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# Prediction of Drug-Drug Interaction during Oral Absorption of Carrier-Mediated Compounds in Humans

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A microscopic mass balance approach has been developed to estimate the extent and rate of absorption for carrier-mediated compounds. For the case of the competitive inhibition in the presence of an inhibitor which shares the same carrier, the fraction dose absorbed (F) and absorption rate constant ($k_a$) of a drug can be calculated from its concentration profile in the intestinal lumen. Absorption parameters obtained by single-pass perfusion experiments were used in the simulation of the absorption of some aminopenicillins. Predicted fractions dose absorbed and absorption rate constants of ampicillin and amoxicillin were significantly reduced in the presence of a 6-times higher molar dose of cyclacillin. The drug-drug interactions on the competitive absorption of carrier-mediated compounds were determined with regard to F and $k_a$. Predicted decreases in F for some aminopenicillins correlated well with decreases in the urinary recovery in humans reported in the literature. Predicted decreases in the mean absorption rate constant ($\overline{k}_a$) explain the delays in the time of peak plasma concentration ($T_{max}$) reported in humans.

**Key words:** Absorption, Absorption rate constant, Aminopenicillin, Bioavailability, Permeability

## INTRODUCTION

In order to describe the kinetics of intestinal absorption, the Michaelis-Menten equation is frequently used. Atkins (1980) has reported a model in which the intestine was assumed to be a series of small segments, with consideration to the solute concentration changes along the length of the intestine. Recently, a macroscopic mass balance has been introduced to predict oral drug absorption in man for compounds which are absorbed by passive or carrier-mediated processes (Sinko *et al.*, 1991; Oh *et al.*, 1991). In that approach, the difference between the rate of mass flowing into and out of the intestine is assumed to be the rate of mass absorbed, so that the integral of its luminal concentration is required to estimate the fraction dose absorbed (F) of a drug (Sinko *et al.*, 1991). For a carrier-mediated compound, its wall permeability is concentration-dependent along the intestine. To predict F, a mean wall permeability was used in a macroscopic mass balance approach (Amidon *et al.*, 1988).

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For predicting oral absorption of suspensions, a mathematical model using a microscopic mass balance approach has been developed (Oh *et al.*, 1993). The mass balance in the elemental volume in the tube is considered at the steady-state assumption. In a microscopic mass balance approach, the concentration profile of a compound in the lumen can be determined, further being used for estimating the extent and rate of absorption. Using this approach, one can modify the mathematical model by adding or deleting other mass transfer process, such as degradation in the intestine or dissolution resistance.

Competitive absorption may occur when two compounds share the same transport system in the intestine. Mutual inhibition studies in the literature support the idea that several β-lactam antibiotics share the same peptide carrier system in rats (Iseki *et al.*, 1984; Okano *et al.*, 1986). The equation for wall permeability in the presence of an inhibitor was used to characterize several cephalosporins (Sinko and Amidon, 19 89). Sinko and Amidon (1989) suggest that macroscopic absorption parameters may be useful for predicting drug-drug and possibly food-drug absorption interactions in the gastrointestinal tract of humans. To estimate the extent and rate of absorption for drugs with

concentration-dependent wall permeabilities, the tube model needs to be further refined. Sjövall *et al.* (1985) have reported the existence of a capacity-limited transport system for aminopenicillins in the human gut. They found that oral cyclacillin interacts with the absorption of oral ampicillin and amoxicillin.

In this report, a microscopic mass balance approach has been developed for predicting the extent and rate of oral absorption of carrier-mediated compounds. Furthermore, competitive inhibition on the absorption of these compounds will be estimated in terms of the fraction dose absorbed as well as the absorption rate constant. Predicted results will correlate with human data reported in order to explain the drug-drug interaction during the intestinal absorption.

## THEORETICAL

For a physical model of absorption the intestine is assumed to be a tube and a stomach is not included. Compounds are assumed to be dissolved fast enough (no dissolution limit), so that the concentration at the beginning of intestine is the same as the dose divided by water volume taken. No metabolism in the intestine is assumed. The compound may be absorbed by both carrier-mediated and passive processes, assuming that the carrier system is evenly distributed along the intestine.

### Fraction Dose Absorbed of Carrier-Mediated Compounds

A schematic model for absorption of a carrier-mediated compound is represented in Fig. 1(A). The carrier system is symbolized by a filled circle. At steady state,

$$Q\cdot C_L|_z - Q\cdot C_L|_{z+dz} - j_w\cdot(2\pi R)\cdot dz = 0 \tag{1}$$

where $j_w$ is mass flux across the wall ($=P_{eff}\cdot C_L$), $P_{eff}$ is the effective wall permeability, $C_L$ is the luminal concentration of a compound, Q is the axial flow rate, z is the axial coordinate down the intestine, and R is the radius of the intestine. Taking a limit for Eq. (1) gives:

$$\frac{dC_L}{dz} = -\frac{2\pi R}{Q}\cdot P_{eff}\cdot C_L \tag{2}$$

The concentration and tube length may be made dimensionless by letting $C^* = C_L/C_s$ and $z^* = z/L$, where $C_s$ is the solubility of a compound and L is the length of the intestine, Eq. (2) now becomes:

$$\frac{dC^*}{dz^*} = -\frac{2\pi RL}{Q}\cdot P_{eff}\cdot C^* \tag{3}$$

Further let:

$$P^*_{eff} = P_{eff}\cdot(R/D)$$

$$Gz = \frac{\pi DL}{Q}$$

where $P^*_{eff}$ is the dimensionless effective permeability ($1/P^*_{eff} = 1/P^*_{aq} + 1/P^*_w$), Gz is the Graetz number and D is the diffusivity of a compound (Amidon, 1983). Then Eq. (3) is rewritten as:

$$\frac{dC^*}{dz^*} = -2GzP^*_{eff}C^* \tag{4}$$

The dimensionless wall permeability ($P^*_w$) for a carrier-mediated and passively absorbed compound is generally defined as (Johnson and Amidon, 1988):

$$P^*_w = \frac{P^*_c}{1+\frac{C_w}{K_m}} + P^*_m \tag{5}$$

where $P^*_c$ and $P^*_m$ are the carrier-mediated and passive membrane permeabilities, respectively, $K_m$ is a Michaelis constant for the carrier system, and $C_w$ is the wall concentration of a compound. $P^*_{eff}$ is assumed to be approximately equal to $P^*_w$ for water soluble drugs (Amidon *et al.*, 1988), which means dimensionless aqueous permeability ($P^*_{aq}$) is large enough so that $C_w = C_L$.

$$P^*_{eff} \approx \frac{P^*_c}{1+\frac{C_s}{K_m}\cdot C^*} + P^*_m \tag{6}$$

Substituting Eq. (6) to Eq. (4), the concentration profile becomes:

$$\frac{dC^*}{dz^*} = -2Gz\left(\frac{P^*_c}{1+\frac{C_s}{K_m}\cdot C^*} + P^*_m\right)\cdot C^* \tag{7}$$

The fraction dose absorbed (F) is defined:

$$F = 1 - \frac{C^*(1)}{Do} \tag{8}$$

where $Do = (M_0/V_0)/C_s$, $M_0$ is a dose administered, and $V_0$ is the volume of water taken with a dose. Do is the dose number which is defined as the ratio of the initial concentration to the solubility of a drug. $C^*(1)$ is the dimensionless luminal concentration at the end of the intestine.

### Absorption Rate Constant

Asumming that the amount disappeared from the lumen is equal to the amount absorbed, the absorption rate constant ($k_a$) is defined as:

$$k_a = -\frac{dC_L/dt}{C_L} = -\left(\frac{Q}{\pi R^2}\right)\frac{dC_L/dz}{C_L} \tag{9}$$

From Eqn. (2) and (9),

$$k_a=\left(\frac{2}{R}\right)\cdot P_{eff}=\left(\frac{2D}{R^2}\right)\cdot P^*_{eff} \quad (10)$$

In a finite volume element of the intestine, $k_a$ can be numerically calculated by $k_a=-(Q/\pi R^2 L)\cdot(\Delta C^*/C^*_z)/\Delta z^*)$. The mean absorption rate constant ($\bar{k}_a$) can be calculated by:

$$\bar{k}_a=\left(\frac{2D}{R^2}\right)\cdot\bar{P}^*_{eff} \quad (11)$$

where $\bar{P}^*_{eff}$ is the mean $P^*_{eff}$ in the intestine.

### Competitive Inhibition

If two compounds share the same carrier system in the intestine, a competitive absorption may occur along the intestine (Fig. 1(B)). The concentration profile of two compounds, A and B, in the intestinal lumen can be simultaneously described using Eq. (4).

$$\frac{dC^*_A}{dz^*}=-2Gz_AP^*_{eff,A}C^*_A \quad (12)$$

$$\frac{dC^*_B}{dz^*}=-2Gz_AP^*_{eff,B}C^*_B \quad (13)$$

As knwon from enzyme kinetics, a competitive inhibitor acts only to increase the apparent $K_m$ for the substrate, and the maximal flux remains unchanged (Segel, 1975). The wall permeabilities of two compounds can be written as (Sinko and Amidon, 1989):

$$P^*_{w,A}=\frac{P^*_{c,A}}{1+\frac{C_B}{K_{i,B}}+\frac{C_{w,A}}{K_{m,A}}}+P^*_{m,A} \quad (14)$$

$$P^*_{w,B}=\frac{P^*_{c,B}}{1+\frac{C_A}{K_{i,A}}+\frac{C_{w,B}}{K_{m,B}}}+P^*_{m,B} \quad (15)$$

where $C_A$ and $C_B$ are luminal concentrations of compounds A and B, $C_{w,A}$ and $C_{w,B}$ are wall concentrations of compounds A and B, $K_{m,A}$ and $K_{m,B}$ are Michaelis constants of compounds A and B for the carrier system, $K_{i,A}$ is a Michaelis constant of compound A in the presence of B, and $K_{i,B}$ is a Michaelis constant of compound B in the presence of A.

Assuming aqueous permeability is large enough, $P^*_{eff}$ is close to $P^*_w$ so that $C_A=C_{w,A}$ and $C_B=C_{w,B}$. It may be expected that the $K_i$ of the inhibitor equal to its $K_m$ in the inhibition study (Sinko and Amidon, 1989): $K_{m,A}\approx K_{i,A}$ and $K_{m,B}\approx K_{i,B}$. And using dimensionless concentrations, Eqs. (14) and (15) become:

$$P^*_{w,A}=\frac{P^*_{c,A}}{1+\frac{C_{s,A}}{K_{m,A}}C^*_A+\frac{C_{s,B}}{K_{m,B}}C^*_B}+P^*_{m,A} \quad (16)$$

$$P^*_{w,B}=\frac{P^*_{c,B}}{1+\frac{C_{s,A}}{K_{m,A}}C^*_A+\frac{C_{s,B}}{K_{m,B}}C^*_B}+P^*_{m,B} \quad (17)$$

From Eqs. (12), (13), (16), and (17), concentration profiles of compounds A and B are:

$$\frac{dC^*_A}{dz^*}=-2Gz_AC^*_A\left[\frac{P^*_{c,A}}{1+\frac{C_{s,A}}{K_{m,A}}C^*_A+\frac{C_{s,B}}{K_{m,B}}C^*_B}+P^*_{m,A}\right] \quad (18)$$

$$\frac{dC^*_B}{dz^*}=-2Gz_BC^*_B\left[\frac{P^*_{c,B}}{1+\frac{C_{s,A}}{K_{m,A}}C^*_A+\frac{C_{s,B}}{K_{m,B}}C^*_B}+P^*_{m,B}\right] \quad (19)$$

Equations (18) and (19) can be simultaneously solved by a numerical method.

The fractions dose absorbed of compound A and B are:

$$F_A=1-\frac{C^*_A(1)}{Do_A} \quad (20)$$

$$F_B=1-\frac{C^*_B(1)}{Do_B} \quad (21)$$

where $Do_A$ and $Do_B$ are dose numbers of compounds A and B and $C^*_A(1)$ and $C^*_B(1)$ are dimensionless concentrations of compounds A and B at the end of the intestine. Similarly to Eqs. (10) and (11), local and mean absorption rate constants of compound A and B can be calculated by:

$$k_{a,A}=\left(\frac{2D_A}{R^2}\right)\cdot P^*_{eff,A} \quad (22)$$

$$k_{a,B}=\left(\frac{2D_B}{R^2}\right)\cdot P^*_{eff,B} \quad (23)$$

$$\bar{k}_{a,A}=\left(\frac{2D_A}{R^2}\right)\cdot\bar{P}^*_{eff,A} \quad (24)$$

$$\bar{k}_{a,B}=\left(\frac{2D_B}{R^2}\right)\cdot\bar{P}^*_{eff,B} \quad (25)$$

where $D_A$ and $D_B$ are the diffusivities of compound A and B, respectively.

## SIMULATION

To solve the differential equations, a Runge-Kutta-Merson method was used. The program written in the Fortran language was compiled with a NDP Fortran-386 compiler (Microway, Inc., MA). The parameters used in the simulation is listed in Table I. The Graetz number which is a scaling factor from the rate to human data was fitted to 1.27 in the literature (Sinko *et al.*, 1989). Intrinsic wall permeabilities of ampicillin, amoxicillin, and cyclacillin were obtained using single-pass perfusion experiments with rat jejunum segments (Sinko and Amidon, 1989; Oh *et al.*, 1992). A luminal volume of 200 ml was used in order to compare model predicted values with human data for aminopenicillins in the literature where the same volume of water was used (Sjövall *et al.*, 1985).

**Table I.** Parameters used in the simulation[a]

| | Ampicillin | Amoxicillin | Cyclacillin | References |
|---|---|---|---|---|
| Dose (mg) | 250 | 250 | 1500 | |
| Solubility (mM) | 54.7 | 15.1 | 94.0 | |
| Do[b] | 0.07 | 0.23 | 0.23 | |
| $P_c^*$ | 0.75 | 0.65 | 1.14 | c,d |
| $P_m^*$ | 0 | 0 | 0 | c,d |
| $K_m$ (mM) | 15.8 | 9.1 | 14.0 | c,d |

[a] $V_L$=200 ml, Gz=1.27.
[b] Do=(Dose/$V_L$)/solubility.
[c] from Oh *et al.* (1992).
[d] from Sinko *et al.* (1991).

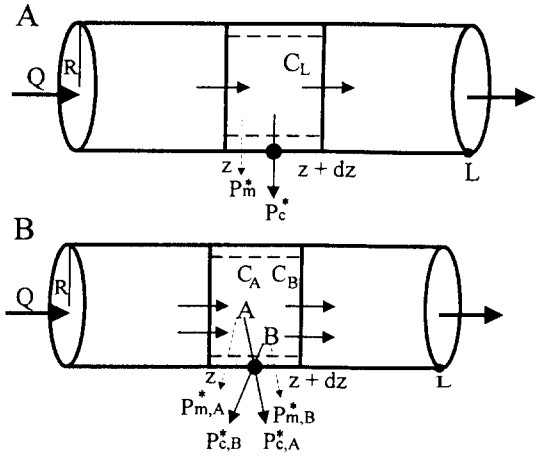


**Fig. 1.** Schematic absorption model and a microscopic mass balance approach (A) for a carrier-mediated compound and (B) for competitive absorption of two compounds which share the same carrier. The carrier system is represented by a filled circle. $P_c^*$ and $P_m^*$ are carrier and membrane permeabilites, respectively. The concentration profile of compound A may be affected by the presence of compound B. No other reactions occur.

## RESULTS AND DISCUSSION

Sjövall *et al.* (1985) showed that the capacity-limited transport in men could play a part in the absorption of the aminopenicillins: ampicillin, amoxicillin, bacampicillin, and cyclacillin. The relative bioavailabilities of single oral doses of ampicillin and amoxicillin were compared with and without concomitant administration of a six-times higher molar dose of cyclacillin. To compare their *in vivo* results with predicted values, the same parameter values were used for simulation (Table I).

The fraction dose absorbed (F) of a drug can be estimated using Eq. (8), in a microscopic mass blance approach. Because it requires the concentration at the end of the intestine, C*(1) should be calculated by a numerical method. On the other hand, an anlytical solution for F can be obtained from a macroscopic mass balance approach (Sinko *et al.*, 1991). For the plug flow model, the fraction dose absorbed is:

$$F = 1 - e^{-2 \cdot An} \tag{26}$$

where An is the absorption number which is defined as $An = Gz \cdot P_{eff}^*$. For a drug which is absorbed by a carrier-mediated process, $P_{eff}^*$ changes with its luminal concentration along the intestine. Therefore a mean wall permeability may be used to estimate F. Table II shows the fractions dose absorbed of aminopenicillins in humans estimated using macroscopic and microscopic approaches from intrinsic wall permeability parameters in rats. There was no significant difference in estimated F using two different approaches and estimated values are close to the experimental values reported in the literature except for ampicillin (Bergan, 1978). Discrepancy in F of ampicillin from reported F is not known, but partly because of variability of estimated parameters in rats. All aminopenicillins have shown dose-dependent F, implying their concentration-dependent wall permeabilities in the intestine (Table II).

**Table II.** Fraction dose absorbed (F) of aminopenicillins in humans estimated using macroscopic and microscopic approaches from intrinsic wall permeability parameters ijn rats

| Compounds | Dose | Estimated F (%) | | Reported |
|---|---|---|---|---|
| | (mg) | Macroscopic Approach[a] | Microscopic Approach | F (%)[b] |
| Ampicillin | 250 | 82.0 | 81.8 | 30-60 |
| | 500 | 79.2 | 78.3 | |
| Amoxicillin | 250 | 75.4 | 74.5 | 75-90 |
| | 500 | 70.8 | 67.8 | |
| Cyclacillin | 250 | 92.4 | 93.0 | >85 |
| | 500 | 90.3 | 91.1 | |
| | 1500 | 82.5 | 80.8 | |

[a] from Sinko *et al.* (1988).
[b] from Bergan (1978).

A microscopic mass balance approach was used to estimate the extent and rate of absorption for some aminopenicillins. Fig. 2(A) shows concentration profiles of ampicillin alone and in the presence of cyclacillin along the intestine. The luminal concentration of ampicillin with cyclacillin is always higher than that of ampicillin alone, suggesting inhibited absorption of ampicillin by cyclacillin. Concentration profiles in the intestine for amoxicillin are shown in Fig. 2(B). Similar concentration profiles of cyclacillin alone (CYC) and in the presence of ampicillin (CYC+AMP) and amoxicillin (CYC+AMX) along the intestine is shown in Fig. 2(C). In the case of cyclacillin, the concentration profiles were shown to be not significant since concentrations of inhibitors were much lower than that of cyclacillin. From the simulated concentration profiles of aminopenicillins in the intestine, absorption rate cons-

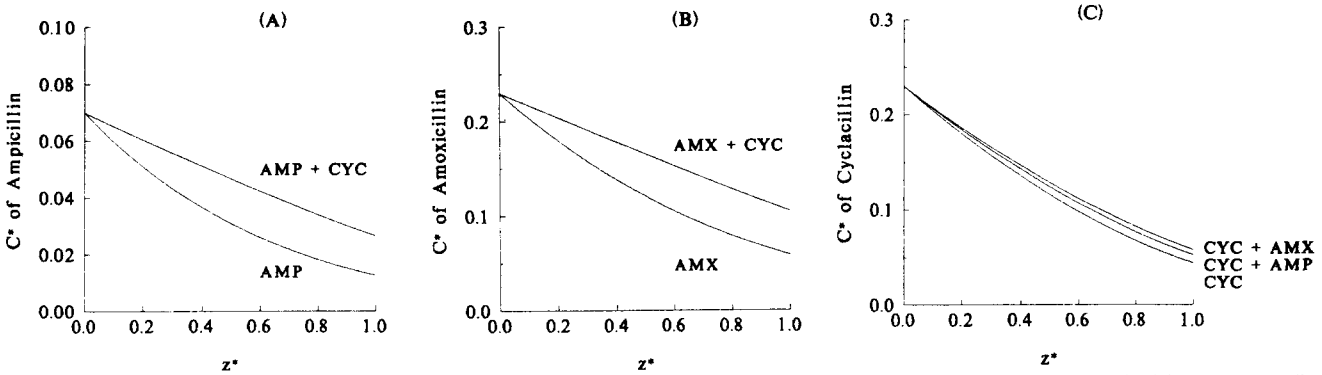


**Fig. 2.** Concentration profiles (A) of ampicillin alone (AMP) and in the presence of cyclacillin (AMP+CYC), (B) of amoxicillin alone (AMX) and in the presence of cyclacillin (AMX+CYC), and (C) of cyclacillin alone (CYC) and in the presence of ampicillin (CYC+AMP) and amoxicillin (CYC+AMX) along the intestine.

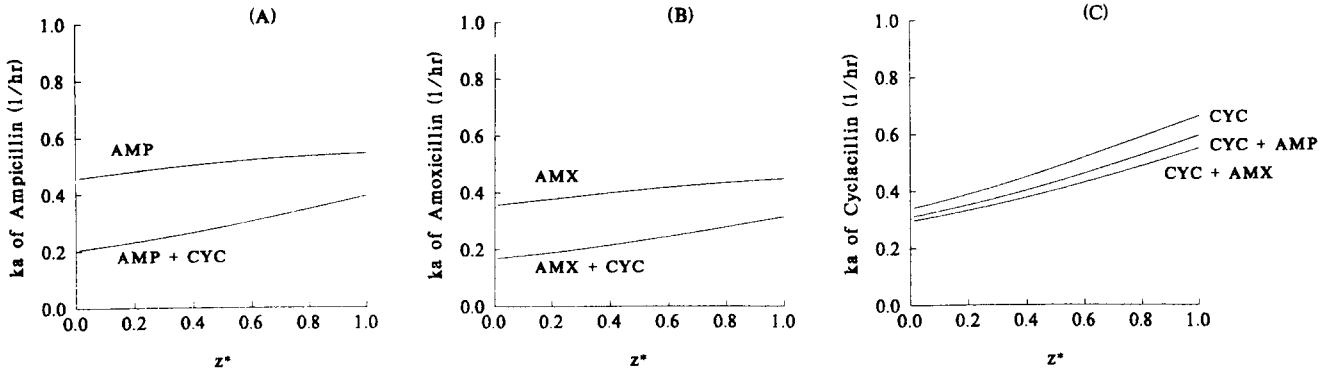


**Fig. 3.** Absorption rate constants ($k_a$) (A) of ampicillin alone (AMP) and in the presence of cyclacillin (AMP+CYC), (B) of amoxicillin alone (AMX) and in the presence of cyclacillin (AMX+CYC), and (C) of cyclacillin alone (CYC) and in the presence of ampicillin (CYC+AMP) and amoxicillin (CYC+AMX) along the intestine.

tants can be illustrated as described in the theoretical section. Fig. 3 shows absorption rate constants for ampicillin, amoxicillin, and cyclacillin along the intestine. Significantly reduced absorption rate constants for ampicillin and amoxicillin were observed in the presence of cyclacillin, an inhibitor. As expected from the concentration profiles for cyclacillin, its $k_a$ profiles in the lumen were not different in the presence of ampicillin or amoxicillin (Fig. 3(C)).

The extent and rate of oral absorption of aminopenicillins were estimated. Fig. 4 shows estimated fractions dose absorbed (F) of ampicillin alone (AMP) and in the presence of cyclacillin (AMP+CYC), amoxicillin alone (AMX) and in the presence of cyclacillin (AMX+CYC), and cyclacillin alone (CYC) and in the presence of ampicillin (CYC+AMP) and amoxicillin (CYC+AMX). Drug-drug interaction on the rate of absorption can be estimated. Fig. 5 shows the estimated mean absorption rate constants for various cases. The fractions dose absorbed and absorption rate constants for both ampicillin and amoxicillin were significantly reduced in the presence of 6 times higher dose of cyclacillin. It should be pointed out that F and $\bar{k}_a$ of cyclacillin were also inhibited during absorption, supporting mutual inhibition of aminopenicillins. However F and $\bar{k}_a$ of cyclacillin did not decrease significantly, again due to a 6 molar times higher concentration than those of others.

It has been reported that concomitant cyclacillin administration caused the decreases in urinary recovery and delays in time of plasma peak concentration ($T_{max}$) of ampicillin and amoxicillin (Sjöval *et al.*, 1985). Fig. 6 shows a plot of reported percent decreases in urinary recovery versus the predicted percent decreases in F of ampicillin (AMP+CYC), amoxicillin (AMX+CYC), and cyclacillin (CYC+AMP and CYC+AMX) in the presence of other penicillin, as an inhibitor. Predicted decreases in F correlated with reported decreases in urinary recoveries ($r^2=0.979$, $p<0.05$). A plot of reported delays in the time of plasma peak concentration ($T_{max}$) versus predicted decreases in the mean absorption rate constant ($\bar{k}_a$) is shown in Fig. 7. Predicted decreases in $\bar{k}_a$ may explain the decreases in $T_{max}$ which are reported in the literature ($r^2=0.983$, $p<0.05$).

In summary there was no significant difference in F in humans estimated using macroscopic and micro-

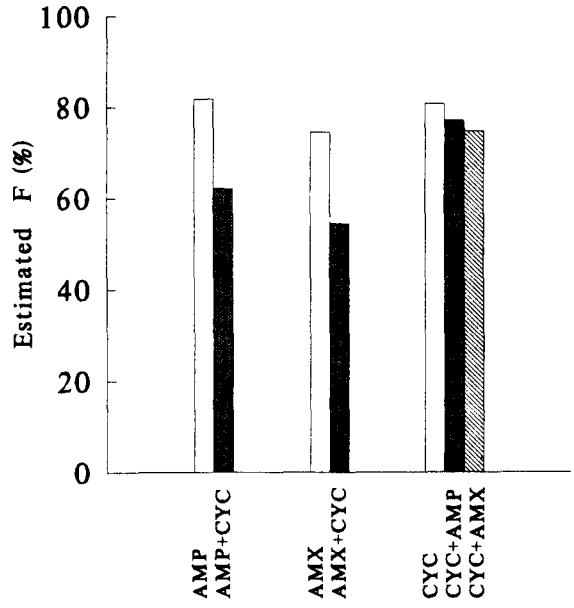


**Fig. 4.** Estimated fractions dose absorbed (F) of ampicillin alone (AMP) and in the presence of cyclacillin (AMP+CYC), amoxicillin alone (AMX) and in the presence of cyclacillin (AMX+CYC), and cyclacillin alone (CYC) and in the presence of ampicillin (CYC+AMP) and amoxicillin (CYC+AMX).

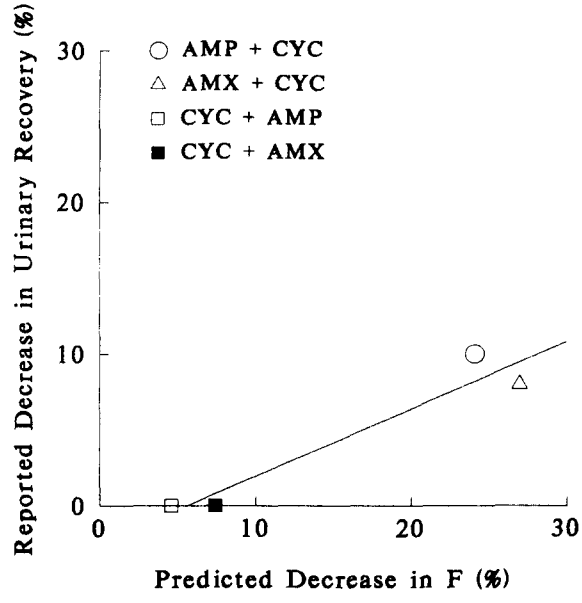


**Fig. 6.** Plot of reported percent decreases in urinary recovery versus predicted percent decreases in fraction dose absorbed (F) of ampicillin (AMP+CYC), amoxicillin (AMX+CYC), and cyclacillin (CYC+AMP and CYC+AMX) in the presence of other penicillin, as an inhibitor.

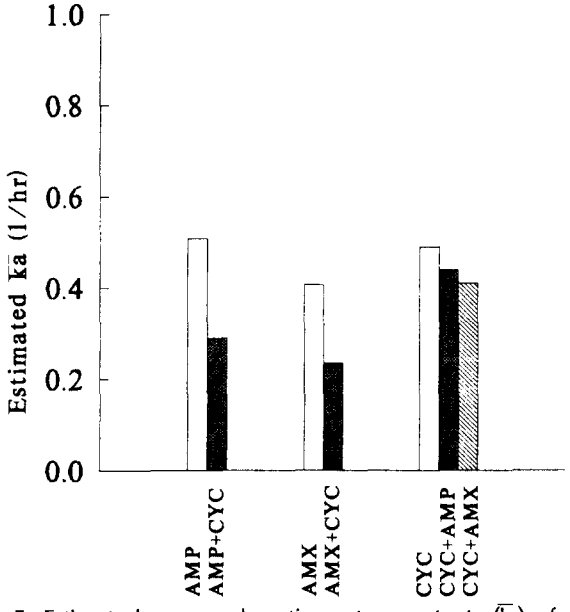


**Fig. 5.** Estimated mean asborption rate constants ($\bar{k}_a$) of ampicillin alone (AMP) and in the presence of cyclacillin (AMP+CYC), amoxicillin alone (AMX) and in the presence of cyclacillin (AMX+CYC), and cyclacillin alone (CYC) and in the presence of ampicilin (CYC+AMP) and amoxicillin (CYC+AMX).

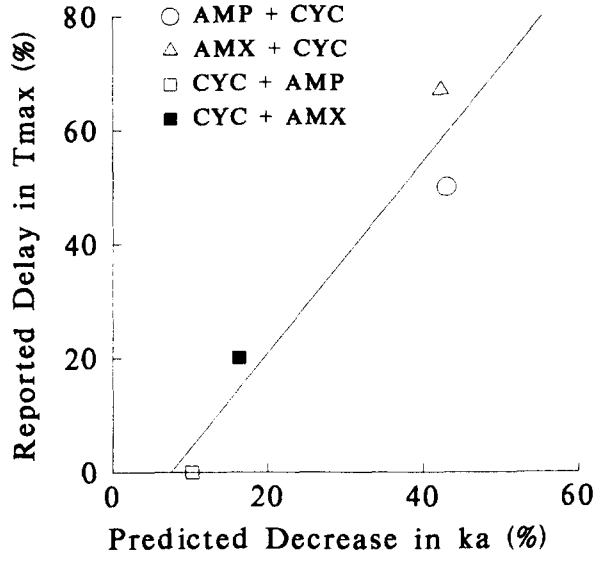


**Fig. 7.** Plot of reported percent delays in time of plasma peak concentration ($T_{max}$) versus predicted percent decreases in mean absorption rate constant ($\bar{k}_a$) of ampicillin (AMP+CYC), amoxicillin (AMX+CYC), and cyclacillin (CYC+AMP and CYC+AMX) in the presence of other penicillin, as an inhibitor.

scopic approaches. Concentration profiles and absorption rate constants were well demonstrated by the equations derived from a microscopic mass balance approach. The fraction dose absorbed and absorption rate constants of ampicillin or amoxicillin were significantly reduced in the presence of a 6 times higher molar dose of cyclacillin. Predicted decreases in F correlated with decreases in urinary recovery reported and

decreases in mean absorption rate constants can explain delays in $T_{max}$ reported in humans.

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