Multi-fraction Absorption Model for Pharmacokinetic Analysis of Diltiazem Tablets

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Pharmacokinetic parameters were evaluated using multi-fraction absorption model of diltiazem in mongrel dogs. A comparison was made between the conventional one compartment model (model A) and one compartment two-fraction absorption model (model B). It was found from this study that model 1 B could explain the concentration-time profile of diltiazem better compared to model 1 A.

LASMA drug concentration data after oral administration of dosage forms were usually analyzed using compartment models with first-order absorption and elimination rate constants. In bioavailability assessment for dosage form development, details of absorption kinetics are important and approximation by an infinite first-order rate process is not always sufficient. However, there are several cases which are not satisfactorily simulated by the conventional models due to dissolution characteristics of dosage forms or physiological factors in the gastrointestinal tract. Discontinuous absorption models have been proposed for the analysis of plasma drug concentration data with irregular absorption profiles, in which the absorption rate constant is variable throughout the process of absorption. However, these models are not always suitable.

In this report, we demonstrate the use of a multi-fraction absorption model applied to evaluate pharmacokinetics of diltiazem HCl in comparison to the conventional one compartment evaluation procedure. In this model, drug in the gastrointestinal tract is assumed to be divided into two fractions, each with its respective lag time and absorption rate constant.

Murata and Moda (1994) used these models to investigate the pharmacokinetic absorption behavior of sustained release diltiazem preparation in dogs.

EXPERIMENTAL

Materials

Diltiazem tablets 60 mg (Diltiazem HCl, Torrent Pharmaceuticals, India) were obtained from local market. HPLC grade Acentonitrile was purchased from Spectrochem Pvt. Ltd., Bombay. All other chemicals used are of analytical grade.

In vivo experiments

Mongrel dogs were fasted for 18th prior to drug administration. One tablet of diltiazem HCl was administered orally to each of three dogs by compulsive swallowing with 30 ml of water. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 15 h. The plasma samples were frozen at -20°C until analysis.

Determination of diltiazem in Plasma:

Diltiazem was extracted from spiked or sample plasma by using disposable extraction cartridges containing C18 packing material.
Table 1: Pharmacokinetic Parameter for Diltiazem in Dogs fitted to Model B

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dog 1</th>
<th>Dog 2</th>
<th>Dog 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>X_{a1} mg</td>
<td>30.1</td>
<td>46.9</td>
<td>34.2</td>
</tr>
<tr>
<td>X_{a2} mg</td>
<td>29.9</td>
<td>13.8</td>
<td>25.8</td>
</tr>
<tr>
<td>K_{a1} h^{-1}</td>
<td>0.6010</td>
<td>0.5353</td>
<td>1.0811</td>
</tr>
<tr>
<td>K_{a2} h^{-1}</td>
<td>0.2437</td>
<td>1.2769</td>
<td>5.3506</td>
</tr>
<tr>
<td>K_{el} h^{-1}</td>
<td>0.7539</td>
<td>0.7294</td>
<td>0.8083</td>
</tr>
<tr>
<td>T_{1} h</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T_{2} h</td>
<td>1.75</td>
<td>1.45</td>
<td>1.46</td>
</tr>
<tr>
<td>Vd/F L</td>
<td>0.0778</td>
<td>0.0911</td>
<td>0.1621</td>
</tr>
</tbody>
</table>

The plasma was passed through cartridges under negative pressure of 10 lb/sq in. Then the cartridges were washed with 2x2 ml of double distilled water and dried under a stream of nitrogen. After drying the drug was eluted from cartridges using 2x2 ml of dichloromethane. Then dichloromethane was evaporated under a stream of nitrogen and the residue was reconstituted with 0.01 M HCl. From this solution 50 ul was injected into the HPLC system.

The mobile phase consisted of acetonitrile: water (40:60) with a final pH 4.0 adjusted with 0-phosphoric acid. The flow rate was 1.5 ml/min. Samples were injected into column (Pecosil ODS 10 um, size 250 cm x 4.6 mm, Perkin Elmer, USA) and the absorbivity of the mobile phase was monitored at 238 nm using a variable wavelength UV detector (Perkin Elmer UV/Visible spectrophotometer detector LC 290). The output was recorded on an integrator (PE Nelson Model 1020, Perkin in Elmer, USA). The retention time of diltiazem was found to be 4.5 min.

Pharmacokinetic Analysis

Plasma diltiazem concentrations after oral administration of diltiazem HCl tablet to three dogs were analyzed with the conventional one compartment model (model A) and with the two-fraction absorption model (model B) shown appendix. In vivo release profiles of diltiazem were calculated by the Wagner-Nelson method. A non-linear regression program was developed in our laboratory similar to the microcomputer program MFA-MULTI that was developed for multi-fraction absorption models based on a simplex method and used for the analysis of serum diltiazem concentration data using integrated equations:

\[
C = C_{i} = \sum_{i=1,2}^{\infty} \frac{FX_{ai}}{Vd K_{ai}} \frac{(K_{ai} - K_{el})}{(e^{K_{el}(t-T_i)} - 1)}
\]

\[C = C_{i} \text{ for } (T_1 < t < T_2)\]

\[C = C_1 + C_2 \text{ for } (t>T_2)\]

In eq. 1, X_{ai} is the amount of drug in the gastrointestinal tract of i^th fraction (i = 1, 2), K_{ai} is the absorption rate constant of i^th fraction (i = 1, 2), K_{el} is the elimination rate constant, Vd is the volume of distribution, F is the fraction of absorption, and T_i is the lag time for the absorption of i^th fraction (i=1,2).

RESULTS AND DISCUSSION

The dissolution profile of the tablets used in this study is shown in Fig. 1. Typical mean serum con-
APPENDIX

Model A

One compartment model with one first-order absorption process and one elimination process.

\[ X_a \xrightarrow{K_a(t \geq T)} X_c \xrightarrow{K_{el}} \]

Model B

One compartment model with first-order absorption process from two fractions and one first-order elimination process.

\[ X_{a1} \xrightarrow{K_{a1}(t \geq T_1)} X_c \xrightarrow{K_{el}} X_{a2} \xrightarrow{K_{a2}(t \geq T_2)} \]

where,

- \( X_a \) = the amount of drug in the gastrointestinal tract
- \( X_{a1} \) = the amount of drug in the gastrointestinal tract of the \( i^{th} \) fraction (\( i = 1, 2 \))
- \( X_c \) = the amount in the central compartment
- \( K_a \) = absorption rate constant
- \( K_{a1} \) = absorption rate constant of the \( i^{th} \) fraction (\( i = 1, 2 \))
- \( F \) = fraction of absorption
- \( T \) = lag time for absorption
- \( T_i \) = lag time for absorption of the \( i^{th} \) fraction (\( i = 1, 2 \))

Table 2: Curve fitting to serum diltiazem concentration in dogs by using model A.

<table>
<thead>
<tr>
<th>Dog</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>( C = -821.1 \ e^{-0.4760(t-0)} + 924.9 \ e^{-0.3198(t-0)} )</td>
</tr>
<tr>
<td>2.</td>
<td>( C = -2639.4 \ e^{-0.7235(t-0.14)} + 2527.1 \ e^{-0.5504(t-0.14)} )</td>
</tr>
<tr>
<td>3.</td>
<td>( C = -1303.9 \ e^{0.9639(t-0.24)} + 1280.5 \ e^{0.7265(t-0.24)} )</td>
</tr>
</tbody>
</table>

Fig. 1. Dissolution profile of diltiazem HCl tablet used in this study.

Fig. 2. Mean (± S.D.) serum concentration of diltiazem in dogs. Key: (O) actual concentration, (△) curve fitted using model A, (□) curve fitted using model B.
model (model A) and multi-fraction absorption model (model B). The serum diltiazem concentration data could not be fitted to model A, but could be well fitted to model B. As shown in figures 2, the observed and calculated plasma concentrations were in good agreement with each other, supporting the validity of the multifraction absorption model (model B). AICs for the model A and model B were 38.6 ± 4.5 and 29.4 ± 9.2, respectively. Table 1 shows the pharmacokinetic parameters estimated using the model B. Table 2 shows the equations used for the fitting of diltiazem serum data by model A in 3 dogs. In model B diltiazem seemed to be divided into two fractions in the gastrointestinal tract with respective absorption rate constants. It is concluded that multifraction absorption models are applicable for the analysis of plasma drug concentration data with irregular absorption profiles.

ACKNOWLEDGEMENTS

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REFERENCES


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