Cefixime absorption kinetics after oral administration to humans

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SUMMARY

Cefixime (CFX) absorption kinetics after oral administration to humans was studied. Four distinct models, incorporating a delay of absorption and first-order elimination kinetics, i.e. first-order absorption (M1), zero-order absorption (M0), Michaelis-Menten type absorption (MM) and Michaelis-Menten type absorption with 'an absorption window' (MM-Δt) were used to fit concentration data of CFX in 10 Chinese men following an oral dose of 400 mg. $r^2$ and AIC were selected as measures of goodness-of-fit. The results show that the MM-Δt model provided a better fit than the other three models. The kinetic parameters were estimated as follows: $V_{max}' = 10.80 \pm 3.80 \text{ mg.l}^{-1}.\text{h}^{-1}$; $K_m' = 88.31 \pm 2.75 \text{ mg.ml}^{-1}$; $\Delta t = 4.75 \pm 0.85 \text{ h}$; $T_{1/2} = 4.20 \pm 0.92 \text{ h}$; $T_{max} = 5.20 \pm 0.92 \text{ h}$; and $C_{max} = 6.04 \pm 1.70 \text{ mg.l}^{-1}$.

INTRODUCTION

Cefixime (CFX) is an orally active third-generation cephalosporin. Several pharmacokinetic studies of the drug have been conducted (1–3). After oral administration of a single dose of 200 or 400 mg, absorption was slow (time of the peak concentration occurs between 3–5 h). Its bioavailability was 40–50% and decreased with oral dose (1). Experimental data in rat demonstrated that CFX was absorbed from the intestinal tract via carrier-mediated transport (1). The aim of the study was to explore models for the oral absorption kinetics of CFX in man.

MATERIALS AND METHODS

Subjects

10 male healthy volunteers, with an average age of 22 ± 2 years (20–24 years) and weight 64 ± 5 kg (56–70 kg) gave informed consent to participate in the study. All subjects had normal hematological, renal and hepatic parameters. They were not receiving any other medication. No drugs were allowed for at least 2 weeks prior to and during the day of the experiment.

Experimental protocol

A 400 mg dose of CFX capsule (4 × 100 mg Cespan, Tienze, Taiwan) was given to each volunteer. All subjects had fasted since 10 p.m. of the previous day, and swallowed the capsule with 250 ml of water. Food
was served 3 h after dosing. Heparinized blood samples were collected prior to dosing and 0.5, 1, 2, 3, 4, 5, 6, 8, 12 and 16 h after dosing. Plasma was separated by centrifugation. All samples were stored at −4°C until assayed. Plasma concentration of CFX were measured by HPLC (5) with UV detection at 280 nm. The sensitivity limit of the assay was 0.05 μg/ml.

Pharmacokinetic analysis

The Wanger-Nelson method was used to analyze CFX absorption kinetics. The percentage of absorption was used to estimate the apparent rate of CFX absorption according to the equation:

\[ \frac{\Delta X_a}{\Delta t/F} = \frac{D (f_{i+1} - f_i)}{100 (t_{i+1} - t_i)} \]  

Eq. 1

where \( f_{i+1} \) and \( f_i \) are the percentage absorption at time \( t_{i+1} \) and \( t_i \), respectively. \( D \) is the dose and \( X_a \) is drug amount at absorption site. The time course of the absorption rate relative to \( F \) was graphically represented by a plot of \( \Delta X_a/\Delta t/F \) vs the midpoint of each interval, i.e. \( (t_{i+1} + t_i)/2 \).

Four distinct compartmental models, incorporating a delay of absorption (lag time, \( T_0 \)) and first-order elimination kinetics, i.e. first-order absorption (\( M_1 \)), zero-order absorption (\( M_0 \)), Michaelis-Menten type absorption (\( MM \)) (6) and Michaelis-Menten type absorption with ‘an absorption window’ (\( MM-\Delta t \)) (7), were used for the data-fitting of the plasma concentrations of CFX.

In the \( MM-\Delta t \) model, the following equations were given:

During absorption (\( T_0 < t < \Delta t + T_0 \))

\[ \frac{dC}{dt} = \frac{V'_\text{max} C'_a}{K'_\text{max} + C'_a} - kC \]  

Eq. 2

The initial conditions are \( C'_a(0) = FD/V \) and \( C(0) = 0 \).

After absorption is over (\( t > \Delta t + T_0 \))

\[ \frac{dC}{dt} = -kC \]  

Eq. 3

where \( V'_\text{max} \) and \( K'_\text{max} \) are ‘apparent Michaelis-Menten constants’, respectively. \( k \) is the elimination constant, \( C \) is the concentration in plasma and \( C'_a \) is the ‘apparent concentration’ at the absorption site (i.e. \( C'_a = X_a/V \)). \( V \) is the apparent distribution volume of the drug and \( \Delta t \) is the duration of absorption.

The estimations of individual parameters with each model were performed by nonlinear regression analysis (8). The goodness-of-fit was assayed by \( r^2 \) and AIC. The likelihood ratio method (9) was also used for comparison of the models. Briefly, the test value, \( \Delta O \), is defined as:

\[ \Delta O = N \times \ln[O_1/O_2] \]  

Eq. 4

where \( O_1 \) and \( O_2 \) are the objective functions of the reduced model and the full models, respectively. The value of \( \Delta O \) is assumed to follow a \( \chi^2 \) (df = 1) distribution under the null hypothesis.

The estimated pharmacokinetic parameters using a selected model were also compared with those estimated using standard noncompartmental analysis. All data were represented as \( \bar{x} \pm s \).

RESULTS AND DISCUSSION

After oral administration, the decline of the concentration was clearly a straight line on log-concentration vs time plots in the 10 men (Fig. 1). Such profiles suggested that a one-compartment model is appropriate to describe CFX pharmacokinetics in man.

The percentages of drug unabsorbed and the apparent absorption rates of CFX vs time in 10 men are shown in Figures 2 and 3, respectively. Simple visual inspection of plots of these data suggested that there is a time lag (about 0.5 h) before the absorption process begins and that the subsequent linear decline reflects