Study of Dose-linearity of Gemfibrozil Pharmacokinetics in Human

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Abstract: To study the dose linearity of gemfibrozil in therapeutic range, the pharmacokinetic of gemfibrozil was assessed in twelve healthy volunteers after administration of single oral does of 300, 600 and 900 mg gemfibrozil in a randomized cross-over design. Serial blood samples were collected at predetermined times before and after drug administration. Serum gemfibrozil concentrations were determined by a validated reversed phase HPLC method. Pharmacokinetic parameters determined by non compartmental methods. The mean elimination half-lives (t1/2) of gemfibrozil, which did not vary with the dose, were 1.3±0,2, 1.2±0.2 and 1.4±0.1 h, respectively after the three administered doses. The peak serum levels (Cmax) and area under the serum level versus time curve (AUC) data showed dose-proportional response. The time to peak serum concentration (tmax), apparent clearance (CL/F) and apparent volume of distribution (Vd/F) did not show significant difference over the administered doses. These findings suggest that gemfibrozil disposition is linear over the dose range studied.

Keywords: Gemfibrozil, dose-dependency, pharmacokinetics, non-linearity

INTRODUCTION

Beginning with the description of clofibrate in 1962, derivatives of fibric acid (fibrates) have been used to treat dislipidaemias. Gemfibrozil (CAS No.25812-30-0) (GEM)1 (Fig. 1) is a fibric acid analog that is indicated for the treatment of hyperlipoproteinemias involving elevated triglycerides. At the present time, it is one of the primary lipid-lowering agents of the fibric acid class that is still marketed in the United States (e.g., Lopid, Parke-Davis).

Absorption of GEM after oral administration is complete in human, with peak plasma concentrations achieved in 1 to 2 h.[4]. In rats as well as humans, GEM undergoes extensive phase I and phase II metabolism.[6,7]. Forland et al.[8] have shown that co-administration of gemfibrozil and colestipol may cause an apparent reduction in GEM absorption. In another study two different sites for absorption of GEM has been postulated.[9]

Considering very large oral dosage forms (300-600 mg) and very low aqueous solubility of GEM, the study of proportionality of pharmacokinetic parameters to the oral administered dose is of great importance. The objective of this study was to determine the dose linearity of gemfibrozil in human volunteers.

MATERIALS AND METHODS

Subjects: Twelve volunteers of 23-35 years old and 65-80 kg weight participated in this study. They were judged healthy by physical and biochemical/ hematological examinations. The protocol received approval of the Ethics committee of the Ministry of Health. All subjects abstained from medications 1 week prior to and during the period of study (three weeks). Subjects had an overnight fast until 4 h after the administration of each gemfibrozil dose following which food and drinks were allowed freely.

Drug administration and sample collection: The study was conducted in a randomized cross-over design with all subjects receiving Lopid 300 mg capsule (BN: 0001088 Parke-davis, Hampshire, UK) equivalent to 300, 600 and 900 mg of gemfibrozil (1, 2 or 3 capsules), at each part of the study, respectively. All drug administrations were separated by a period of 1 week to allow for complete drug washout. On each study day, the drug was administered with 200 mL water. Venous blood (3 mL) was taken from the forearm by venipuncture prior to (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h after each drug intake. The blood samples were centrifuged at 1000 g for 20 min and the

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The elimination half-life ($t_\text{\tiny 1/2}$) was calculated as $0.693 \cdot k^{-1}$, where $k$ is the elimination rate constant which is the absolute value of the slope of the least-squares regression line for $n$ terminal data points ($n = 5$). The area under the serum drug concentration versus time curve (AUC$_\text{\tiny 0-\infty}$) was estimated by the trapezoidal method. The AUC was extrapolated to infinity by adding the AUC$_\text{\tiny 0-\infty}$ to C$_\text{\tiny 0}$/k where, C$_\text{\tiny 0}$ is the last quantified serum drug concentration. The clearance was calculated as ‘oral clearance’ (CL/F) = Dose/AUC, while the apparent volume of distribution (V$_\text{\tiny d}$/F) was estimated as ‘Oral Clearance/k relative to the bioavailability (F) of gemfibrozil.

The highest observed serum concentration for the drug C$_\text{\tiny max}$ and the time to reach it, t$_\text{\tiny max}$ were obtained directly from the serum concentration time curve.

Statistical evaluations were performed using ANOVA analysis. Linear regression procedure were utilized to determine whether C$_\text{\tiny max}$ and AUC values were proportional to the administered dose (300-900 mg). All results are reported as means±SD.

RESULTS AND DISCUSSION

The serum concentration-time profiles showed a mono-exponential decline and followed a similar pattern for all three doses (Fig. 2). There were high intra-and inter-individual variations in the observed pharmacokinetic parameters. The t$_\text{\tiny max}$ was around 1 to 2 h in three doses and the variation was independent of dose (Table 1). The levels of gemfibrozil declined with elimination half-life of 1.4±0.3, 1.1±0.2 and 1.3±0.1 h following doses of 300, 600 and 900 mg of the drug, respectively. The oral clearance showed values of 8.8±4.1, 7.1±0.9 and 6.6±1.6 l h$^{-1}$ in three respective doses. No significant differences as a function of administered doses were observed in the ANOVA of the t$_\text{\tiny max}$, CL/F and V$_\text{\tiny d}$/F of the drug at the different doses (p>0.05) C$_\text{\tiny max}$ and AUC parameters increased linearly with increase in dose (Fig. 3 and 4). Observed C$_\text{\tiny max}$ values ranged from 9.9 to 21.2, 22.4 to 35.8 and 26.5 to 61.9 μg mL$^{-1}$ while the AUC(0–∞) values were 16.8 to 72.8, 68.3 to 101.3 and 95.3 to 229.6 μg h mL$^{-1}$ after the 300, 600 and 900 mg doses, respectively.

It has been reported that gemfibrozil is almost completely absorbed from GI tract[1]. It has also been noted that GEM undergoes extensive hepatic metabolism and metabolites are mostly cleared from the body by kidney.[2-3] Gemfibrozil has a solubility of around 0.0019% in water and acidic solutions[12] According to Bipharmaeutics Classification System (BCS)[13] which classifies the drugs according to their solubility and permeability and considering the Dose (mg)/aqueous
Table 1: Pharmacokinetic parameters after single oral administration of 300, 600 and 900 mg gemfibrozil in twelve human healthy volunteers (mean±SD)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Cmax (ug mL⁻¹)</th>
<th>Tmax (h)</th>
<th>AUC(0-8) (ug h mL⁻¹)</th>
<th>AUC(0-∞) (ug h mL⁻¹)</th>
<th>CL (L h⁻¹)</th>
<th>Vd (L)</th>
<th>T1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>15.1±(4.2)</td>
<td>1.0±(0.5)</td>
<td>36.9±(4.7)</td>
<td>39.5±(6.1)</td>
<td>8.8±(4.1)</td>
<td>16.7±(2.9)</td>
<td>1.4±(0.3)</td>
</tr>
<tr>
<td>600</td>
<td>28±(8.4)</td>
<td>1.8±(0.8)</td>
<td>80.3±(16.3)</td>
<td>85.2±(10.7)</td>
<td>7.1±(0.9)</td>
<td>11.6±(2.1)</td>
<td>1.1±(0.2)</td>
</tr>
<tr>
<td>900</td>
<td>40.8±(12.6)</td>
<td>1.9±(0.6)</td>
<td>132±(35.3)</td>
<td>143±(39.8)</td>
<td>6.6±(1.6)</td>
<td>12.3±(3.4)</td>
<td>1.3±(0.1)</td>
</tr>
</tbody>
</table>

p value: 0.72, 0.49, 0.46, 0.41, 0.21, 0.17, 0.07
Slope*: 0.043, 0.001, 0.159, 0.174, -0.604, -0.007, 0.00
R²**: 1.0, 1.0, 1.0, 1.0, -1.0, -0.8, -0.3

*Slope obtained from the linear regression of each parameter versus administered dose.
** Correlation coefficient obtained from the linear regression of each parameter versus administered dose

Legend for figures:

Fig. 3: The correlation between Cmax and administered dose in twelve healthy volunteers after single oral doses of 300, 600 and 900 mg (mean±SD)

\[ y = 0.0429x + 2.5292 \]
\[ R^2 = 0.9985 \]

Fig. 4: The correlation between AUC(0-∞) and administered dose in twelve healthy volunteers after single oral doses of 300, 600 and 900 mg (mean±SD)

\[ y = 0.1756x - 14.725 \]
\[ R^2 = 0.9949 \]

solubility (mg mL⁻¹) ratio with the cutoff of 250 mL to define a drug by good solubility which has been used by FDA in SUCAP guidance[4], it seems that the absorption of GEM is completely controlled by its solubility. Extensive metabolism, large oral doses of GEM along with its very low aqueous solubility may lead to a non-proportional dose absorption and metabolism. This study showed that the main pharmacokinetic parameters obey those of linear pharmacokinetics. The terminal elimination half life calculated from serum concentration data did not change over the doses studied (p = 0.07). The dose normalized AUC(0-8 h), AUC(0-∞) and Cmax also did not show significant differences. Their p values obtained from one way ANOVA were 0.46, 0.41 and 0.72, respectively. Although a decrease in CL was observed by increasing the dose from 300 to 900 mg, this decrease was not statistically significant (p = 0.21) and the regression line of CL versus dose showed a slope of -0.007 which was comparable to the one obtained from Vd versus dose (slope = -0.004). Both slopes were not significantly different from zero. Therefore, predicted proportional changes in plasma concentration of GEM are observed over the dose range of 300 to 900 mg. There was no complaining of any side effects over entire dose range.

CONCLUSIONS

This single dose study demonstrated that gemfibrozil shows a fast absorption and a linear pharmacokinetic over the 300 to 900 mg dose range. When gemfibrozil doses of 300 to 900 mg were administered to healthy adult volunteers, Cmax and AUC increased in a dose-proportional manner.

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REFERENCES


