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Case Report

Clinical Pharmacology of Enalapril and Enalaprilat in Infants and Children

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Abstract

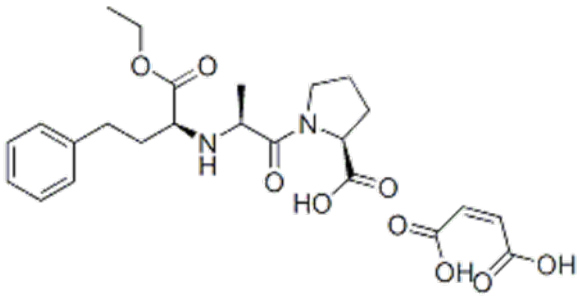
Enalapril maleate is a prodrug that is hydrolysed by esterase to produce enalaprilat which is a potent inhibitor of the angiotensin-converting enzyme. Enalapril maleate is administered orally, the oral bioavailability is about 60%, whereas enalaprilat is administered intravenously, and both drugs are eliminated by renal route. The initial oral dose of enalapril is 40 μg/kg once-daily in infants and in children the initial oral dose is 2.5 mg once-daily. Enalapril controls the heart disease, restores ventricle physiology, and lowers blood pressure in infants and children. Enalapril is effective for congestive heart failure, for the chronic heart failure, and reduces pulmonary resistance. The elimination half-life of enalapril is about 10 hours in infants aged < 20 days and about 3 hours in older infants and children. Enalapril interacts with felodipine, metformin, and rifampicin and the co-administration of enalapril with furosemide causes acute kidney injury. Enalapril treats severe heart failure, a dose of 0.01 mg/kg of enalapril has been recommended in preterm infants, and enalapril lowers the diastolic blood pressure. Enalapril crosses the human placenta in-vivo but a study performed with the perfusion of the placenta reveals that enalaprilat does not equilibrate between the maternal and foetal comportments and enalaprilat poorly migrates into the breast-milk. The aim of this study is the review the published data on the enalapril dosing, efficacy, safety, effects, pharmacokinetics, drug interaction and treatment in infants and children and the transfer across the human placenta and the migration into the breast-milk.

ABBREVIATION

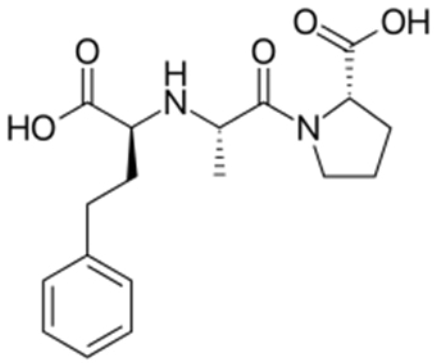
ACE: Angiotensin-Converting Enzyme

INTRODUCTION

Angiotensin-converting enzyme (ACE, kinase II, dipeptidyl carboxy-peptidase) is an ectoenzyme and glycoprotein with an apparent molecular weight of 170 kDa. Human ACE contains 1277 amino acid residues and two homologues domains, each with a catalytic site and a Zn^{2+}-binding region. ACE has a large amino-terminal extracellular domain, a short carboxyl-terminal intracellular domain, and a 22 amino acid transmembrane hydrophobic region that anchors the ectoenzyme. ACE is rather nonspecific and cleaves dipeptide units from substrates with diverse amino acid sequences. Preferred substrates have only one free carboxyl group in the carboxyl-terminal amino acid, and proline must not be the penultimate amino acid; thus, the enzyme does not degrade AngII. ACE is identical to kinase II, the enzyme that inactivate does not degrade AngII. ACE is identical to kinase II, the enzyme that inactivates bradykinin and other potent vasodilator peptides. Although slow conversion of AngI to AngII occurs in plasma, the very rapid metabolism that occur in-vivo is due largely to the activity of membrane-bond ACE present on the luminal surface of endothelial cells throughout the vascular system. The ACE gene contains an insertion/deletion polymorphism in intron 16 that explains the large phenotypic variance in serum ACE levels. The metabolism of bradykinin may confer an increased risk of hypertension cardiac hypertrophy, atherosclerosis, and diabetes nephropathy. Enalapril maleate is a prodrug that is hydrolysed by esterases in the liver to produce enalaprilat, the active dicarboxylic acid. Enalaprilat is a potent inhibitor of ACE with a K_1 of 0.2 nM. Enalapril is absorbed rapidly when given orally and has an oral bioavailability of about 60% (not reduced by food). Although peak concentrations of enalapril in plasma occur within an hour, enalaprilat concentration peak only after 3 to 4 hours. In adults, enalapril has an elimination half-life of about 1.3 hours, but enalaprilat, because of tight binding to ACE, has a plasma elimination half-life of about 11 hours. Elimination is by the kidneys as either intact enalapril or enalaprilat. The oral dose of enalapril ranges from 2.5 to 40 mg daily, with 2.5 and 5 mg daily appropriate for the initiation of therapy for heart failure and hypertension, respectively. Enalaprilat is not absorbed orally but is available for intravenous administration when oral therapy is not appropriate. For adult hypertensive patients, the dosage is 0.625 to 1.25 mg given intravenously over 5 min and this dosage may be repeated every 6 hours. Enalapril and enalaprilat are effective in the treatment of cardiovascular disease, heart failure, and diabetic nephrotoxicity [1].



Enalapril maleate molecular structure (molecular weight = 492.5 grams/mole)



Enalaprilat molecular structure (molecular weight = 348.4 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "enalapril dosing infants, children", enalapril efficacy, safety infants, children", "enalapril effects infants, children", "enalapril pharmacokinetics infants, children", "enalapril drug interactions", "enalapril treatment infants, children", "enalapril placental transfer", and "enalapril migration into the breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], NEOFAX® by Young and Mangum [2], and The British National Formulary for Children [3] were consulted.

RESULTS

Administration schedules of enalapril maleate to infants and children Oral treatment of enalapril maleate to infants [2] Infants. Begin the treatment with 40 µg/kg once-daily (0.04 mg/kg once-daily). Usual maximum dose of 150 µg/kg per dose (0.15 mg/kg per dose 4 times-daily), and titrate the subsequent doses and interval based on amount and duration of response. The dosage may need to be increased every few days.

Intravenous treatment of enalapril at to infants [2] Infants. Begin the treatment with 10 µg/kg once-daily. Titrate subsequent doses and interval based on amount and duration of response and the dosage may need to be increased every few days.

Oral treatment of enalapril maleate to children [3]

Oral treatment of hypertension under expert supervision

Children aged 1 month to 11 years. Give initially 100 µg/kg once-daily, monitor the blood pressure carefully for 1 to 2 divided doses, and then increase the dose if necessary up to 1 mg/kg daily in 1 to 2 divided doses.

Children aged 12 to 17 years with body-weight up to 50 kg. Give initially 2.5 mg once-daily, monitor the blood pressure carefully for 1 to 2 hours, and the maintenance dose consists in 10 to 20 mg daily in 1 to 2 divided doses.

Children aged 12 to 17 years with body-weight ≥ 50 kg. Give initially 2.5 mg once-daily, monitor the blood pressure carefully for 1 to 2 hours, and the maintenance dose consists in 10 to 20 mg daily in 1 to 2 divided doses (maximum dose = 40 mg daily).

Oral treatment of heart failure under expert supervision

Children aged 1 month to 11 years. Give initially 100 µg/kg once-daily, monitor the blood pressure carefully for 1 to 2 hours, and then increase the dose if necessary up to 1 mg/kg daily in 1 to 2 divided doses.

Children aged 12 to 17 years with body-weight up to 50 kg. Give initially 2.5 mg once-daily, monitor the blood pressure carefully for 1 to 2 hours, and the maintenance dose consists in 10 to 20 mg daily in 1 to 2 divided doses.

Children aged 12 to 17 years with body-weight ≥ 50 kg. Give initially 2.5 mg once-daily, monitor the blood pressures carefully for 1 to 2 hours, and the maintenance dose consist in 40 mg daily.

Oral treatment of proteinuria in nephritis under expert supervision

Children aged 1 month to 11 years. Give initially 100 µg/kg once-daily, monitor the blood pressure carefully for 1 to 2 hours, and then increase the dose if necessary up to 1 mg/kg daily in 1 to 2 divided doses.

Children aged 12 to 17 years with body-weight up to 50 kg. Give initially 2.5 mg once-daily, monitor the blood pressure carefully for 1 to 2 hours, and the maintenance dose consists in 10 to 20 mg daily in 1 to 2 divided doses.

Children aged 12 to 17 years with body-weight ≥ 50 kg. Give initially 2.5 mg once-daily, monitor the blood pressures carefully for 1 to 2 hours, and the maintenance dose consist in 10 to 20 mg daily in 1 to 2 divided doses (maximum dose = 40 mg daily).

Oral treatment of diabetic nephrotoxicity

Children aged 12 to 17 years with body-weight up to 50 kg. Give initially 2.5 mg once-daily, monitor the blood pressure carefully for 1 to 2 hours, and the maintenance dose consists in 10 to 20 mg daily in 1 to 2 divided doses.

Children aged 12 to 17 years with body-weight ≥ 50 kg. Give initially 2.5 mg once-daily, monitor the blood pressure carefully for 1 to 2 hours, and the maintenance dose consists in 10 to 20 mg daily in 1 to 2 divided doses (maximum dose = 40 mg daily).

Efficacy and safety of enalapril in infants and children

Enalapril is efficacy and safe in infants in treating heart disease [4]. Enalapril is efficacy and safe in preterm and term

infants for treating structural cardiac disease [5]. Enalapril is efficacy and safe in infants to restore ventricle physiology [6]. Enalapril is clinically safe and effective for infants with cardiac failure secondary to ventricular impairment, valvar regurgitation, or after cardiac surgery [7]. An enalapril initial dose of 2.5 mg in children weighing < 50 kg and 5 mg in children weighing > 50 kg (mean = 0.08 mg/kg) administered once-daily effectively lowers the blood pressure within 2 weeks and the decrease of blood pressure is dose dependent [8]. Valsartan and enalapril provides comparable blood pressure reductions and effective blood pressure control and are well tolerated in hypertensive children [9].

Effects of enalapril and enalaprilat in infants and children

In infants with congestive heart failure, mean baseline ACE activity is significantly higher than in control infants (36.4+7.2 mu/ml versus 26.9+6.9 mu/ml, P-value < 0.05) [10]. Enalapril is effective for the treatment of chronic heart failure in children when it is administered orally, once-daily or twice-daily, and the daily dose ranges from 0.1 to 0.5 mg/kg. Enalaprilat is effective for the treatment of chronic heart failure in children when it is administered intravenously, once-daily to thrice-daily, in a dose ranging from 0.01 to 0.05 mg/kg [11]. Enalapril may benefit of heart failure associated with large ventricular septal defects and normal or mildly pulmonary resistance [12].

Pharmacokinetics of enalapril in infants and children

Nakamura et al. [13], studied the pharmacokinetics of enalapril in 14 infants and children, aged 10 days to 6.5 years, with congestive heart failure caused by congenital heart disease. The oral dose of enalapril maleate ranges from 0.05 to 0.3 mg/kg.

Table 1 Pharmacokinetic parameters of enalapril which are obtained in 14 infants and children with congestive heart failure and enalapril maleate are administered as a single dose. Figures are the mean and (range), by Nakamura et al [13].

Age and sample size	**Enalapril maleate dose (mg/kg)**	**$AUC_{0\text{-}24\,h}$ (ng/ml*h)**	**Elimination half-life (h)**
< 20 days (N = 3)	0.05 – 0.30	269 (162 – 425)	10.3 (4.2 – 13.4)
>20 days to 6.5 years (N = 11)	0.05 – 0.30	82.7 (23.7 – 168)	2.7 (1.3 – 6.3)

This table shows that AUC and the elimination half-life of enalapril are greater in infants aged < 20 days than in older infants and children. Enalapril is cleared from the body by metabolism and by renal route and both elimination pathways increase with infant maturation and child development.

Pharmacokinetics of enalaprilat in infants and children

Table 2 Pharmacokinetic parameters of enalaprilat which are obtained in 14 infants and children with congestive heart failure following enalapril maleate administration which is administered as a single dose. Figures are the mean+SD and (range), by Nakamura et al. [13].

Age and sample size	Enalapril maleate dose (mg/kg)	Enalaprilat peak conc. (ng/ml)	Tmax (h)	Enalaprilat $AUC_{0\text{-}24\,h}$ (ng/ml*h)
< 20 days (N = 3)	0.0 – 0.30	---	4.00	691 (447 – 892)
>20 days to 6.5 years (N = 11)	0.05 – 0.30	9.0±4.7	7.3±2.4	138 (43.4 – 285)

Tmax = time to reach the peak concentration. This table shows that AUC of enalaprilat is greater in infants aged < 20 days than in older infants and children. Enalaprilat is cleared from the body by renal route and the renal function increases with infant maturation and child development.

Interaction of enalapril with drugs

The co-administration of enalapril and felodipine affects the pharmacokinetics of felodipine, but not that of enalapril [14]. An infant affected by initial congestive cardiac failure, after starting the treatment with enalapril in association with furosemide, develops acute kidney injury [15]. Drug-drug interaction is observed between metformin and enalapril [16]. Enalapril reduces the systemic vascular resistance more effectively when given in combination with ticlopidine than with aspirin [17]. There is an interaction between rifampicin and enalapril causing reduced hypotensive efficacy of enalapril [18].

Treatment with enalapril in infants and children

Two weeks after starting enalapril, the clinical features of heart failure improve in all the infants, the mean+SEM plasma sodium concentration increases from 129+2.4 to 136+1.1 mmol/L and plasma urea concentration falls from 7.0+0.85 to 2.9+0.85 mmol/L. These data suggest that enalapril is a potentially useful treatment for severe heart failure in infancy [19]. Oral administration of enalapril of 0.1 mg/kg causes severe hypotension and renal failure in a preterm infant. A starting oral dose of 0.01 mg/kg is recommended in preterm infants [20]. Enalapril tablet and enalapril suspension are well tolerated in children and there is no clinically significant adverse-effects. The bioavailability of enalapril oral suspension 10 mg is similar to that of 10 mg enalapril tablet [21]. In doxorubicin-treated long-term survivors of childhood cancer, enalapril induces improvement in left-ventricular structure. The primary defect, which is left-ventricular wall thinning, continues to deteriorate, and thus the short-term improvement is mostly related to lower diastolic blood pressure [22]. Enalapril is a clinically effective and useful angiotensin-converting enzyme inhibitor for the management of children with chronic congestive heart failure [23].

Transfer of enalapril and enalaprilat across the human placenta

Enalapril crosses the human placenta in the maternal and foetal directions in similar quantity [24]. Miller et al. [25], studied the kinetics of enalaprilat across the human perfused placenta. The peak concentration and the AUC values for enalaprilat in the maternal perfusate are approximately three times higher than in the foetal perfusate and the drug concentrations does not equilibrate between maternal and the foetal perfusate during 4

to 6 hours of perfusion. At the end of the perfusion period, the mean percent of total drug added in the maternal perfusate is 59%, with 23% in the foetal perfusate and the remaining (18%) in the placental tissue. Enalaprilat crosses the human perfused placental from the maternal to foetal compartment but enalaprilat does not equilibrate between the maternal and foetal compartments.

Migration of enalapril and enalaprilat into the breast-milk

One mother taking a single oral dose of enalapril 5 mg and 2 mothers taking a single dose 10 mg 3 to 45 days postpartum had undetectable enalaprilat milk concentration (<0.2 μg/ml) [26]. One woman who had been taking oral enalapril 10 mg daily for 11 months has the peak enalapril milk concentrations of 2 μg/ml 4 hours after a dose and the peak enalaprilat concentration is 0.75 μg/L 9 hours after the dose [27]. Five women who received enalapril at a single dose 20 mg, the average peak enalapril milk concentration is 1.7 μg/L (range, 0.54 to 5.9). The average peak enalaprilat concentration is 1.7 μg/L (range, 1.2 to 2.3) after 4 hours in 4 of 5 women. The average peak enalaprilat concentration is 1.7 μg/L, peaks occurred at various times over the 24 hour period, and the breasted infants receives < 2 μg daily of enalaprilat [28].

DISCUSSION

Enalapril maleate is a prodrug that is hydrolysed by esterases in the liver to produce enalaprilat which is a potent inhibitor of angiotensin-converting enzyme with a K_i of 0.2 nM. Enalapril is absorbed rapidly when given orally and has an oral bioavailability of about 60% which is not reduced by food whereas enalaprilat is not absorbed by the gastrointestinal-tract and it is administered intravenously. Both enalapril and enalaprilat are cleared from the body by renal route. Enalapril and enalaprilat are effective in the treatment of cardiovascular disease, heart failure, and diabetic nephrotoxicity [1]. In infants, the initial oral dose of enalapril is 40 μg/kg once-daily and the initial intravenous dose of enalaprilat is 10 μg/kg once-daily [2]. In children, aged up to 11 years, the oral dose of enalapril is 100 μg/kg once-daily and in older children the initial dose is 2.5 mg/kg once-daily [3]. Enalapril has been found efficacy and safe in infants and children [4-9]. Enalapril is efficacy and safe for the control of heart disease [4], and enalapril is efficacy and safe for the treatment of structural cardiac disease [5] in infants and children. Enalapril restores ventricle physiology in infants [6] is efficacy and safe for the treatment of cardiac failure secondary to ventricular impairment, valvar regurgitation or after cardiac surgery in infants [7], lowers blood pressure in children [8]. Enalapril and valsartan produce similar blood pressure in hypertensive children [9]. The effects of enalapril and enalaprilat have been studied in infants and children [10-12]. Enalapril is effective in the control of congestive heart failure in infants [10], enalaprilat controls the heart failure when it is administered at a dose ranging from 0.01 to 0.05 mg/kg in children [11], and enalapril may benefit of heart failure associated with large ventricular septal defects [12]. The pharmacokinetics of enalapril and enalaprilat have been studied in infants and children [13]. In infants aged < 20 days, the mean elimination half-life of enalapril is 10.3 hours and in older infants and children it is 2.7 hours. Enalapril is cleared from the body by metabolism and renal route and both elimination pathways increase with infant maturation and child development. The mean enalaprilat AUC is 961 ng/ml*h in infants aged < 20 days and 138 ng/ml*h in older infants and children. Enalaprilat is eliminated by kidney and the renal function increases with infant maturation and child development. Enalapril interacts with drugs [14-18]. Enalapril affects the felodipine pharmacokinetics [14]. The co-administration of furosemide with enalapril develops acute kidney injury in an infant [15]. A drug-drug interaction is observed between metformin and enalapril [16]. Enalapril combined with ticlopidine reduces the systemic vascular resistance more effectively than with aspirin [17], and rifampicin associated with enalapril causes reduced hypotensive efficacy of enalapril [18]. The treatment with enalapril has been studied in infants and children [19-23]. Enalapril treats severe heart failure in infants [19], causes severe hypotension and renal failure in a preterm infants [20], the bioavailability of enalapril tablet is similar to that of enalapril suspension [21], enalapril induces improvement of left-ventricular structure and lowers diastolic blood pressure in children with cancer who are treated with doxorubicin [22], and enalapril manages chronic congestive heart failure in children [23]. An in-vivo study reveals that enalapril crosses the human placenta [24] and an investigation performed with the perfusion of the human placenta indicates that the transfer of enalaprilat from the maternal to foetal compartment is incomplete [25]. The available data on the migration of enalaprilat into the breast-milk consist in three letters to the editor [26-28]. After a single administration of enalapril, enalaprilat is not detected in the breast-milk [26] and following repeated administration of enalapril, enalaprilat poorly penetrates into the breast-milk [27,28].

CONCLUSION

In conclusion, enalapril maleate is a prodrug that is hydrolysed by esterases in the liver to produce enalaprilat. Enalapril is administered orally, the bioavailability is about 60% whereas enalaprilat is not absorbed by the gastrointestinal-tract and it is administered intravenously. Enalapril is effective in the treatment of cardiovascular disease, heart failure and diabetic nephrotoxicity. In infants, the initial oral dose of enalapril is 40 μg/kg once-daily, the initial intravenous dose of enalaprilat is 10 μg/kg once-daily, and in children the initial oral dose of enalapril is 2.5 mg/kg once-daily. Enalapril and enalaprilat are eliminated by renal route. The elimination half-life of enalapril increases with infant maturation and child development. Enalapril interacts with drugs and the association of furosemide with enalapril induces acute kidney injury in an infant. The treatment with enalapril improves heart failure, causes hypotensive effects, and manages chronic congestive heart failure in infants and children. An in-vivo study showed that enalapril crosses the human placenta and an investigation performed with the perfusion of the human placenta reveals the transfer-rate of enalaprilat is incomplete and enalaprilat poorly migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of enalapril and enalaprilat in infants and children.

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