Pediatr Nephrol (1995) 9: 382–385

Pediatric Nephrology

Invited review

Recognition and management of angiotensin converting enzyme inhibitor fetopathy

Aileen B. Sedman, David B. Kershaw, and Timothy E. Bunchman

Pediatric Nephrology Service, University of Michigan Medical Center, Box 0297-L2602, 1521 Simpson Road East, Ann Arbor, MI 48109-0297, USA

Received December 6, 1994; received in revised form December 9, 1994; accepted December 12, 1994

Abstract. Angiotensin converting enzyme (ACE) inhibitors are extensively used for the treatment of hypertension, to decrease proteinuria, and to mitigate hyperfiltration. These drugs now have been shown to be fetotoxic causing profound fetal hypotension, renal tubular dysplasia, anuria-oligohydramnios, growth restriction, hypocalvaria, and death when used in the second and third trimesters of pregnancy. We recommend that ACE inhibitors not be used in pregnancy. However, if a child is born with ACE inhibitor fetopathy, aggressive therapy with dialysis to remove the inhibitor may mitigate the profound hypotensive effects. Therapy will depend on the specific ACE inhibitor, and care recommendations cannot be generalized for the entire class of drugs as their protein binding and volume of distribution differ substantially.

Key words: Angiotensin converting enzyme inhibitors – Fetopathy – Therapy

Introduction

Since their first discovery in 1965, angiotensin converting enzyme (ACE) inhibitors have come to be regarded as a major advance in the treatment of hypertension [1]. Previous classes of antihypertensives such as β-adrenergic receptor blockers and diuretics tend to increase peripheral resistance and alter the metabolism of electrolytes, glucose, and lipids. ACE inhibitors, on the other hand, decrease vascular resistance, improve glucose handling, and control left ventricular mass [1]. ACE inhibitors produce little change in heart rate or cardiac output. They also have provided an improved quality of life for the young hypertensive patient especially when compared with β-blockers or other central nervous system suppressants which may cause decreased motivation, depression, and decreased school performance. The fact that ACE inhibitors impede the progression of nephropathy associated with diabetes, both in type I and II, made it probable that large numbers of women of childbearing age could be placed on these medications [2].

The ACE inhibitors are competitive inhibitors of kininase II. They affect both the angiotensin/aldosterone and bradykinin/prostaglandin systems (Fig. 1). ACE inhibitors affect the renal microvasculature resulting in dilatation of glomerular efferent arteries and a decrease in filtration pressure. Excretion of ACE inhibitors is principally renal. They are also known to cross the human placenta. In the fetus, it is presumed that these agents are at least partly excreted into the amniotic fluid and recycled by swallowing. The renin-angiotensin system is critically important under conditions of low renal perfusion pressure such as exist in the fetus. Angiotensin-mediated arteriolar resistance is essential to the maintenance of glomerular filtration and production of urine. Activation of bradykinin by suppression of angiotensin II can compromise the glomerular filtration rate by virtue of bradykinin's vasodilatory effect on the efferent arteriole (Fig. 1). Angiotensin II also may have a specific action on growth of its target tissues. Cells such as the adrenocortical cells can be induced to divide by angiotensin II. The mechanism by which angiotensin II induces hypertrophy of its target tissues is largely unknown but may involve a direct action on proto-oncogene synthesis or an indirect action on growth factor secretion [3].

Animal studies

Reports of fetal wastage in ACE inhibitor-exposed experimental animals occurred as early as 1980 [4]. The first adverse outcome in a human pregnancy was reported in 1981 and subsequently other cases implicating both captopril and enalapril as fetotoxins were reported in 1982 by

Correspondence to: A. B. Sedman

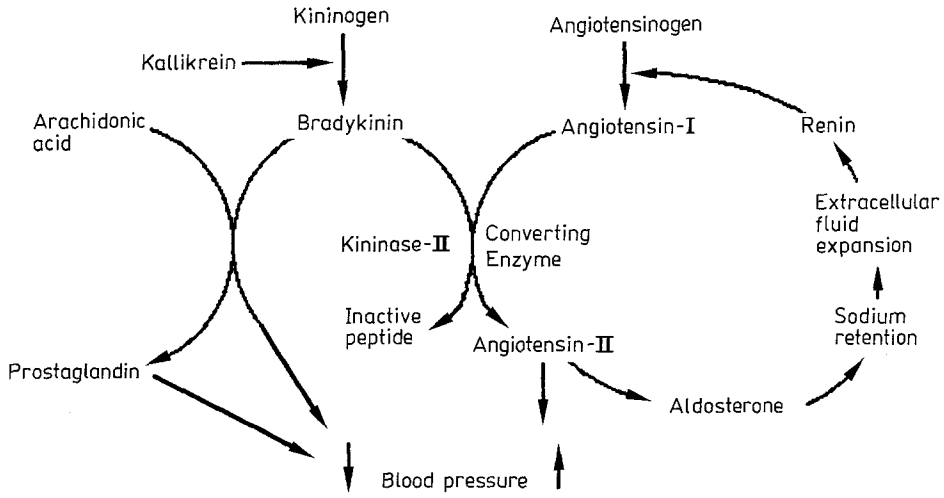

Fig. 1. Actions of angiotensin converting enzyme inhibitors on angiotensin/aldosterone and bradykinin/prostaglandin systems

Table 1. Reports of angiotensin converting enzyme (ACE) inhibitor fetopathy in the literature[a]

	n	IUGR	Oligohydramnios	Hypotension anuria	Mortality
Case reports	14	9/14	10/14	9/14	8/14
Case series	42	11/38	4/11	4/11	6/42
Totals	56	20/52 36%	14/25 56%	13/25 52%	14/56 25%

IUGR, Intrauterine growth retardation
[a] Compiled from Pryde et al. [13]

Guignard [5], and 1984 by Boutroy et al. [6], Caraman et al. [7], and Rothberg and Lorenz [8]. Animal models of ACE inhibitor fetopathy are relatively confusing. In rats, the development of the renin-angiotensin system is very late in gestation, and, therefore, results from rat studies have uniformly failed to reveal any adverse effects on fetuses. In late gestation and lactation studies in which ACE inhibitor exposure occurred during the critical period of rat fetal renin synthesis, neonates did demonstrate adverse effects, with pup deaths occurring during lactation.

Rabbits are particularly sensitive to ACE inhibitors; administration of 2–5 mg/kg per day of captopril in pregnant rabbits yielded pregnancy loss rates from 37% to 92% [4, 9]. Rabbit fetuses in late gestation are highly sensitive to toxic effects of ACE inhibitors. When administered in a human therapeutic range, ACE inhibitors produce fetal deaths in middle to late gestation with a peak effect on gestational day 26 (term gestation = 47 days) [9, 10].

The chronically catheterized sheep model was used by Broughton-Pipkin et al. in 1982 [9] and was shown to be an excellent model to study cardiovascular and renal changes occurring in the maternal and fetal compartments during pregnancy. When captopril was given to sheep from gestation day 119–133 (term = 147), maternal blood pressure was transiently reduced and returned to normal within 2 h. However, fetal blood pressure remained reduced for up to 2 days and seven of eight lambs were stillborn.

A recent study utilizing a crossover design in 12 sequentially pregnant baboons treated with placebo versus a therapeutic dose of enalapril demonstrated a high rate of affected fetuses. Of 13 fetuses in the enalapril arm, 8 had adverse outcomes, with 3 of the 13 having fetal deaths versus 0 adverse outcomes or deaths in the placebo arm. No gross abnormalities were noted on autopsy of the dead fetuses other than low birth weight. No histology was done [11].

Clinical studies

Data concerning adverse effects of ACE inhibitors on human fetuses were first noted in 1981 by Duminy and Burger [12]. Warnings about the use of ACE inhibitors in human pregnancy appeared in the literature as early as 1985. Despite this information, reviews of ACE inhibitors often made no mention of the adverse fetal effects; and certainly, in the obstetrical community, there did not seem to be widespread knowledge of fetotoxicity. In 1993, Pryde, et al. [13] summarized affected cases from the literature and added 3 more (Table 1). Subsequent petitioning of the Food and Drugs Administration (FDA) concerning these cases led to an FDA bulletin on March 16, 1992 emphasizing the warning information regarding use of ACE inhibitors in pregnancy. A box warning was required for all ACE inhibitors which stated that when ACE inhibitors were used in pregnancy during the second and third trimesters they could cause injury and even death to the developing fetus. There has been no absolute proof that first trimester exposure has adverse fetal effects; however, Piper et al. [14] did report one instance of encephalocele occurring in a fetus with first trimester exposure. The most common effects reported are second and third trimester onset of oligohydramnios and growth restriction followed by a neonatal course associated with prolonged profound hypotension and anuria. If the oligohydramnios is severe enough, a Potter-like sequence and pulmonary hypoplasia can occur. Hypocalvaria also has been reported and thought to be secondary to poor perfusion of plate-like bone structure in the skull [15]. Although persistence of patent ductus arteriosus may have an association, the high rate of this defect in premature infants makes the data inconclusive. Pathological examination of the kidneys in 10 cases

Table 2. Data from three patients at University of Michigan Medical Center with ACE inhibitor fetopathy

	Maternal disease Medication	Infant gestation Birth weight	Signs and symptoms	Dialysis	ACE levels before dialysis	ACE levels after dialysis	Lisinopril level (ng/ml)	Outcome
Case 1	18 years primigravida renal HTN lisinopril	32 weeks 1,480 g	Oligohydramnios IUGR hypocalvaria hypotension renal failure normal-sized kidneys	2.5%–4.25% 20 ml/kg q 1/2° –q 3° Dialysis/plasma = 0.52 (ratio of lisinopril)	7.5 μmol/ml (normal 20–30 μmol/ml)	19.5 μmol/ml	serum 6.3 dialysate 3.3	Chronic renal failure transplant normal cognition decreased growth
Case 2	30 years primigravida essential HTN enalapril 7.5 mg p.o. qd	32 weeks 980 g	Oligohydramnios IUGR hypocalvaria hypotension renal failure normal-sized kidneys	2.5% 20 ml/kg q 1/2° –q 1°	1.1 U/ml (normal = 20–30 U/ml)	9.2 U/ml		Death day 9 from perforated bowel
Case 3	26 years, G2, P0-1 lupus captopril 150 qd lasix, atenolol	33 weeks 1,440 g	Oligohydramnios IUGR hypocalvaria hypotension renal failure normal-sized kidneys					Death day 1

HTN, Hypertension

showed normal to large-sized kidneys with renal tubular dysgenesis. Barr et al. [15] have made specific recommendations that ACE inhibitors be considered fetopathic instead of teratogenic in that the effects are secondary to hypotension and poor perfusion without evidence that there is actual early malformation of the fetus.

There now have been approximately 56 cases of ACE fetopathy in the literature [13]. These infants are affected by intrauterine growth retardation, oligohydramnios, hypotension and anuria, with a mortality rate of approximately 25%. Three cases in our institution, previously reported [13], exemplify the classic findings. These are tabulated in Table 2.

Case reports

Case 1

This was the 32-week, 1,480-g infant of an 18-year-old prima gravida who had been treated with lisinopril throughout her pregnancy for renovascular hypertension. Spontaneous rupture of membranes and fetal distress led to the premature delivery of the infant who was noted to have severe oligohydramnios, intrauterine growth retardation, hypocalvaria, profound hypotension, and renal failure with a renal ultrasound that showed normal-sized kidneys. ACE levels prior to dialysis were 7.4 μmol/ml, normal being 20–30 μmol/ml. After standard peritoneal dialysis was started, these levels rose to 19.5 μmol/l. Lisinopril levels in the serum were 6.3 ng/ml while those in the dialysate were 3.3 ng/ml. Renal biopsy at 4 weeks showed acute tubular necrosis

Table 3. Pharmacokinetics of ACE inhibitors[a]

ACE	Onset/ duration (h)	Time to peak serum levels (h)	Percentage absorbed	Active metabolite	*t*1/2 Normal renal function	*t*1/2 Impaired renal function	Elimination 24 h		% protein bound	Dialyz-ability	Volume of distribution
							Total	Unchanged			
Benazepril	1/24	0.5–1	37%	Benazeprilat	10–11 h	Prolonged	NA	trace	95%	yes	0.12 l/kg
Captopril	0.25/dose-related	0.5–1.5	75%		<2 h	3.5–32 h	>95%	40%–50% in urine	25%–30%	yes	0.7 l/kg
Enalapril	1/24	0.5–1.5 (enalaprilat 3–4)	60%	Enalaprilat	1.3 h	NA	94% urine and feces	54% in urine (40% enalaprilat)	50%–60%	yes	0.375 l/kg
Enalaprilat	0.25/~6	NA	NA		11 h	Prolonged	NA	>90% (urine)		yes	0.375 l/kg
Fosinopril	1/24	~3	36%	Fosinoprilat	12 h (Fosinoprilat IV)	Prolonged	50% urine 50% feces	negligible	95%	no	0.14 l/kg
Lisinopril	1/24	~7	25%		12 h	Prolonged	NA	urine 100%	small	yes	1.8 l/kg
Quinapril	1/24	1	60%	Quinaprilat	2 h (Quinaprilat)	Prolonged	~80% urine ~37% feces	trace	97%	no	
Ramipril	1–2/24	1 (ramiprilat 2–4)	50%–60%	Ramiprilat	1–2 h (Ramiprilat)	Prolonged	80% urine 40% feces	<2%	56%–73%	unknown	unknown

NA, Not available

[a] Compiled from Facts and Comparisons, Inc., St. Louis, Mo. USA, January 1994 and direct communication with innovator companies

and renal tubular dysplasia. This infant was supported on dialysis until renal transplant occurred at 22 months of age. The child had a successful transplant and is now stable at 4 years of age with normal cognitive development. His severe intrauterine growth retardation was never completely corrected; and, although he resumed a normal growth velocity after transplant, he is still –4 SD below the curve and is a candidate for growth hormone therapy.

Case 2

This was a 32-week, 980-g infant born of a 30-year-old prima gravida who had essential hypertension which initially had been treated with labetalol. She was switched to enalapril with the belief that it would be a better drug during pregnancy. This infant was also born with oligohydramnios, intrauterine growth retardation, hypocalvaria, hypotension, and renal failure with normal-sized kidneys. His ACE level before dialysis was 1.1 μmol/ml, normal being 20–30 μmol/ml. ACE levels increased with peritoneal dialysis, but the baby remained profoundly hypotensive and had necrotizing enterocolitis, perforated viscus, and subsequently died on day 9 of life. At autopsy, the baby had hypocalvaria. The kidneys were normal sized with tubular dysplasia. The lungs were hypoplastic.

Case 3

This was a 33-week gestation infant who had been noted at 19 weeks of gestation to have severe oligohydramnios. She was the child of a 26-year-old woman with an 8-year history of systemic lupus erythematosus whose hypertension was controlled with a combination of captopril, 150 mg every day, furosemide, and atenolol. Oligohydramnios and growth restriction were noted beyond the 14th week of gestation. The 1,440-g female was delivered from a breech presentation and had Apgar scores of 1 and 5, was basically unresponsive to support and died at 14 h of life with normal-sized kidneys but no urine output. This baby also had significant hypocalvaria. Renal histopathology showed normal-sized kidneys with renal tubular dysplasia.

Pharmacokinetics of ACE inhibitors

There are now seven ACE inhibitors marketed in the United States. They include enalapril, captopril, lisinopril, ramipril, fosinopril, benzapril, and quinapril. Characteristics of these drugs are listed in Table 3, reflecting their protein binding, volume of distribution, and potential dialyzability. Both fosinopril and quinapril are very highly bound to plasma proteins and, therefore, dialysis would not be predicted to be helpful in children who have been exposed to these drugs. Exchange transfusions may be helpful but no such cases have been reported. Enalapril, captopril, and lisinopril are predicted to be somewhat dialyzable. Our data in the infant who received lisinopril and was successfully dialyzed demonstrate that ACE activity was lower than normal prior to dialysis and subsequently returned to normal level after dialysis. Lisinopril levels in the serum were approximately twice the level of those in the dialysate after a 1-h pass. As ACE levels returned to normal, urine output increased from 0.2 ml/kg per hour up to 2.5 ml/kg per hour. This child then continued to have urine output although he was never adequately able to regain full kidney function. Early hemodialysis would have been better than peritoneal dialysis to facilitate the clearance, but the infants were too hypotensive to attempt hemodialysis.

Summary

In summary, ACE inhibitors have been shown to cause fetal toxicity, including profound fetal hypotension, anuria, oliguria, and growth restriction. Animal data have also documented these effects. Recognition of the syndrome would include noting the kidneys are normal size on renal ultrasound but that there is profound renal failure with little urine output. Clearly, early fetal loss with severe prematurity could be occurring with an ACE inhibitor exposure, and may be missed. Once a child is noted to have fetal toxicity, management should include assessment of type of drug. Decisions made about method of dialysis will be dependent on the characteristics of that particular ACE inhibitor. Highly protein-bound drugs are less amenable to clearance by dialysis, but exchange transfusion while on hemodialysis could be a helpful therapy.

The best 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 trimester of pregnancy. If the drug is inadvertently administered during this period, it is estimated that 50% of the infants will be affected and 25% will die. The drug should be stopped if at all possible. As new drugs are manufactured that mimic the effect of ACE inhibitors, such as ACE receptor blockers, the same type of fetal effects could be anticipated. Extensive animal testing in sheep and higher primates should be performed in order to predict toxicity.

Acknowledgement. We wish to thank Dr. Mason Barr for his support and Ruth Primas for preparation of the manuscript.

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