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Pharmacokinetic Evaluation of Flurbiprofen Sustained Release Capsule

Kyoung Ho Park[1†], Min Hwa Lee[1,2], Min Yeol Yang[3] and Chong Won Lee[3]

[1]*Department of Pharmacy, Seoul National University Hospital, Seoul 110-744, Korea*
[2]*College of Pharmacy, Seoul National University, Seoul 151-742, Korea and*
[3]*Samil Pharm. Co., Ltd., Seoul 137-061, Korea*

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플루르비프로펜 서방캅셀의 약물속도론적 평가

박경호[1†] · 이민화[1,2] · 양민열[3] · 이종원[3]
[1]서울대학교병원 약제부, [2]서울대학교 약학대학, [3]삼일제약주식회사

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In vitro dissolution test and pharmacokinetic study in human volunteers were conducted to evaluate the pharmacokinetic characteristics of 150 mg furbiprofen sustained-release capsule (FPSR-150). As a reference product, 50 mg flurbiprofen conventional-release capsule (FPCR-50) was used. Dissolution tests of two products were run using the paddle method in 450 : 540 (v/v %) mixture of simulated gastric and intestinal fluids (K.P. VI) by adjusting medium pH according to time. FPCR-50 was dissolved very rapidly, and it took about 1.5 hr for FPCR-50 to be dissolved over 90%, whereas 15 hr for FPSR-150. Also, in pharmacokinetic study, ten healthy male volunteers were administered one capsule of FPSR-150 or two capsules of FPCR-50 (FPCR-100) with randomized two period cross-over study. Significant differences between FPCR-100 and FPSR-150 were found in mean times to reach peak concentration, mean resident times and mean terminal phase half-lives, while not in AUC/Dose (Student's t-test). In ANOVA for AUC/Dose to compare the bioavailabilities of two FP products, there was no significant difference. From the comparison of the simulated steady-state plasma concentration-time curves following multiple medications of FPCR-50 (3 capsules a day, dosing interval=8 hrs) and FPSR-150 (1 capsule a day) based on the above results obtained from single doses of two FP products, it was noted that the medication of FPSR-150 is more useful in clinical application rather than FPCR-50.

Keywords—Flurbiprofen, Pharmacokinetics, Bioavailability, Dissolution, Sustained-release capsule, Steady-state, Simulation

Flurbiprofen [2-(2-fluoro-4-biphenyl)-propionic acid, FP] was first synthesized in the laboratories of the Boots Company PLC, Nottingham, England, and has been widely used clinically as one of the most potent non-steroidal anti-inflammatory drugs (NSAIDs).[1)] Its analgesic, anti-inflammatory and antipyretic activities are obtained mainly from the inhibition of the synthesis of cyclooxygenase depenent prostaglandins.[2,3)] A wide range of studies, both laboratory and clinical, have shown FP to be relatively well tolerated, even in long-term treatment, with minimal effects on the gastrointestinal tract,[4,5)] and FP products are presently marketed in over 20 countries. But, because of short elimination half-life of FP in human,[7-11)] dosage regimens of FP 50 mg conventional release (FPCR-50) products are recommended as three or four times a day to obtain safe and desired

†To whom correspondence should be addressed

clinical effects in a variety of rheumatic diseases, both inflammatory and degenerative. Since these regimens have potential possibility of non-compliance, reduction of dosing freqency from three or four to once a day is of potential benefit and convenient to patients. The Boots Company already launched a FP 200 mg sustained release capsule (FPSR-200) in the market. However this products was not available in Korea market where FPCR-50 products were widely used.

In 1990, a FP 150 mg sustained release capsule (FPSR-150) was designed instead of FPSR-200 in Samil Pharm. Co., Ltd, Seoul, Korea, because 200 mg of FP a day may be a high dose to Korean patients. In fact, according to the our survey about FP medications in Seoul National University Hospital (unpublished), the commonly used dose of FP was 150 mg or less a day to adult patients with various FP products. In the present study, *in vitro* dissolution patterns and pharmacokinetic characteristics of FPCR-150 in Korean were evaluated, since little informations are currently available concerning pharmacokinetic charateristics of FP products, especially FP sustained-release product, in Korean.

Experimental

Chemicals and apparatus

Flurbiprofen (powder) was supplied by Samil Pharm. Co., Ltd. Methanol and acetonitrile were obtained from Merck Co. (Rahway, N.J., U.S.A.). Other chemicals were reagent grade and used without further purification. The dissolution apparatus consisted of a dissolution tester (Copley-Hanson, Model 72RL), a peristaltic pump (Ismatec) and a spectrophotometer system (Cecil, Model CE 595). HPLC system consisted of a solvent delivery system (Biorad, Model 1330), an injector (Rheodyne, Model 7125), a reversed-phase (RP-18) column (4.6 mm×20 cm, 10 μm particle size, Waters Assoc.), a programmable fluorescence detector (Biosystem, Model 980), and a recoder (Linear, Model 1200).

Subjects

Ten healthy male volunteers were between 21 and 35 years of age (mean: 23 years). Their body weight were between 54 and 68 kg (mean: 61 kg) and were within ± 10% of their ideal weights obtained from their heights and ages. All subjects had no significant abnormal physical findings or

Table I—*The Demographic Data and the Results of Blood Chemistry Tests in 10 Healthy Male Volunteers.*

Subject No.	Age (yr)	Height (cm)	Weight (kg)	Smoke*	Total Protein (g/100 ml)	Albumin (g/100 ml)	SGOT (IU/L)	SGPT (IU/L)	BUN (g/100 ml)	Serum Creatinine (g/100 ml)
1	21	170	68	L	7.5	4.2	12	8	13	1.3
2	22	169	55	X	7.7	4.3	16	11	14	1.0
3	28	173	66	X	7.3	4.1	21	14	23	1.3
4	21	186	65	X	7.8	4.4	21	6	12	1.2
5	21	155	54	X	7.7	4.4	12	8	11	1.2
6	23	173	60	M	7.8	4.3	24	22	10	1.1
7	29	178	63	L	7.5	4.1	14	6	14	1.3
8	24	170	54	X	8.0	4.2	17	9	14	1.2
9	21	173	67	L	7.4	4.4	15	9	13	1.1
10	21	177	72	H	7.3	4.0	20	18	11	1.2
Mean	23	172	61	–	7.6	4.2	17	11	14	1.2
SD	3	8	7	–	0.2	0.1	7	5	4	0.1

*L: Light<0.5 pack/day, M: Middle<1 pack/day, H: Heavy>1 pack/day, X: Nonsmoker
! Normal ranges of blood chemistry tests
Total protein (6.8-8.0 g/ml), Albumin (3.3-5.0 g/100 ml), SGOT(<40 IU/L), SGPT(<40IU/L), BUN(10-26 mg/100 ml), Serum Creatinine (0.7-1.4 mg/100 ml)

hematologic laboratory values at the pre-treatment evaluation. All volunteers were instructed to refrain from taking alcohol- or xanthine-containing beverages and any drugs for 1 week prior to and during the study. All subjects were fully informed of the nature and intent of the study, and written informed consents were obtained. The demographic data, including name, sex, age, height, weight, smoking habits and the results of blood chemistry test were shown in Table 1.

FP Products

FPSR-150 and FPCR-50 manufactured by Samil Pharm. Co., Ltd. were used as the test and the reference products, respectively. And FPSR-200 (Boots Co., Nottingham, England) was also included in the dissolution test.

Dissolution Test of FP Products

The dissolution tests were conducted to evaluate *in vitro* dissolution patterns of FPSR-150 and FPSR-200 compared to FPCR-50 at 37± 0.5℃ and agitation of 100± 5 rpm by the paddle method described in KP VI. The dissolution media were composed of simulated gastric fluid and intestinal fluid, KP VI, (450 : 540, v/v%). During the dissolution tests, the pH of medium was adjusted with 0.2 M HCl or 0.2 M NaOH according to the time schedule, such as pH 2.5 during 0-1 hr, pH 4.5 during 1-3 hr and pH 6.8 during 3-19 hr, respectively. The experiment was repeated five times for each product. Samples were withdrawn at 20, 40, 60, 90, and 120 min for FPCR-50 and at 4, 10, 15, and 19 hrs for FPSR-150 and FPSR-200, respectively, after starting the dissolution test. The FP concentrations in samples were assayed automatically at 285 nm with a six-channel U.V. spectrophotometer which was connected to the dissolution tester.

Pharmacokinetic Studies of FPCR-50 and FPSR-150

Ten subjects were assigned in a random manner into Group 1 (n=5) and Group 2 (n=5). On each study day, after an overnight fast, a heparin lock was inserted into arm vein of each subject and blank blood was withdrawn prior to the drug administration. Two capsules of FPCR-50 (denoted FPCR-100) or one capsule of FPSR-150 were administered to subjects along with 150 m*l* of water at 8 : 30 in the morning. In Period I, Group 1 and 2 received FPCR-100 and FPSR-150, respectively. No food was allowed for the first 4 hr, and then meals of uniform composition were provided at 13 : 00 (lunch) and at 18 : 30 (dinner). After Period I, drug wash-out period for one week was given to all subjects. In Period II, the procedure was repeated in cross-over fashion. During each test period, all subjects were fully ambulatory but not allowed to engage in excessive or unusual exercise.

Five ml of blood samples were withdrawn at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hr in the case of FPCR-100 and at 1, 2, 3, 4, 5, 6, 8, 12, 24 and 48 hr in the case of FPSR-150, respectively, after the oral administrations of FP products with disposable syringe through an indwelling cannular or venipuncture, and then discharged into centrifuge tubes containing heparin as an anticoagulant. The plasma samples were separated immediately and frozen −70℃ until the assay of FP. During the study, all subjects were questioned regarding the occurrence of adverse reactions after drug administrations.

Assay of FP in Plasma using HPLC

FP in plasma was quantitated with a slightly modified HPLC method[12-15] after protein precipitation with acetonitrile. 100 μ*l* of plasma was transferred to an 1.5 m*l* centrifuge tube (Eppendorf® tube). After the addition of 250 μ*l* of acetonitrile, the tubes were vortexed for 10 seconds and centrifuged at 10000 rpm for 1 min using a microcentrige (Beckman). The supernatant was separated from the precipitate, and 50 μ*l* of the supernatant was injected directly onto the column. The concentrations of samples were calculated from the calibration curve over the range of 0.5-50 μg/m*l* of FP in plasma.

The mobile phase was a mixture of acetonitrile: water: phosphoric acid (650 : 350 : 0.5, v/v), and its flow rate was 1.5 m*l*/min. The excitation and emission wavelengths of the fluorescence detector were 250 nm and 315 nm, respectively.

Pharmacokinetic Analysis[16,17]

The model-independent pharmacokinetic para-

meters following single oral administrations of two FP products were determined from plasma FP concentration-time curve of the each subject. Peak concentration (C_{max}) and time to peak concentration (t_{max}) were obtained from measured concentrations at various times. The area under the plasma concentration-time curve (AUC) and the area under the first-moment of the plasma concentration-time curve (AUMC) from time zero to time infinity were calculated by trapezoidal rule and extrapolation method. In present study, since two FP products were administered orally, mean resident time (MRT_{ev}) was considerated as a factor which contains mean absorption time (MAT) and mean resident time after injection (MRT_{iv}), also, the ratio of clearance to bioavailability (CL/F) was calculated.

$$t_{1/2ter}=\frac{0.693}{\lambda} \quad (1)$$

$$AUC=\int_0^T Cp\ dt+\frac{Cp(T)}{\lambda} \quad (2)$$

$$AUMC=\int_0^T t\ Cp\ dt+\frac{T\cdot Cp(T)}{\lambda}+\frac{Cp(T)}{\lambda^2} \quad (3)$$

$$MRT_{ev}=MAT+MRT_{iv}=\frac{AUMC}{AUC} \quad (4)$$

$$CL/F=\frac{D_{oral}}{AUC} \quad (5)$$

Where, $t_{1/2ter}$ is the half-life of terminal phase, and T and Cp(T) are the last sampling time and the concentration at that time, respectively, and λ is the slope of terminal phase.

Simulation of Steady-State Plasma Concentrations

In order to evaluate the sustained plasma concentration and convinience of FPSR-150 compared to FPCR-50, the model dependent pharmacokinetic parameters following single oral administrations of FPSR-150 and FPCR-100 to 10 healthy volunteers were calculated by fitting the mean plasma concentrations of two products at various sampling times to suitable two-exponential decay model with oral administration using the MULTI program[18] at personal IBM-AT computer. And pharmacokinetic parameters obtained from single doses were applied to simulate the steady state concentration-time curves following multiple dosing regimens of FPSR-150 (1 capsule a day, interval 24 hr) and FPCR-50 (3 capsules a day, interval 8 hr).

Statistical Analysis

Statistical analysis was performed using the Student's t-test to see any diffeence in pharmacokinetic parameters between FPSR-150 and FPCR-100. In order to compare the bioavailabilities (AUC/Dose) of two FP products, ANOVA (crossover designed 2×2 Latin square method) was performed ($\alpha=0.05$, $\beta=0.2$).

Results and Discussion

Chromatograms of FP in Plasma using HPLC

Typical chromatograms of plasma spiked with FP (10 μg/ml) and plasma obtained from volunteer 3, demonstrate the specificity of this method by absense of interfering peaks (see Fig. 1). The calibration curve between FP concentrations and peak heights were linear over ranges of 0.5-25 μg/ml with a correlation coefficient of 0.9998. The retention time of FP was 3 min. The intra- and inter-assay coefficients of variation ranged from 4.2% and 6.7% for 25 μg/ml samples (n=6) to 9.7% and 15.2% for 0.5 μg/ml samples (n=6), respectively. Low limit of quantitation or detection was 0.1 μg/ml of FP. Although the metabolites of FP were not considered, this assay method is thought very simple and convenient to assay FP only in plasma.

Dissolution Patterns of FP Products

Fig. 2 shows the dissolution profiles of the two FP products. The pHs of dissolution medium were adjusted to 2.5, 4.5 and 6.8 during 0-1 hr, 1-3 hr and 3-19 hr, respectively. Mean dissolved percents of FPCR-50 were 44.7% and 96.6% at 1 hr and 2 hr, respectively, those of FPSR-150 and FPSR-200 were 19.4% and 21.9% at 4 hr, 90.7% and 91.1% at 15 hr, and 95.0% and 95.4% at 19 hr, respectively. Although FPSR-150 and FPSR-200 have same dissolution patterns, relatively large different dissolution patterns were observed between FPSR-150 and FPCR-50.

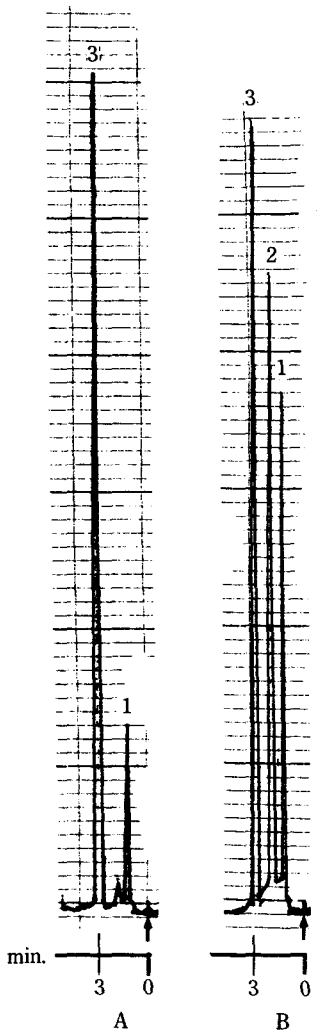

Figure 1—Chromatograms of (A) plasma spiked FP (25 μg/ml) and (B) plasma obtained from a volunteer who administered FPSR-150 orally. Key: 3; FP, 2 and 1; unknown peaks.

Monitorings of Side Effects of FP Products during Human Study

Side effects of FP during human study were monitored by a physician, and subject 7 and 9 claimed moderate gastric pains at 1 hr in study I and II, but recovered at 3 hr after drug administrations. No subjects except subject 7 and 9 claimed any disturbances of FP products.

Plasma Concentrations of FP after Single Oral Doses of FP Products

The concentrations of FP in plasma were detected by the assay method of this study until 24 hr and 48 hr after the oral administration of FPCR-100 and FPSR-150, respectively. The dose of FPCR-50 product was designed to 100 mg of FP (2 capsules of FPCR-50, denoted FPCR-100) instead of same dose (3 capsules of FPCR-50, denoted FPCR-150) to FPSR-150, because FPCR-50 product was rapidly absorbed, and the administration of FPCR-150 may cause high concentrations of FP early time and induce side effects of FP. Also, the dose-dependent pharmacokinetic characteristics were not reported on single or multiple dosings of FP products in therapeutic doses.[7-9] The mean plasma concentration-time profiles of FPCR-100 and FPSR-150 in 10 subjects were shown in Fig. 3.

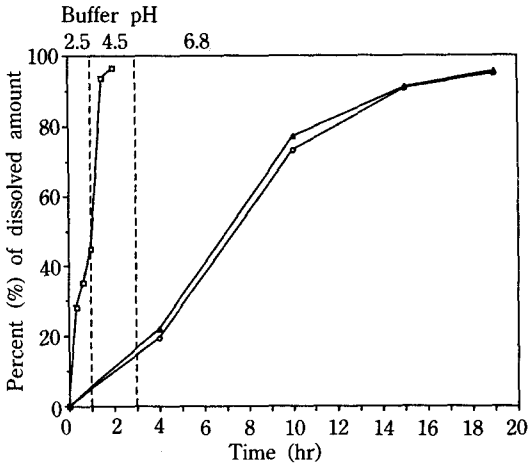

Figure 2—The dissolution profiles of FPCR-50, FPSR-150 and FPSR-200 in KH_2PO_4 buffer, respectively. The pH of the medium was adjusted according to time. Key: —□—; FPCR-50, —○—; FPSR-150, —▲—; FPSR-200.

Comparisons of Pharmacokinetic Characteristics of FP after Single Oral Doses of FP Products

The mean AUCs of FPCR-100 and FPSR-150 were 85.30 and 119.03 μg·hr/ml, respectively, as shown in Table II. The AUCs on unit doses (AUC/Dose) of two products were not significantly different each other. And there was no differences between the bioavailabities (F) of two products. Also, the mean CL/F of FPCR-100 and FPSR-150 were 19.95 and 20.73 ml/hr/kg, which were not

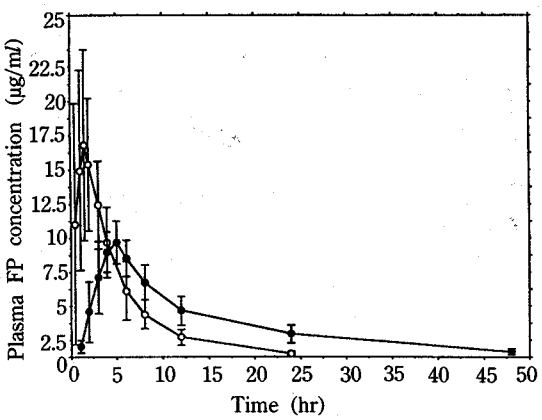

Figure 3—The mean plasma concentration-time curves of FP in 10 volunteers after single oral administrations of FPCR-100 and FPSR-150, respectively.
Key: —○—; FPCR-100, —●—; FPSR-150

significantly different each other.

The mean $t_{1/2ter}$ and mean MRT_{ev} of FPCR-100 and FPSR-150 products were significantly different, such as 4.46± 0.84 and 12.84± 5.26 hr for $t_{1/2ter}$ ($P<10^{-4}$), and 5.86± 1.16 and 18.27± 6.12 hr for MRT_{ev} ($P<10^{-3}$) (Table II), respectively. The mean C_{max} and mean t_{max} of FPCR-100 and FPSR-150 products were determined from measured concentrations and times, and were significantly different each other, such as 28.91± 7.44 (converted as a dose FPCR-150) and 8.97± 1.23 μg/ml for C_{max} ($P<10^{-4}$), and 1.6± 0.9 and 4.7± 1.0 hr for t_{max} ($P<10^{-4}$) (Table II), respectively.

In ANOVA[19] of AUC/Dose between FPCR-100 and FPSR-150 products, the difference of bioavailability to the reference drug was 7.83%, and there was not significant difference in F-test ($p>0.05$). Also confidence level of the difference in AUC/Dose to reference drug was 19.1% ($\alpha=0.05$, $\beta=0.2$), less than 20%, than it was found that two FP-products are equivalant in AUC/Dose.

Simulations of Steady-State Concentration-Time Curves on Multiple Dosings of FP Products

The mean plasma concentration versus times following single oral administrations of FPCR-100 and FPSR-150 in 10 subjects displayed apparent two exponential decay behavior, and were fitted to Eq. 7 using MULTI program.[18]

Table II—*Pharmacokinetic Parameters Obtained Following Single Oral Administrations of FPCR-100 and FPSR-150, Respectively.*

Parameters	FPCR-100	FPSR-150	p-values (Student's t-test)
AUC (μg hr/ml)	89.87± 18.12 (130.26± 22.08)*	120.80± 15.41	p>0.4
C_{max} (μg hr/ml)	19.27± 4.96 (28.91± 7.44)*	8.97± 1.23	p<0.0001
t_{max} (hr)	1.6± 0.9	4.7± 1.0	p<0.0001
MRT_{ev} (hr)	5.68± 1.16	18.27± 6.12	p<0.001
$t_{1/2ter}$ (hr)	4.46± 0.84	12.84± 5.26	p<0.0001
CL/F (ml/hr/kg)	19.95± 4.84	20.73± 3.21	p>0.1

*Calculated C_{max} and AUC when the dose of FPCR-100 was normalized to the same dose as FPSR-150.

$$Cp=Ae^{-\alpha t}+Be^{-\beta t}+Me^{-Kat} \quad (7)$$

where, Cp is the plasma concentration in μg/ml and A, B, M, α, β, and Ka are standard symbols used to describe two-exponential decay behavior of oral dose.

Using model dependent parameters of each products obtained from Eq. 7, the steady-state plasma concentrations of FP versus times were simulated for the multiple dosage regimens of FPCR-50 (3 capsules a day with 8 hr of dosing interval) and FPSR-150 (1 capsule a day with 24 hr of dosing interval), respectivey, and were shown in Fig. 4 from 72 hr to 96 hr after starting multiple dosing of each product. It was found that dosage regimen of 1 capsule of FPSR-150 a day is more useful than that of 3 capsules of FPCR-50 divided 3 times with 8 hr interval from comparing simulated steady-state plasma profiles of the two FP products with multiple dosing schedule.

From the results of present study, such as sustained dissolution profiles, prolonged $t_{1/2ter}$, MRT_{ev} and t_{max} of FPSR-150 compared to FPCR-50, and comparisons bewteen simulated steady-state concentrations versus time following multiple same

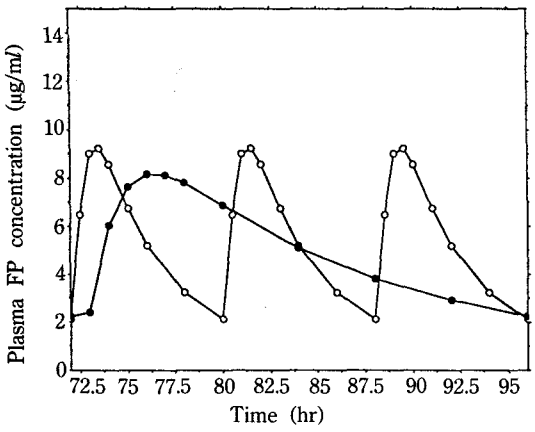

Figure 4—The simulated plasma FP concentration-time curves after multiple oral administrations of FPCR-50 (three capsules a day, dosing interval=8 hr) and FPSR-150 (one capsule a day), respectively.
Key: —○—; FOCR-50, —●—; FPSR-150

doses a day (dosing schedule is different) of two products, it was found that FPSR-150 product is well prepared, and more useful rather than FPCR-50 in patients who need long therapy with FP products.

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