Pharmacokinetics of Two Rectal Dosage Forms of Ketoprofen in Patients after Anal Surgery

Ikuo KANAMOTO, Teruaki NAKAGAWA, Isamu HORIKOSHI,* Tamotsu KOIZUMI,** Kenji TAZAWA and Masao FUJIMAKI***

Department of Hospital Pharmacy, * Faculty of Pharmaceutical Sciences, ** and 2nd Department of Surgery, *** Toyama Medical and Pharmaceutical University, 2630, Sugitani, Toyama, 930-01, Japan
(Received July 22, 1987)

Two kinds of dosage forms of commercially available suppositories containing ketoprofen (KP), fatty suppositories (FS) and gelatin capsulated suppositories (GCS), were administered to patients immediately after anal surgery, and results obtained were compared. No difference was found in each corresponding pharmacokinetic parameter of the two dosage forms. However, when these parameters were compared with those from healthy subjects, significant differences were found in the values of peak level ($C_{\text{max}}$), peak time ($T_{\text{max}}$) and terminal phase half-life ($t_{1/2}$). $C_{\text{max}}$ decreased by one half, and $T_{\text{max}}$ and $t_{1/2}$ increased two and four times longer, respectively, those from healthy subjects. The absorption rate constant ($k_a$) in patients was significantly ($p < 0.01$) smaller than that in healthy subjects. However, the distribution volume/bioavailability ($V_d/F$), elimination rate constant ($k_e$), and area under the curve (AUC) differed only slightly. Consequently, the flip-flop phenomena could be seen in the time profiles of plasma KP concentration of patients.

These results suggested that the rectal suppository of KP should be administered with care, especially in the patients operated on under spinal anesthesia.

Keywords — ketoprofen; rectal administration; pharmacokinetics; patient

Introduction

Ketoprofen (KP), 2-(3-benzoylphenyl) propionic acid, widely used for a treatment of arthritis, is an aryl-alkanoic acid nonsteroidal anti-inflammatory drug. Numerous pharmacokinetic studies of KP in healthy subjects have already been reported.1–5) Recently, two kinds of suppositories of KP, fatty suppositories (FS) and gelatin capsulated suppositories (GCS) have been developed for sale by four pharmaceutical companies. Since a semi-synthetic glyceride is used in FS as the suppository base and it melts at body temperature, the release of drug from FS is thought to be temperature dependent. The release of drug from GCS is thought to be dependent on the volume of water in the rectum because drug absorption from the rectum will not begin until the gelatin capsule absorbs water and swells and bursts.6) It has been known that the lag time of drug release from FS in vitro is significantly shorter than that from GCS.7) Our previous study of administration of these suppositories to healthy subjects showed that a significant difference was found in the lag time of absorption but no difference was found with other corresponding pharmacokinetic parameters of FS and GCS.8)

Comparison of pharmacokinetics of KP in patients and in healthy subjects after rectal administration have not been well studied.9) To properly evaluate the two dosage forms, it is important to administer FS and GCS to both patients and healthy subjects and to compare the differences in pharmacokinetic behaviors.

Materials and Methods

Materials — Two types of commercially available suppositories were purchased; Fatty suppositories (KP, 75 mg, lot No. 5EIF) from Rhône Poulenc Co., Ltd. and gelatin capsulated suppositories (KP, 75 mg, lot No. 50420) from Iwaki Pharm. Co., Ltd. Pure KP and diclofenac sodium (internal standard) were supplied by Rhône Poulenc Co., Ltd.

Protocol — Eight patients having hemorrhoids (six men and two women; age range 23 to 70 years) participated in this study after being fully informed of the purpose of the study and
obtaining written consents. Before the experiment, all patients were clinically examined. Patients with definite cardiac, renal, hepatic or gastrointestinal disease, with severe infection, or who were pregnant were excluded.

The patients had hemorrhoidectomies under spinal anesthesia. Each patient received a single dosage of KP (75 mg) rectally after the operation and was confined to bed. Each 5 ml of venous blood sample was collected in a heparinized tube (Venojects, Terumo Co., Ltd, Tokyo, Japan) before and 1, 2, 4, 6 and 8 h after rectal administration. Plasma was separated by centrifugation and stored at $-20^\circ$C until it was analysed.

**Measurement of KP in Plasma** — KP levels in plasma samples were determined by a high performance liquid chromatographic method using diclofenac sodium as an internal standard.

The analytical procedure was same as described previously.\textsuperscript{8}

**Pharmacokinetic Analysis** — The one compartment model was fitted to plasma KP concentrations after rectal administration using a nonlinear least-squares computer program MULTI.\textsuperscript{10}

The terminal phase half-life ($t_{1/2}$) was calculated from Eq. 1:

$$t_{1/2} = 0.693/K$$  \hspace{1cm} (1)

Where $K$ is the rate constant of the terminal phase of elimination.

The peak time ($T_{\text{max}}$) and the peak level ($C_{\text{max}}$) were derived from Eqs. 2 and 3, respectively.

$$T_{\text{max}} = 1/(k_a - k_e) \cdot \ln(k_a/k_e) + t_{\text{lag}}$$ \hspace{1cm} (2)

$$C_{\text{max}} = \frac{(F \cdot \text{dose}/V_d) \cdot \{k_a/(k_a - k_e)\} \cdot \{e^{-k_e(T_{\text{max}} - t_{\text{lag}})} - e^{-k_a(T_{\text{max}} - t_{\text{lag}})}\}}{\{e^{-k_a(T_{\text{max}} - t_{\text{lag}})} - e^{-k_a(t_{\text{lag})}}\}}$$ \hspace{1cm} (3)

Where $F$ is the bioavailability factor.

The area under plasma concentration against time curve ($AUC$) was obtained from Eq. 4:

$$AUC = (F \cdot \text{dose})/(V_d \cdot k_e)$$  \hspace{1cm} (4)

Each value is given as the mean $\pm$ S.D. Statistical comparison of mean pharmacokinetic data was carried out using the Student's $t$-test.

**Results**

**Comparative Pharmacokinetics of KP Derived from Two Types of Suppositories in Patients after Surgery**

The average plasma KP concentration-time profile after rectal administration of two types of suppositories in patients are shown in Fig. 1. The curve for FS was slightly different from that of GCS. The mean pharmacokinetic data of two dosage forms in healthy subjects and patients after surgery are summarized in Table I. The calculated peak time ($T_{\text{max}}$) of FS and GCS were $2.10 \pm 0.37$ and $2.27 \pm 0.52$ h, respectively. The corresponding peak level ($C_{\text{max}}$) was $2.21 \pm 0.22$ and $2.36 \pm 0.71 \mu g/ml$, respectively. The lag time prior to the start of absorption ($t_{\text{lag}}$) derived from GCS was somewhat longer than that derived from FS, but the difference was not statistically significant. Therefore, no marked difference was found in any of the pharmacokinetic parameters of the two dosage forms.

**Comparative Pharmacokinetics of KP Derived from FS in Healthy Subjects and Patients after Surgery**

![Fig. 1. Plasma KP Concentration–Time Profile after Rectal Administration of KP (75 mg) in Patients](image-url)
TABLE 1. Pharmacokinetic Parameters of KP Derived from Two Rectal Dosage Forms in Healthy Subjects and Patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FS</td>
<td>GCS</td>
</tr>
<tr>
<td>$k_a$ (h$^{-1}$)</td>
<td>1.62±0.41</td>
<td>1.84±0.44</td>
</tr>
<tr>
<td>$V_d/F$ (l)</td>
<td>6.19±0.40</td>
<td>6.35±0.52</td>
</tr>
<tr>
<td>$k_{el}$ (h$^{-1}$)</td>
<td>0.94±0.18</td>
<td>0.92±0.14</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>0.78±0.18</td>
<td>0.77±0.12</td>
</tr>
<tr>
<td>$t_{ug}$ (h)</td>
<td>0.18±0.11$^{c)}$</td>
<td>0.33±0.06</td>
</tr>
<tr>
<td>$T_{max}$ (h)</td>
<td>1.03±0.30</td>
<td>1.11±0.15</td>
</tr>
<tr>
<td>$C_{max}$ (μg/ml)</td>
<td>5.72±0.83</td>
<td>5.96±0.10</td>
</tr>
<tr>
<td>$AUC$ (μg·h/ml)</td>
<td>13.49±2.88</td>
<td>13.29±2.37</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. $^{a)}$ Significantly different from healthy subjects ($p < 0.01$). $^{b)}$ Significantly different from healthy subjects ($p < 0.05$). $^{c)}$ Significantly different from healthy subjects ($p < 0.05$).

The average plasma KP concentration–time profile and pharmacokinetic parameters in patients after surgery were compared with those observed in healthy subjects which was previously reported.\(^8\) The average plasma concentration–time plots of FS for patients and healthy subjects are shown in Fig. 2 and the plasma KP concentration–time curve for patients differed from that for healthy subjects. In the case of patients, $C_{max}$ was lower and $T_{max}$ was longer than those of healthy subjects, and the decline of the plasma level in terminal phase was slower. Table 1 shows that the $k_a$ for patients was only one fifth of that for healthy subjects. $C_{max}$ for patients was about one half of that for healthy subjects and $T_{max}$ for patients was two times larger than that for healthy subjects. On the other hand, $k_{el}$ did not differ between the two groups. The terminal phase half-life for patients (3.09 ± 1.30 h) was about four times longer than that for healthy subjects (0.78 ± 0.18 h). This behavior is due to the flip-flop effect.\(^11\) However, no significant difference in $AUC$ was observed between the two groups (13.49 ± 2.88 and 15.26 ± 3.21 μg·h/ml, respectively). The extent of bioavailability of KP in patients and healthy subjects was essentially equal. The apparent volume of distribution divided by $F$ for patients was also

---

**Fig. 2.** Plasma KP Concentration–Time Profile after Rectal Administration of KP (FS, 75 mg)

Each value is the mean ± S.D. for 4 patients (○) and 10 healthy subjects (●).

**Fig. 3.** Plasma KP Concentration–Time Profile after Rectal Administration of KP (GCS, 75 mg)

Each value is the mean ± S.D. for 4 patients (△) and 10 healthy subjects (▲).
close to that for healthy subjects (5.96 ± 3.94 and 6.19 ± 0.401, respectively).

Comparative Pharmacokinetics of KP Derived from GCS in Healthy Subjects and Patients after Surgery

The average plasma KP concentration–time profiles after administration of GCS for patients and healthy subjects are shown in Fig. 3. Similar results were obtained on kinetics of KP for the two groups after GCS administration as those after FS administration. Additionally, a significant difference was found in $t_{\text{lag}}$ between patients and healthy subjects (0.47 ± 0.11 and 0.33 ± 0.06 h, respectively).

Discussion

The KP release from FS is thought to be dependent on the body temperature, and that from GCS is thought to be dependent on the volume of water in the rectum. We had already reported that, in the case of healthy subjects, a significant difference was found between the values of $t_{\text{lag}}$ of FS and of GCS. But, in this experiment, no difference was found between corresponding pharmacokinetic parameters of the two dosage forms in patients. These results are probably due to the following reasons: The patients who were administered FS were not administered GCS, though in the previous experiments each healthy subject was administered FS and GCS twice. Consequently, most S.D. of pharmacokinetic parameters in patients became larger than those in healthy subjects.

The plasma KP concentration–time profile of patients after anal surgery was significantly different from that of healthy subjects. $T_{\text{max}}$ increased about two times, $C_{\text{max}}$ decreased one half, and $t_{1/2}$ was prolonged three to four times in patients. Prolonged $t_{1/2}$ may clinically be advantageous, but decreased plasma concentration may be the cause of less efficacy. Analgesic efficacy by spinal anesthesia is known to continue for about 4 h, so we could not appropriately estimate the effect of KP in patients.

We believe that the variety in kinetics of KP in patients was mainly due to decrease in the absorption rate. The decrease in absorption rate is probably due to the following reasons. 1. The decrease of blood flow rate in the rectum due to spinal anesthesia. 2. The impairment of tissue at the absorption site by surgical injury. 3. The change of absorption site by resting in bed. Further study will be needed to reveal the correlation between the decrease in absorption rate and its cause.

We must be aware of the fact that the pharmacokinetics of KP from rectal suppositories in patients after surgery are significantly different from that in healthy subjects.

References

Pharmacokinetics of Ketoprofen

