no metabolism and no binding to serum proteins other than ACE. The half-life of the drug in adults is 12–13 hours.[20]

The peak serum concentration of lisinopril after a 10-mg dose is about 42 ng/ml.[21] In our patient, the mother received 10 mg/day throughout pregnancy, providing a steady-state concentration probably less than 42 ng/ml, assuming the usual increase in glomerular filtration that occurs with pregnancy. The initial serum concentration of lisinopril in the neonate was 7 ng/ml before dialysis was started. Since there was no urine or stool output before this time, it appears that fetal levels are approximately 20% of maternal levels.

Lisinopril has a very large volume of distribution 124 ± 16 L,[20] and hence serum concentrations may not be a true reflection of the amount of drug in the body. Examination of the concentrations in serum and dialysate revealed a substantial amount was removed by dialysis. The infant was not fed during the first 4 weeks of life and had two meconium stools and minimal urine output during this time, indicating that most of the drug was removed by dialysis.

Recent changes in package insert labeling, stating "when used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus" strongly discourage the drugs' use during pregnancy. However, through ignorance or the need to treat severe refractory hypertension, they will occasionally be given to pregnant women despite extreme risk to the fetus and neonate. Health care providers must be aware of the potential problems in the newborn after exposure. In infants with severe oliguria or anuria, the prolonged serum half-life of lisinopril and other drugs of this class may prolong renal failure and hypotension. In such circumstances we believe immediate hemodialysis or peritoneal dialysis is indicated.

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