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PHARMACOKINETIC–PHARMACODYNAMIC MODELLING FOR CAPTOPRIL IN HEALTHY ANAESTHETIZED PIGLETS

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ABSTRACT

The use of the angiotensin converting enzyme inhibitor, captopril, specially in children, has been empirical. This is because the relationship between the pharmacokinetics and pharmacodynamics of captopril has not been clearly defined. It is not usually feasible to obtain the serial kinetic–dynamic data necessary to study this relationship in infants. The piglet was therefore investigated as an animal model in which to study the relationship between the kinetics and dynamics of captopril. The standard pharmacokinetic parameters for captopril in healthy anaesthetized piglets were found to be within the range reported for humans. Cl_{TB} was estimated to be $1{\cdot}42 \pm 0{\cdot}33\ L\,h^{-1}\,kg^{-1}$; $t_{1/2}$ was $0{\cdot}44 \pm 0{\cdot}08$ h; V_{dss} was calculated to be $0{\cdot}64 \pm 0{\cdot}13\ L\,kg^{-1}$; $t_{1/2}$ and $AUC_{0-\infty}$ was estimated to be $145 \pm 27\ ng\,h\,mL^{-1}$. The observed haemodynamic response was qualitatively similar to that in humans. Aortic pressure was reduced by $42 \pm 18\%$; heart rate was reduced by $21 \pm 11\%$. A parametric pharmacokinetic (two-compartment)–pharmacodynamic (linear) model has been established to describe plasma captopril concentration and aortic pressure relationship. Based on the observed results, the piglet was considered to be a viable model for our purpose.

KEY WORDS: captopril; pharmacokinetics; pharmacodynamics; piglets

INTRODUCTION

The angiotensin converting enzyme (ACE) inhibitor, captopril, has been used in the treatment of hypertension and congestive heart failure (CHF) in children[1,2] and in adults.[3] However, the use of captopril has been empirical because a clear relationship between its pharmacokinetics and its pharmacodynamics has not, hitherto, been elucidated. In order to study the relationship between the pharmacokinetics and pharmacodynamics of captopril, it is necessary to have pharmacokinetic data and relevant serial

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pharmacodynamic data. Such data are not presently available for paediatric patients.

In an earlier study we evaluated the pharmacokinetics of captopril in infants with congestive heart failure.[4] Unfortunately, it was not feasible to obtain serial haemodynamic data. Although all the infants were undergoing cardiac catheterization at the time of the first dose of captopril, the pharmacodynamic data obtained were not sufficient to allow modelling of the concentration–effect relationship. An appropriate animal model would provide data suitable for an initial study of kinetic–dynamic relationships.

Swine have long been used in cardiovascular research[5] because of their anatomic and physiologic similarities to humans[6]. It has been reported that the first 2·5 weeks of a piglet's life correspond to the first 6 months of the human infant's life.[7] The anaesthetized piglet was chosen in the hope that it would mimic the acute studies in sedated infants undergoing cardiac catheterization. The objectives of this study are, therefore, to evaluate the piglet as an appropriate animal model and to define a relationship between the pharmacokinetics and pharmacodynamics of captopril.

METHODS

Five healthy piglets, of the Yorkshire strain, were studied. The average age of the animals was $12 \pm 1{\cdot}6$ d (range, 10–14 d) and their average weight was $4 \pm 0{\cdot}2$ kg (range, 3·8–4·2 kg).

The surgical procedure for this preparation has been previously described.[8] In brief, general anaesthesia was induced and maintained with oxygen ($4\ L\ min^{-1}$), nitrous oxide ($4\ L\ min^{-1}$), and halothane (1·2% for induction and 0·75% for maintenance of anaesthesia). An electromagnetic flow probe was placed around the main pulmonary artery. Catheters were placed in the main pulmonary artery, aorta, left ventricle, and right and left atria. A Mikro-Tip® hi-fi catheter (size 5F) (Millar Instruments, Inc.), was used to measure the rate of change of left ventricular pressure, LV dP/dt, a measure of myocardial contractility. The ductus arteriosus was ligated. After the surgery was completed the animals were allowed to stabilize for approximately 0·5 h. The animals were considered to be in a haemodynamically stable condition if three consecutive measurements of aortic pressure taken approximately 5 min apart were within 5% of each other. Captopril (E. R. Squibb and Sons, Inc.) was dissolved in sterile normal saline and $0{\cdot}2\ mg\ kg^{-1}$ was administered as an intravenous (iv) bolus into the right atrium. Blood samples of 1 mL each were collected before and at 0·33, 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, and 120 min after the dose for the determination of concentrations of unchanged captopril in plasma. Plasma captopril concentrations were measured using the HPLC method developed and validated in our laboratory.[9] Intraday and interday variations of quality control samples were 10% or less at concentrations ranging from 10 to

1500 ng mL^{-1}. The accuracy for this assay is within 8%. Heart rate, main pulmonary artery flow, LV dP/dt, and pressures in the right and left atria, pulmonary artery, aorta, and left ventricle were also measured at the intervals mentioned above. A sham experiment was also performed in order to confirm the stability of the preparation over 2 h, i.e., the above procedures were followed except that sterile normal saline was injected instead of the captopril solution.

Models proposed by Holford and Sheiner[10] were used to study the concentration–effect relationship of captopril. Pharmacokinetic and pharmacodynamic data were evaluated in two stages. The first stage involved pharmacokinetic analysis; plasma concentration–time data were analysed using PCNONLIN.[11] A two-compartment open model, with elimination from the central compartment, was found to best describe the data. The choice of model was based on the Akaike information criterion (AIC).[12] Kinetic parameters generated were used as constants in the second-stage analysis. A series of kinetic–dynamic models comprising equation (1) below and one of the pharmacodynamic models, the linear, E_{max} and sigmoidal E_{max} models,[10] were created using PCNONLIN.[11] Equation (1) describes the time course of C_e, drug concentration at the hypothetical effect compartment:

$$C_e = \frac{DK_{e0}}{V_c}\left[\frac{(K_{21}-\alpha)e^{-\alpha t}}{(\beta-\alpha)(K_{e0}-\alpha)} + \frac{(K_{21}-\beta)e^{-\beta t}}{(\alpha-\beta)(K_{e0}-\beta)} + \frac{(K_{21}-K_{e0})e^{-K_{e0}t}}{(\alpha-K_{e0})(\beta-K_{e0})}\right] \quad (1)$$

where D is the dose, K_{e0} is the equilibration rate constant, V_c is the volume of distribution of the central compartment, α and β are exponential rate constants for a two-compartment model, K_{21} is the transfer rate constant from compartment 2 to compartment 1, and t is the time after the dose. These kinetic–dynamic models were used to estimate pharmacodynamic parameters. Applying the same criteria as described for the kinetic analysis, it was found that the time courses of aortic pressure were best described by a linear pharmacodynamic model:

$$E = SC_e + E_0 \quad (2)$$

where E is the effect being considered, S is the slope of the line relating concentration and effect and E_0 is the baseline effect.

A paired t test was used to determine significant differences between haemodynamic parameters from their corresponding baseline values. A p value of less than 0·05 was considered to indicate a statistically significant difference.

RESULTS

The sham experiment (i.e., no captopril given) with one healthy piglet confirmed the findings of other investigators[8] in that this surgical preparation was found to be stable for at least 2 h.

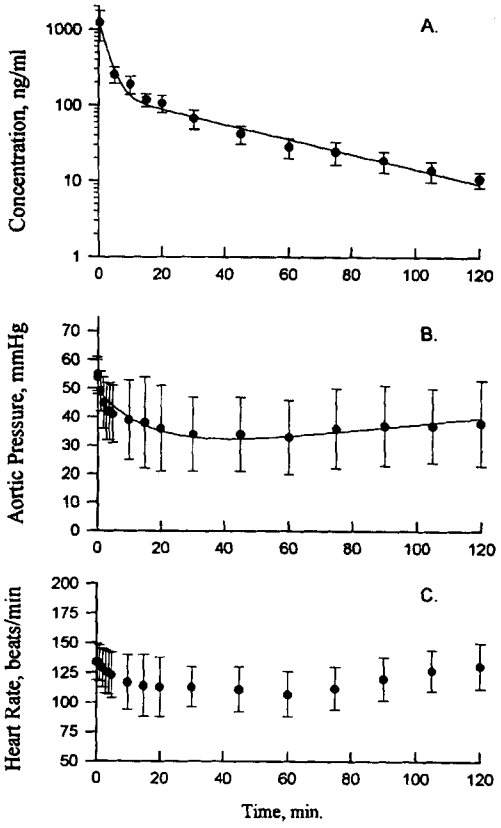

Figure 1. Plasma concentration (A), aortic pressure (B), and heart rate (C) versus time profiles for captopril after a 0·2 mg kg^{-1} iv captopril dose to five piglets (means ± SD shown)

The plasma concentration (mean ± SD) versus time profile of unchanged captopril after a 0·2 mg kg^{-1} iv dose to five piglets is shown in Figure 1(A). The pharmacokinetic parameters, calculated after a single dose, for unchanged captopril are summarized in Table 1.

The terminal elimination half-life, $t_{1/2}$, was estimated to be 0·44 ± 0·08 h (range, 0·35–0·54 h) for unchanged captopril after a 0·2 mg kg^{-1} iv dose of captopril. Total body clearance, Cl_{TB}, was estimated to be 1·42 ± 0·33 L kg^{-1} h^{-1} (range, 1·15–1·98 L kg^{-1} h^{-1}) and the volume of distribution at steady state, V_{dss}, was calculated to be 0·64 ± 0·13 L kg^{-1} (range, 0·51–0·78 L kg^{-1}). The area under the plasma concentration versus time curve, $AUC_{0-\infty}$, was 145 ± 27 ng h mL^{-1} (range, 101–173 ng h mL^{-1}).

The maximum percentage changes (± SD) in haemodynamic parameters were as follows: significant decreases were observed in pulmonary artery pressure (−22 ± 13; $p = 0·008$), aortic pressure (−42 ± 18; $p = 0·003$), heart rate

Table 1. Pharmacokinetic parameter estimates for unchanged captopril after a 0·2 mg kg^{-1} iv captopril dose to five piglets (two-compartment open model with bolus input)

Piglet	α (min^{-1})	β (min^{-1})	V_c (L kg^{-1})	K_{21} (min^{-1})	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng h mL^{-1})	Cl_{TB} (L h^{-1} kg^{-1})	V_{dss} (L kg^{-1})
1	0·0726	0·0215	0·57	0·0391	0·54	147·91	1·35	0·78
2	0·4029	0·0243	0·11	0·0579	0·48	173·40	1·15	0·51
3	0·5616	0·0243	0·14	0·0945	0·48	159·36	1·25	0·68
4	0·7145	0·0333	0·16	0·1162	0·35	100·78	1·98	0·76
5	0·4195	0·0322	0·15	0·0883	0·36	145·30	1·38	0·51
Mean	0·4342	0·0271	0·28	0·0792	0·44	145·35	1·42	0·64
SD	0·2381	0·0053	0·17	0·0306	0·08	27·28	0·33	0·13

(-21 ± 11; $p = 0{\cdot}01$), and LV dP/dt (-46 ± 20; $p = 0{\cdot}006$). Changes in cardiac output (-25 ± 27) and systemic and pulmonary vascular resistances (-20 ± 31 and 42 ± 41 respectively) were not significant.

Aortic pressure (mean ± SD) versus time is shown in Figure 1(B). Apart from the values obtained in the first 2 min of sampling, all aortic pressure values are significantly lower than the baseline value. The time course for heart rate is similar to that of aortic pressure (Figure 1(C)). However, only the average maximum reduction in heart rate (60 min) was significantly different from the baseline value; therefore, a pharmacokinetic–pharmacodynamic fit was not performed. The values of the compartmental pharmacokinetic model parameters (in the healthy piglets) used in the kinetic–dynamic model are summarized in Table 1. The pharmacokinetic–pharmacodynamic model parameters describing the relationship between C_e and aortic pressure in the healthy piglets are summarized in Table 2.

Table 2. Pharmacokinetic–pharmacodynamic model parameter estimates for aortic pressure after a 0·2 mg kg^{-1} iv captopril dose to five piglets

Piglet	K_{e0}[a] (min^{-1})	S[b] (mmHg mL ng^{-1})	E_0[c] (mmHg)
1	0·017 32	−0·418	46·03
2	0·006 33	−0·369	57·79
3	0·009 00	−0·584	43·64
4	0·005 90	−0·320	53·99
5	0·010 99	−0·300	60·49
Mean	0·009 91	−0·399	52·39
SD	0·004 63	0·113	7·32

[a]Equilibration rate constant.
[b]Slope of line predicted by linear pharmacodynamic model.
[c]Baseline effect.

DISCUSSION

The sham experiment suggested that the surgical preparation is relatively stable over at least 2 h. Halothane has been shown to be a negative inotrope in newborn piglets.[7] However, baseline haemodynamic measurements were made before drug administration, while the animal was stable under anaesthesia. This implies that any further changes in haemodynamic parameters after the administration of captopril were indeed drug induced and not due to surgical trauma or the anaesthetic agent. While it is possible that surgical trauma and/or the use of an anaesthetic agent may affect the intensity or indeed the nature of the response to the drug, the observed changes in aortic pressure were qualitatively similar to changes in blood pressure observed in humans after captopril administration.[13,14] The qualitative similarity in pressure response to captopril when administered to humans (no halothane present) provides evidence that the effect observed in the piglets is indeed brought about by captopril. Heart rate in the piglets decreased significantly and, while the degree of the bradycardia may have been increased by halothane,[7] a significantly decreased heart rate was also observed in sedated infants (no halothane present) 1 h after receiving captopril, during cardiac catheterization[4] and in adult hypertensive patients.[15]

Pharmacokinetic parameters in the piglets are found to be similar to that of humans. In the piglets, $t_{1/2}$ was estimated to be $0{\cdot}44 \pm 0{\cdot}08$ h. Estimates for $t_{1/2}$ of unchanged captopril in healthy adult humans range from 0·35 to 1·9 h.[16,17] V_{dss} was calculated to be $0{\cdot}64 \pm 0{\cdot}13\ \mathrm{L\,kg^{-1}}$ in the piglets and is reported to be $0{\cdot}7$–$0{\cdot}75\ \mathrm{L\,kg^{-1}}$ in healthy adult humans.[17,18] Cl_{TB} was $1{\cdot}42 \pm 0{\cdot}33\ \mathrm{L\,kg^{-1}\,h^{-1}}$ in the piglets and is reported to be $0{\cdot}8 \pm 0{\cdot}05\ \mathrm{L\,kg^{-1}\,h^{-1}}$ in healthy adults.[18]

It is generally recognized that a relationship between plasma captopril concentration and effect is lacking in humans; the most recent example has been reported by Al-Furaih *et al.*[13] When these data are examined closely, the apparent lack of concentration–effect relationship can be attributed to a delay in the onset of action. The piglet data reported in this study also show this phenomenon (Figures 1(A)–(C)). By introducing an effect compartment with an equilibration delay,[10] a relationship between plasma captopril concentration and effect could be established. Judging by errors in parameter estimates (Tables 1 and 2, Figures 1(A)–(C)), it becomes evident that aortic pressure is more responsive to plasma captopril concentration changes than heart rate. The latter tends to be more variable, less responsive, and the magnitude of change is relatively small. The heart rate, therefore, is not good for modelling purposes. The linear pharmacodynamic model was found to be adequate to describe the effect data because a maximum reponse (E_{max}) was not observed. In cases where a maximum effect is reached, a different pharmacodynamic model such as the E_{max} model[10] can easily be incorporated.

The effects of captopril are caused by more than one mechanism. Primarily, inhibition of ACE in tissue and plasma leads to reduction of circulating levels

of the potent endogenous vasoconstrictor angiotensin II. However, captopril's effects on aldosterone secretion, bradykinin degradation, and vasoactive prostaglandins must also be taken into account.[19] These modes of reactions may account for most of the delay in the onset of action because the average K_{e0} value (Table 2) is less than half of that of β (Table 1). This difference in the parameter values suggests that equilibration delay plays a minor role in the onset delay. Although the heart rate data (Figure 1(C)) were not analysed due to lack of statistical difference, it is quite obvious that the maximum effect was not achieved until 20–60 min after captopril administration.

Due to the huge difference in the K_{e0} and β values, one may have to exercise caution in interpreting steady-state concentration and effect relationships. If captopril were to be introduced at a constant rate of iv infusion, although this is not common practice in clinical situations, the concentration of the drug would reach a steady state before that of the effect.

In conclusion, the anaesthetized piglet is a viable model in which to study the relationship between the pharmacokinetics and pharmacodynamics of captopril.

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