Pharmacokinetic Study of Ketoprofen After Oral Administration of Sustained Release and Non-Sustained Release Dosage Forms

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Abstract:

Six healthy male subjects involved in a crossover bioavailability study to compare the pharmacokinetics of ketoprofen after single oral administration of the drug (100mg) as non sustained release or sustained release pellets dosage forms. A specific and sensitive high performance liquid chromatographic assay procedure was used to analyse the plasma and urine samples. The absorption from sustained release pellets dosage form was slower and more sustained than from non sustained release capsules, but almost complete. The bioavailability properties of this sustained release pellets dosage form of ketoprofen appears suitable for clinical use with reduced frequency of daily dosing.

KEY WORDS: Pharmacokinetics, Sustained Release, Ketoprofen, In-vivo

Introduction

Ketoprofen is a potent analgesic and non-steroidal anti-inflammatory drug in animals (1). and man(2). It has been demonstrated that ketoprofen in clinically effective in clinical studies involving more than four thousands patients (3). Ketoprofen, like most of other non-steroidal anti-inflammatory agents is rapidly eliminated from the body after dosing (4). Therefore in order to maintain therapeutic plasma levels these compound must be administered frequently. To reduce the frequent dose administration and avoid possible patient non-compliance (5,6), the use of a sustained release dosage form has been considered. It has been shown that use of a sustained release, once daily , dosage form has pharmacokinetic
and clinical advantages in the field of non-steroidal anti-inflammatory therapy (7). Here we compare the pharmacokinetics of a new sustained release pellets formulation of ketoprofen with those of ketoprofen administered as commercially available ketoprofen capsules.

Materials and Methods

Six healthy male volunteers aged between 18-32 years (mean value 19.5±1.1) and weighed between 60-83 kg (mean value 71.5±7.6) participated in this study. The volunteers were found to be healthy by medical examination and by biomedical and hematological tests. Prior to the start of the trial, each volunteer received 100 mg of ketoprofen in two different dosage forms on two separate occasions each separated by a period of one week. The dosage forms were 100 mg of ketoprofen as Orudis capsules Lot DD3340, (2x50 mg capsules, May and Baker, U.K.) and sustained release pellets Lot B containing ketoprofen (Biovail S.A.) placed in a hard gelatine capsule. The drug was administered in crossover studies as a single dose. On the day of dosing dose was taken in the morning), a light breakfast of tea and toast (no butter) was taken by subjects at least one hour prior to dose administration. A light lunch was allowed not earlier than four hours after the time of the dosing. the special diet was employed to facilitate the control of the urinary pH (around 6.0). The fluid intake (200 ml/hour of water, tea, or coffee) provided a more or less constant urine flow rate. The drug was usually administered in the morning and each dose equivalent to 100 mg of ketoprofen was taken with 100 ml of water.

Blood and Urine Sampling:

Control samples (blanks) of urine and plasma were collected just before drug administration. Blood samples (10 ml), were collected into heparinized glass tubes at 0.85, 1.35, 1.85, 2.35, 3.35, 4.35, 5.6, 3.5, 8.35, 11.35, 16.35, 24.35, 28.35 hours after drug administration. Plasma separated immediately after collection from heparinized blood (by centrifugation at 3500 r.p.m. for 5 minutes), was stored in a refrigerator (4 °C) until analysis. Urine samples were generally collected hourly for the first 16 hours after administration and then every 2-4 hours for the remaining period up to 28 hours. All the samples were stored over 5 ml of a
mixture of toluen/carbon tetrachloride (1:2 v/v as a bacteriostate) in a refreragerator (4 °C) until analysis.

Assay Procedure:

Ketoprofen concentrations were measured in plasma as free drug and in urine after acid hydrolysis using a modified high performance liquid chromatographic procedure (8). The assay procedure was reproducible and it was linear over the range of 8mg/l to 0.25 mg/l of ketoprofen in plasma and over the range of 400 mg/l to 8 mg/l of ketoprofen in urine.

Stability Test:

As indicated previously all the samples were stored in the refrigerator (4 °C) while waiting for analysis. Therefore this condition necessitated a stability test of the drug in biological samples and in solution under this condition. Stability of ketoprofen in urine and in plasma over a period of 35 days were studied, when they were stored at 4 °C. Stability of ketoprofen in alkaline solution, (as solvent), with pH of 10.5, and 11.5, was also studied, when they were stored at 4 °C over a period of seven months.

Pharmacokinetic Analysis:

From the time course of drug plasma levels the kinetic parameters were determined for each of the six subjects using the method of Wagner and Nelson (9). The elimination half lives were calculated from the first phase of elimination using the method of least squares. Area under the plasma concentration versus time curves (AUC) were estimated using the trapezoidal method and extrapolated to infinity for all of the six subjects. The model independent parameter of total body clearance, C1, was calculate using equation

\[ C1 = \frac{F \cdot D}{AUC} \]

Where \( F \) is the fraction of oral dose absorbed and taken to be unity for ketoprofen and \( D \) is
the dose administered. The apparent volume of distribution \( V_{(\text{area})} \) was calculated as follow (10).

\[
V_{(\text{area})} = \frac{\text{F.D.}}{\text{AUC}} \cdot k_{\text{el}}
\]

The urinary data were used to calculate the elimination half life of ketoprofen using the method of least squares of urinary excretion rate against time (mid-point method), the area under the plasma-time curve, (AUC), and total urine recovery of drug, \( A_{e} \), and their ratio were calculated and compared for the two different dosage forms.

Results and Discussion

A stability study indicated that ketoprofen was stable in urine and in plasma at least for 30 days when they were stored at 4 °C (Table 1). Stability of ketoprofen in alkaline solution (as solvent), with pH of 10.5, and 11.5, was shown no degradation over a period of seven months.

Plasma Pharmacokinetics of Ketoprofen

The mean plasma levels of ketoprofen in six healthy subjects after administration of equal to 100 mg ketoprofen as sustained and non-sustained release dosage forms are shown in figure 1. Administration of non-sustained released forms indicates that the absorption of the drug was very rapid and peak plasma levels were reached within 1.35-2.35 hours after dosing. This rapid absorption was followed by a rapid exponential decrease with mean plasma half life of 1.33 hours (ranging from 1.11-1.56 hour). Sustained release pellets administration produce a much slower absorption and peak plasma levels which reached within 3.35-7.35 hours after dosing. Practically the mean plasma levels remained steady between 3- 8 hours after drug administration and then decreased slowly.

Pharmacokinetic parameters of ketoprofen were calculated using individual data after administering 100 mg ketoprofen as sustained and non-sustained release dosage forms. Individual and mean standard deviation for the parameters of highest observed plasma ketoprofen concentration \( C_{\text{max}} \), time of \( C_{\text{max}} \), area under the plasma ketoprofen.
concentration against time curve and relative bioavailability of different dosage forms of ketoprofen are reported on table (2). These analysis of pharmacokinetic data confirms that peak plasma levels after administration of the sustained release formulation were significantly lower and reached substantially later compare to when conventional capsules, were administered. The area under the plasma ketoprofen concentration against time curve after oral administration of non-sustained released and sustained release dosage forms were essentially equal. Finally, the mean percentage of relative bioavailability (sustained release pellets forms versus conventional capsules) in the six subjects was about 102 % (range 78.9%-118.5%) which indicates a very good and reliable absorption of drug from sustained release dosage form.

**Urinary Excretion of Ketoprofen**

Ketoprofen (free plus conjugated) was also quantified in urine following the administration of ketoprofen as non-sustained and sustained release pellets dosage forms. Figure 2 shows the mean cumulative drug excreted for the six subjects. The urinary data were used to compare the two dosage forms of ketoprofen. The mean standard deviation values for percentage of administered dose excreted as free plus conjugated drug from time zero to infinity were 80.6 ± 11.5 and 80.9±11.5 for non- sustained released and sustained release dosage forms respectively. Practically the excretion of ketoprofen seems nearly complete by the first 24 hours after the drug administration, since 89.3 percent and 77.3 percent of the total ketoprofen recovered (from time zero to infinity) was excreted within the first 24 hours after dosing.

**Comparison of Plasma and Urinary Data**

The total amount of drug excreted in the urine after oral administration was used to calculate the elimination half - life (9). This elimination half-life calculated from urine data 1.55±0.43 hours, is in reasonable agreement with the values derived form the plasma data. 1.33±0.17 hours. Comparison of the area under the plasma time curve , (AUC) , total urinary recovery of drug, \( A_e \) and their ratio \( A_e / (AUC) \) , for different dosage forms are in good agreement and shown in table 3. As expected, administration of non-sustained release
dosage form of ketoprofen showed a very rapid absorption of the drug. This rapid absorption of drug produce a substantial plasma drug concentration and the plasma concentration declined quickly. The mean results of urinary excretion rates of the drug support very clearly the information obtained from plasma, figure 3. Urinary clearances of ketoprofen after oral administration of non - sustained release form was extensive and rapid, as it has been noted by other authors (11-13), with 50 to 90 % of the dose in the urine for 24 hours. Furthermore, following a single oral dose of non-sustained release dosage form, 85% (average of six subjects) of total ketoprofen excreted in the 24 hour urine, is cleared within the first 10 hours, which is in agreement with the other previously recorded results (14).

Sustained release pellets dosage forms of ketoprofen eliminate the pronounced plasma peak of drug after non-sustained release dosage form administration and they deliver the drug steadily. Although in the first 10 hours there is a very broad sustained peak in plasma levels, nevertheless the drug is delivered over a 24 hour period. The mean results of urinary excretion rates of the drug support the information obtained from plasma. Following a single oral dose of sustained release pellets form of ketoprofen 66% (average of six subjects) of the total of ketoprofen excreted in 24 hours urine, is cleared within the first 10 hours.

Figure 1 clearly indicates that from about four hours to twenty eight hours the concentration in the plasma after the sustained release form administration was higher than after non-sustained release form administration. Urinary data support this argument. Plasma and urinary data clearly indicate that the bioavailability of sustained release pellets dosage form relative to the non-sustained release form in close for the six subjects.

As indicated in figure 1 the sustained release pellets produce a considerbely lower peak plasma level. Since the drug is in the form of small pellets they are widely Scattered as they pass down the gastro intestinal tract (15). Therefore it is possible to minimize the inter-individual variation caused by differences in transit time with pellet formulation.

Since this sustained release pellets form is approximately bioequivalent to the conventional ketoprofen capsules, it can be used without any major alteration in the inter-individual variability in systemic availability of ketoprofen drug substances from the formulation.
Table 1: Investigation of the stability of ketoprofen in urine and plasma for 30 and 35 days respectively at 4 °C.

<table>
<thead>
<tr>
<th>biological fluid</th>
<th>drug concen.</th>
<th>mean peak height ratios at start of storage</th>
<th>mean peak height ratios at after storage</th>
<th>%recovery of drug after storage</th>
<th>mean %recovery of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma +</td>
<td>4</td>
<td>0.210±0.008</td>
<td>0.190±0.002</td>
<td>92.1</td>
<td>101.1</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.380±0.009</td>
<td>0.420±0.016</td>
<td>110.2</td>
<td></td>
</tr>
<tr>
<td>urine *</td>
<td>8</td>
<td>0.080±0.001</td>
<td>0.0700±0.0004</td>
<td>107.6</td>
<td>103.9</td>
</tr>
<tr>
<td></td>
<td>24.5</td>
<td>0.200±0.001</td>
<td>0.210±0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>0.410±0.002</td>
<td>0.440±0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#Mean±standard deviation

*The number of replicates for each concentration is 6

+The number of replicates for each concentration is 5
Table 2: Individual pharmacokinetic parameters in six healthy male subjects after single oral administration of ketoprofen (100mg).

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>Mean±S.D.</th>
<th>stat.comp of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/l)</td>
<td>N.S.R.</td>
<td>7.8</td>
<td>8.0</td>
<td>12.6</td>
<td>10.05</td>
<td>8.5</td>
<td>9.5</td>
<td>9.4±1.8</td>
</tr>
<tr>
<td></td>
<td>S.R.</td>
<td>1.7</td>
<td>2.3</td>
<td>2.45</td>
<td>2.2</td>
<td>2.1</td>
<td>2.4</td>
<td>2.2±0.3</td>
</tr>
<tr>
<td>Time of $C_{\text{max}}$ (h)</td>
<td>N.S.R.</td>
<td>1.35</td>
<td>1.35</td>
<td>1.35</td>
<td>1.85</td>
<td>2.35</td>
<td>1.35</td>
<td>1.6±0.4</td>
</tr>
<tr>
<td></td>
<td>S.R.</td>
<td>4.35</td>
<td>4.35</td>
<td>4.35</td>
<td>5.35</td>
<td>7.35</td>
<td>3.35</td>
<td>5.0±1.4</td>
</tr>
<tr>
<td>AUC (mg.h/l)</td>
<td>N.S.R.</td>
<td>19.6</td>
<td>22.5</td>
<td>27.5</td>
<td>26.3</td>
<td>22.9</td>
<td>26.5</td>
<td>24.2±3.0</td>
</tr>
<tr>
<td></td>
<td>S.R.</td>
<td>23.3</td>
<td>24.8</td>
<td>29.7</td>
<td>22.4</td>
<td>26.2</td>
<td>24.6</td>
<td>24.6±3.1</td>
</tr>
<tr>
<td>Relative Bioavailability (%)</td>
<td>N.S.R.</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>S.R.</td>
<td>118.5</td>
<td>109.9</td>
<td>108.1</td>
<td>85.2</td>
<td>114.5</td>
<td>78.9</td>
<td>102.5±16.4</td>
</tr>
</tbody>
</table>

*Defined as standard formulation  
N.S.R.= Non sustained release form  
S.R.= sustained release form  
S.D.= standard deviation  
stat.comp.= statistical comparison of Data.
Table 3: Comparison of total urinary recovery ($A_\infty$), area under the plasma-time curve (AUC) and their ratio in six subjects after oral administration of ketoprofen (100mg).

<table>
<thead>
<tr>
<th>parameter</th>
<th>dosage</th>
<th>Individual Results</th>
<th>Mean±S.D</th>
<th>stat.comp of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt;</td>
<td>N.S.R.</td>
<td>19.6</td>
<td>22.5</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>S.R.</td>
<td>23.3</td>
<td>24.8</td>
<td>29.7</td>
</tr>
<tr>
<td>$A_{\infty}$</td>
<td>N.S.R.</td>
<td>72.7</td>
<td>82.4</td>
<td>96.2</td>
</tr>
<tr>
<td></td>
<td>S.R.</td>
<td>86.3</td>
<td>89.2</td>
<td>92.5</td>
</tr>
<tr>
<td>$A_{\infty}$ /AUC&lt;sub&gt;∞&lt;/sub&gt;</td>
<td>N.S.R.</td>
<td>3.7</td>
<td>3.7</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>S.R.</td>
<td>3.7</td>
<td>3.6</td>
<td>3.1</td>
</tr>
</tbody>
</table>

N.S.R.=Non sustained release form  
S.R.=sustained release form  
S.D.=standard deviation  
ns=not significant  
stat.comp.=statistical comparison of data
Figure 1: Mean Plasma levels (SE) of ketoprofen against time in six subjects after oral administration.
Figure 2: Mean cumulative urinary excretion (SE) of ketoprofen in six subjects after oral administration.
Figure 3: Mean plasma levels (M.P.L.) and mean urinary excretion rates (M.U.E.R.) of ketoprofen in six subject after oral administration.
References