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Review Article

Clinical Pharmacology of Captopril in Infants and Children

Gian Maria Pacifici*

Department of Pharmacology, University of Pisa, Italy

Abstract

Captopril is a potent angiotensin-converting enzyme inhibitor with a Ki of 1.7 nM. Captopril may be administered orally or intravenously and the oral bioavailability is about 75%. Most of the drug is eliminated in urine, 40 to 50% as captopril, and the rest as captopril disulphide dimers and captopril-cysteine disulphide. Captopril may be used in the treatment of congestive cardiac failure, and in moderate to severe hypertension in infants and children. The oral test dose of captopril is 10, 10 to 50, or 100 μg/kg thrice-daily in preterm infants, term infants, and older infants, respectively, and in children the oral test dose is 100 to 300 μg/kg twice-daily or thrice-daily. Captopril has been found efficacy and safe in treating heart failure in infant and in reducing hypertension in infants and children. The effects of captopril are: reduction of blood pressure, decrease pulmonary-to-systemic blood flow ratio, decrease systemic vascular resistance, and reduce aldosterone and natriuretic peptide blood concentrations in infants and children. Captopril causes different adverse-effects. The elimination of captopril is about 3 hours in infants and children. Captopril interacts with allopurinol, carnosine, potassium-sparing diuretics, or verapamil. Captopril treats infantile haemangioma, is a systemic vasodilator and reduces the blood pressure in hypertensive infants and children, and captopril poorly migrates into the breast-milk. The aim of this study is to review the published data of captopril dosing, efficacy and safety, effects, adverse-effect, pharmacokinetics, interaction with drugs, and treatments in infants and children, and the migration of captopril into the breast-milk.

***Corresponding author**

Gian Maria Pacifici, Department of Pharmacology,University of Pisa, Associate professor of Pharmacology, via Sant'Andrea 32, 56127 Pisa, Italy, Email: pacifici44@tiscali.it

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- Breast-milk

INTRODUCTION

Drugs that interfere with the renin-angiotensin system play a prominent role in the treatment of cardiovascular disease. Besides β_1 blockers that inhibit renin release, the following three classes of inhibitors of the renin-angiotensin system are utilized therapeutically: (1) angiotensin-converting enzyme inhibitors, (2) angiotensin receptors blockers, and (3) direct renin inhibitors. All of these classes of agents will reduce the actions of AngII and lower blood pressure, but each has different effects on the individual components of the renin-angiotensin system [1].

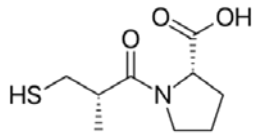
Mechanisms of captopril action

The angiotensin-converting enzyme inhibitors inhibit the conversion of AngI to AngII. Inhibitors of AngII production lowers blood pressure and enhances natriuresis. The angiotensin-converting enzyme is an enzyme with many substrates; thus, there are other consequences of its inhibition, including inhibition of the degradation of bradykinin, which has beneficial antihypertensive and protective effects. Angiotensin-converting enzyme inhibitors increase by 5-fold the circulating levels of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline, which may also contribute to the cardioprotective effects of angiotensin-converting enzyme inhibitors. Angiotensin-converting enzyme inhibitors will increase renin release and the rate of formation of AngI by interfering with both short and long-loop negative feedbacks on renin release. Accumulating AngI is directed down alternative metabolic routes, resulting in the increased production of vasodilator peptides such as Ang (1-9) and Ang(1-7) [1].

Absorption, distribution, metabolism, and excretion of captopril

Captopril is a potent angiotensin-converting enzyme inhibitor with a K_i of 1.7 nM. Given orally, captopril is absorbed rapidly and has a bioavailability of about 75%. The bioavailability is reduced by 25 to 30% with food. Peak concentration in plasma occurs within an hour, and the drug is cleared rapidly, with a half-life of about 2 hours in adults. Most of the drug is eliminated in urine, 40 to 50% as captopril, and the rest as captopril disulphide dimers and captopril-cysteine disulphide. In adults, the oral dose of captopril ranges from 6.25 to 150 mg twice-daily to thrice-daily, with 6.25 mg thrice-daily or 25 mg twice-daily appropriate for the initiation of therapy for heart failure or hypertension, respectively [1]. Captopril may be used in the management of infants with congestive cardiac failure. It is also used to control hypertension in older children, but intravenous labetalol followed

by oral nifedipine or amiodarone offers a more reliable strategy for controlling serious hypertension in infancy. Captopril is also used to reduce proteinuria in nephrotic syndrome [2]. Captopril is used in the treatment of moderate to severe hypertension. Afterload reduction in infants with congestive heart failure. Monitor frequent assessment of blood pressure, particularly after the first dose. Monitor periodic assessment of renal function and serum potassium concentration. The use of captopril is contraindicated in infants with bilateral renovascular disease or with unilateral renal artery stenosis in a solitary kidney, as the loss of adequate renal perfusion could precipitate acute renal failure [3].



Captopril molecular structure (molecular weight = 217.29 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "captopril dosing infants, children", captopril efficacy, safety infants, children", "captopril effects infants, children, "captopril adverse-effects infants, children", "captopril pharmacokinetics infants, children", "captopril drug interactions", "captopril treatment infants, children", and "captopril migration into the breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] are consulted.

RESULTS

Administration schedules to infants and children

Oral administration to infants [2]: In **preterm infants** (< 37 weeks of postmenstrual age), start by giving a test dose of 10 µg/kg of captopril and monitor blood pressure carefully. If there are no averse-effects, give 10 µg/kg thrice-daily. This dose can be increased progressively, as necessary, to no more than 100 µg/kg thrice-daily. In **term infants**, the initial test dose is 10 to 50 µg/kg. The same dose is given thrice-daily or twice-daily in the absence of adverse-effects and can be increased, if required, to a maximum of 2 mg/kg daily. In **older infants** start by given 100 µg/kg test dose and monitor blood pressure every 15 min for at least two hours. Start treatment by giving this dose thrice-daily or twice-daily, and increase the dose cautiously to a total day dose of no more than 4 mg/kg daily [2].

Treatment to children [4]

Oral treatment of hypertension:

- **Children aged 1 to 11 months.** The test dose is 100 µg/kg (maximum per dose = 6.25 mg). Monitor the blood pressure carefully for 1 to 2 hours; the usual dose is 100 to 300 µg/kg twice-daily or thrice-daily, and then increase the dose if necessary up to 4 mg/kg daily in divided doses the ongoing doses should only be given if the test dose is tolerated. The treatment is initiated under specialist supervision.
- **Children aged 1 to 11 years.** The test dose is 100 µg/kg (maximum per dose = 6.25 mg). Monitor the blood pressure carefully for 1 to 2 hours; the usual dose is 100 to 300 µg/kg twice-daily or thrice-daily, and then increase the dose if necessary up to 6 mg/kg daily in divided doses the ongoing doses should only be given if the test dose is tolerated. The treatment is initiated under specialist supervision.
- **Children aged 12 to 17 years.** The test dose is 100 µg/kg, alternatively the test dose is 6.25 mg. Monitor the blood pressure carefully for 1 to 2 hours; the usual dose is 12.5 to 25 mg twice-daily or thrice-daily, and then increase the dose if necessary up to 150 mg daily in divided doses, the ongoing doses should only be given if the test dose s tolerated. The treatment is initiated under specialist supervision.

Oral treatment of heart failure:

- **Children aged 1 to 11 months.** The test dose is 100 µg/kg (maximum per dose = 6.25 mg). Monitor the blood pressure carefully for 1 to 2 hours; the usual dose is 100 to 300 µg/kg twice-daily or thrice-daily, and then increase the dose if necessary up to 6 mg/kg daily in divided doses the ongoing doses should only be given if the test dose is tolerated. The treatment is initiated under specialist supervision.
- **Children aged 1 to 11 years.** The test dose is 100 µg/kg (maximum per dose = 6.25 mg). Monitor the blood pressure carefully for 1 to 2 hours; the usual dose is 100 to 300 µg/kg twice-daily or thrice-daily, and then increase the dose if necessary up to 6 mg/kg daily in divided doses, the ongoing doses should be only given if the test dose is tolerated. The treatment is initiated under specialist supervision.
- **Children aged 12 to 17 years.** The test dose is 100 µg/kg, alternatively the test dose is 6.25 mg. Monitor the blood pressure carefully for 1 to 2 hours; the usual dose is 12.5 to 25 mg twice-daily or thrice-daily, and then increase the dose if necessary up to 150 mg daily in divided doses, the ongoing doses should only be given if the test dose is tolerated. The treatment is initiated under specialist supervision.

Oral treatment of proteinuria in nephritis:

- **Children aged 1 to 11 months.** The test dose is 100µg/kg. Monitor the blood pressure carefully for 1 to 2 hours; the usual dose is 100 to 300 µg/kg twice-daily or thrice-daily, and then increase the dose if necessary up to 4 mg/kg daily in divided doses, the ongoing dose should only be given if the test dose is tolerated. The treatment is initiated under specialist supervision.
- **Children aged 1 to 11 years.** The test dose is 100 µg/kg (maximum per dose = 6.25 mg). Monitor the blood

pressure carefully for 1 to 2 hours; the usual dose is 100 to 300 μg/kg twice-daily or thrice-daily, and then increase the dose if necessary up to 6 mg/kg daily in divided doses, the ongoing doses should only be given if the test dose is tolerated. The treatment should be initiated under specialist supervision.

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Oral treatment of diabetic nephropathy in type 1 diabetes mellitus:

- **Children aged 12 to 17 years.** The test dose is 100 μg/kg, alternatively the test dose is 6.25 mg. Monitor the blood pressure carefully for 1 to 2 hours; the usual dose is 12.5 to 25 mg twice-daily or thrice-daily, and increase the dose if necessary up to 100 mg daily in divided doses, the ongoing doses should only be given if the test dose is tolerated. The treatment is initiated under specialist supervision.

Efficacy and safety of captopril in infants and children

Captopril is useful and safe in the control of severe heart failure in infancy [5]. Captopril has proven to be an effective antihypertensive agent in children over a broad age range and for a variety of clinical conditions [6]. Captopril is found to be an effective and safe drug for the treatment of children with severe hypertension [7].

Effects of captopril in infants and children

Six infants with congestive heart failure were given captopril to observe the effect on blood pressure. There is a significant fall in systolic (P-value < 0.02) and diastolic (P-value < 0.01) blood pressures at 90 minutes after the first dose [8]. Captopril acutely decreases the pulmonary-to-systemic blood flow ratio in infants with large left-to-right shunts who have elevated systemic vascular resistance [9]. Captopril acutely reduces the systemic vascular resistance and increases both cardiac output and stroke volume in children with congestive cardiomyopathy [10]. During short-term therapy, median serum aldosterone levels fall from 138 to 88.5 pg/ml (p-value < 0.05), and plasma atrial natriuretic peptide decreases from 144 to 94 pg/ml (p-value < 0.05) [11].

Adverse-effects caused by captopril in infants and children

Adverse-effects due to captopril are not dose-related in newborns and infants however the renal adverse-effects occur more often in younger infants [12]. Seventeen episodes of unpredictable decrease in blood pressure more than 40% from baseline occur during the reduced maintenance therapy. Four infants have seven episodes; the blood pressure decreases by 57±10% baseline; this decrease persists for 17±6 hours and is unresponsive to volume re-expansion and inotropic therapy. All seven episodes are accompanied by oliguria (urine output less than 1 ml/kg per hour), that persists for 18±12 hours. These episodes are accompanied by neurologic signs (subtle seizures, lethargy, and/or apnoea), within 18±6 hours after the onset of oliguria [13]. Two children with congenital nephrotic syndrome are described: one with Finnish-type nephrosis and the other with diffuse mesangial sclerosis. Both children have a prolonged and sustained clinical response with good physical health and normal growth patterns using captopril and indomethacin as their sole treatment [14]. An infant treated with captopril suffers from respiratory difficulties due to having upper airway oedema since 3 months of age [15].

Pharmacokinetics of captopril in infants

Pereira et al. [16], studied the pharmacokinetics of captopril in 10 infants aged 6.8±4.6 months (Table 1).

This table 1 shows that captopril is rapidly absorbed as the peak concentration occurs after 1.6 hours, is rapidly eliminated as the half-life is 3.3 hours which is similar to that of the adult value, and there is a remarkable interindividual variability in the pharmacokinetic parameters.

Pharmacokinetics of captopril in children

Mulla et al. [17], investigated the pharmacokinetics of captopril in 18 children aged 33.6±8.1 years weighing 77.4±13.6 kg and having a body mass index of 25.1±2.5 kg/m^2. After an overnight fast, each subject was given a single 25 mg oral dose of captopril (formulations were solution, suspension, or tablet), with 0.25 litre of water.

The Table 2 shows that the peak concentration is higher following the administration of captopril tablets, the two AUC values are similar with the three captopril formulations, and there is a remarkable interindividual variability in the pharmacokinetic parameters.

The Table 3 shows that Tmax is identical following the three captopril formulations, the elimination half-life is longer for the captopril suspension, and there is a remarkable interindividual variability in Tmax and in the elimination half-life.

Interaction of captopril with drugs

Among patients taking dipeptidylpeptidase-4 inhibitors for type 2 diabetes mellitus, concurrent use of such inhibitors with bumetanide, captopril, acetaminophen, and pantoprazole is associated with an increased risk of hypoglycaemia compared with the use of dipeptidylpeptidase-4 inhibitors alone [18]. The co-administration of captopril and allopurinol synergistically reduces features of the metabolic syndrome, especially hypertension, insulin resistance, and dyslipidaemia [19]. Carnosine in its concurrent use with captopril could act as a beneficial free radical scavenger, with less danger of overdose, in the inhibition of angiotensin-converting enzyme activity [20]. The combination of captopril and potassium supplements or potassium-sparing diuretics represents a potentially important drug interaction [21]. Verapamil therapy combined with captopril and spironolactone impairs the blood pressure which in normalized with only twice-daily administration of captopril [22].

Table 1: Pharmacokinetic parameters of captopril which are obtained in 10 infants. Captopril was administered orally at a dose of 1 mg/kg, by Pereira et al. [16].

	Peak concentration (ng/ml)	Tmax (h)	Elimination half-life (h)	Total body clearance (L/h/kg)
Mean	350	1.6	3.3	1.1
Standard deviation	±184	±0.4	±3.3	±0.4

Table 2: Summary statistics for peak concentration, AUC_{0-t}, and $AUC_{0-\infty}$ of captopril which are obtained in 18 children using three captopril formulations, by Mulla et al. [17].

	Peak concentration (ng/ml)			AUC_{0-t} (ng/ml*h)			$AUC_{0-\infty}$ (ng/ml*h)		
Formulation	Solution	Suspension	Tablet	Solution	Suspension	Tablet	Solution	Suspension	Tablet
N	18	17	18	18	17	18	18	17	18
Mean	362	387	486	1,232	1,184	1,495	1,515	1,412	1,673
SD	±247	±313	±294	±889	±769	±971	±1.234	±899	±1,119
Minimum	75.3	57.3	70.9	223	244	384	232	337	434
Maximum	800	1,095	1,008	3,253	2,694	3,517	4,617	3,427	4,328

Table 3: Summary statistics for Tmax and elimination half-life of captopril which are obtained in 18 children using three captopril formulations, by Mulla et al. [17].

	Tmax (h)			Elimination half-life (h)		
Formulation	**Solution**	**Suspension**	**Tablet**	**Solution**	**Suspension**	**Tablet**
N	18	17	18	18	17	18
Mean	1.0	1.0	1.0	2.2	3.2	2.3
SD	NC	NC	NC	±1.0	±1.6	±1.1
Minimum	0.5	0.5	0.5	0.7	1.5	0.3
Maximum	4.0	6.0	6.0	4.2	6.7	4.1

Tmax = time to reach the peak concentration. NC = not computed.

Treatment of infants and children with captopril

The response of infantile haemangioma to captopril supports a critical role for the renin-angiotensin system in infantile haemangioma and represents a paradigm shift in the understanding and treatment of this enigmatic condition [23]. Captopril is a selective systemic vasodilator and reduces ventricular left-to-right shunt and assesses the global haemodynamic status in infants [24]. Five children, aged 6 to 26 months, with hypertension were treated with captopril for 6 to 26 months. Hypertension is cured and significant adverse-effects consist in renal insufficiency but they are limited or transient [25].

Migration of captopril into the breast-milk

Captopril was administered at a dose of 100 mg thrice-daily to 12 lactating mothers. The peak blood concentrations of captopril, after the administration of the seventh day, averages to 713±141 ng/ml, compared to peak milk concentrations of 4.7±0.7 ng/ml. Time to reach peak blood concentrations averages to 1.1±0.2 hour, while the time to peak milk concentrations averages to 3.8±0.6 hours. These data suggest that the human breast-milk selectively restricts the passage of captopril from blood into milk [26]. Captopril was administered at an oral dose of 100 mg thrice-daily to 11 lactating mothers. The mean concentrations in the plasma and in the breast-milk are 713 and 4.7 ng/ml, respectively, and the concentration of captopril in the breast-milk to plasma ratio is 0.007 suggesting that captopril poorly migrated into the breast-milk [27].

DISCUSSION

Captopril is a potent angiotensin-converting enzyme inhibitor with a K_i of 1.7 nM. Captopril may be administered orally or intravenously and the oral bioavailability is 75% but food reduces the oral bioavailability by 25 to 30%. Most of captopril is eliminated in the urine, 40 to 50% as unchanged drug, and the rest as captopril disulphide dimers and captopril-cysteine disulphide [1]. Captopril is used in the management of congestive cardiac failure, in the reduction of proteinuria in nephrotic syndrome in infants [2], and in the treatment of moderate to severe hypertension in infants [3]. The blood pressure should be assessed carefully for 1 to 2 hours during the treatment. The initial oral test dose of captopril is 10, 10 to 50, or 100 µg/kg thrice-daily in preterm infants, term infants and older infants, respectively [2]. In children, the initial oral test dose is 100 to 300 µg/kg twice-daily or thrice-daily [4]. Captopril has been found efficacy and safe in infants and children [5-7]. Captopril has been found useful and safe in the control of severe heart failure in infants [5], is an affective hypertensive agent in children [6, 7]. The effects of captopril have been described in infants and children [8-11]. Captopril reduces the systolic and diastolic blood pressures in infants [8], and decreases the pulmonary-to-systemic blood flow ratio in infants who have elevated systemic vascular resistance [9]. Captopril reduces the systemic vascular resistance in children

and increases both cardiac output and stroke volume in children with cardiomyopathy [10], and decreases the aldosterone serum levels and the plasma atrial natriuretic peptide concentration [11]. Captopril induces adverse-effects in infants and children [12-15]. The adverse-effects induced by captopril are not dose-related in infants; however the renal adverse-effects occur more often in younger infants [12]. The treatment of hypertension with captopril is associated to adverse-effects such as unpredictable decrease in blood pressure which is followed by oliguria and neurologic signs such as subtle seizures, lethargy, and/or apnoea [13]. Two children with congenital nephrotic syndrome were treated with captopril; one developed Finnish-type nephrosis and the other has diffuse mesangial sclerosis [14]. An infant treated with captopril suffers from respiratory difficulties and has the upper airway oedema since 3 months of age [15]. The pharmacokinetics of captopril have been studied in infants [16] and in children [17]. Both studies report a captopril elimination half-life of about 3 hours. The pharmacokinetics of captopril have been studied in children following the administration of three captopril formulations which are: solution, suspension, and tablet. Higher values of peak concentration and AUC are found with captopril tablet formulation, whereas the time to reach the peak concentration (Tmax) is identical with the three formulations of captopril and the longest elimination half-life is found with captopril suspension. However, little variation of captopril elimination half-life is observed with the three formulations. Captopril interacts with drugs [18-22]. Patients treated with dipeptidylpeptidase-4 inhibitors for type 2 diabetes mellitus have increased risk of hypoglycaemia when are co-treated with bumetanide, captopril, and pantoprazole [18]. Captopril and allopurinol synergistically reduce the hypertension, insulin resistance, and dyslipidaemia [19]. The co-administration of captopril and carnosine has beneficial free radical scavenger, with less danger of overdose, in the inhibition of angiotensin-converting enzyme activity [20]. The combination of captopril and potassium supplements or potassium-sparing diuretics represents a potential important drug interaction [21], and the combination of captopril with verapamil or the combination of captopril with spironolactone may impair the blood pressure and the blood pressure could be normalized with only twice-daily captopril [22]. The treatment of infants and children with captopril has been reported [23-25]. Captopril treats the infantile haemangioma which supports a role for the renin-angiotensin system and represents a paradigm in the understanding and treatment of this enigmatic condition [23]. Captopril is a selective systemic vasodilator and reduces ventricular left-to-right shunts and assesses the global haemodynamic status in infants [24]. Children with hypertension are cured with captopril and the treatment has limited adverse-effects [25]. The migration of captopril into the breast-milk has been reported in two studies [26,27], and captopril poorly migrates into the breast-milk.

In conclusion, captopril is a potent angiotensin-converting enzyme inhibitor with a K_i of 1.7 nM. Captopril is used in the treatment of congestive cardiac failure and in the treatment of moderate to severe hypertension in infants and children. Captopril may be administered orally or intravenously and the oral bioavailability is about 75%, but food may reduce the bioavailability by 35 to 30%. Captopril is eliminated as unchanged drug in the urine for 40 to 50% of the dose and the remaining is eliminated as captopril disulphide dimers and captopril-cysteine disulphate. The initial oral test dose of captopril is 10, 10 to 50, or 100 μg/ml thrice-daily in preterm infants, term infants, and older children, respectively. In children, the initial oral test dose is 100 to 300 μg/ml twice-daily or thrice-daily. Captopril has been found efficacy and safe in infants and children but it may induce adverse-effects. Captopril reduces the systemic and diastolic blood pressures, decreases the pulmonary-to-systemic blood flow ratio, and decreases the serum aldosterone concentration and the plasma atrial natriuretic peptide concentration. The elimination half-life is about 3 hours in infants and children. The treatment of infants and children with captopril has been studied: captopril is effective in curing the infantile haemangioma, has vasodilator, and hypertensive effects, and captopril poorly migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of captopril in infants and children.

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