

Effects of JOINS[®] on the pharmacokinetic profiles of aceclofenac in healthy Korean volunteers: an open-label, multiple-dose, one sequence, two-period study

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JOINS, an herbal anti-arthritic drug, was developed for the treatment and pain relief of knee osteoarthritis. It was approved for use in Korea by the Ministry of Food and Drug Safety in 2001. The aim of this study was to investigate the effect of JOINS on the pharmacokinetic (PK) profiles of aceclofenac in healthy adults. A PK drug-drug interaction study was conducted in 61 healthy subjects by using an open-label, multiple-dose, one sequence, two-period design. Blood samples were collected for plasma concentrations of aceclofenac during the reference period (aceclofenac 100 mg alone) and interaction period (aceclofenac 100 mg + JOINS 300 mg). The area under the curve within a dosing interval (τ) at steady state ($AUC_{\tau,ss}$) and the C_{max} at steady state ($C_{max,ss}$) of aceclofenac were analyzed by a non-compartment model using the Phoenix[®] WinNonlin[®] software version 6.3 (Pharsight, Mountain View, CA, USA). The 90% CIs of the geometric mean ratios (GMRs) of the $AUC_{\tau,ss}$ of aceclofenac with JOINS to without JOINS (D4/D3 and D11/D3) were 0.9593–1.0130 and 0.9745–1.0291, respectively, and the corresponding values for the $C_{max,ss}$ of aceclofenac with JOINS to without JOINS (D4/D3 and D11/D3) were 0.8578–0.9795 and 0.8510–0.9717. Aceclofenac alone or co-administered with JOINS was safe and well tolerated with no serious adverse drug reactions or significant differences in the severity of adverse events (AEs) between the two treatment groups. We conclude that co-administration of aceclofenac with JOINS does not influence the PK and safety profiles of aceclofenac.

Introduction

Osteoarthritis (OA) is the most common chronic joint disease causing pain, ankylosis, edema, and joint degeneration. With the increase in the elderly population and obesity, the incidence of osteoarthritis is gradually increasing.[1] According to the 5th Korea National Health and Nutrition Examination Survey

(KNHANES) in 2010, 14.7% of adults aged over 50 years and 29.6% of the elderly aged over 70 years were suffering from osteoarthritis.

According to the recommendation of Osteoarthritis Research Society International (OARSI) for the management of hip and knee osteoarthritis,[2] acetaminophen is recommended as the first-line treatment for pain relief,[3] however, it shows low efficacy in some patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used because they are reported to be more effective for achieving pain relief than is acetaminophen.

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However, the Drug Utilization Review (DUR) in Korea forbids administration of more than two concomitant NSAIDs because of the occurrence of side effects such as hemorrhages, heartburn, nausea, and upper gastrointestinal ulcer bleeding.

Aceclofenac is an NSAID that blocks the production of prostaglandins by inhibiting cyclooxygenase (COX).[4,5] It is the most frequently prescribed drug for the treatment of OA in Korea. In a randomized, double-blind trial, the clinical efficacy of aceclofenac for knee OA was similar to that of diclofenac and piroxicam.[6] Furthermore, the risk of gastrointestinal side effects was lower in the aceclofenac group than in the diclofenac group in preclinical trials[6] and in a multicenter, randomized, double-blind study of OA patients.[7]

JOINS is an herbal anti-arthritis agent extracted from *Clematis mandshurica*, *Trichosanthes kirilowii*, and *Prunella vulgaris*. It was developed by SK Chemical Co. Ltd. and its use was approved by the Korean Ministry of Food and Drug Safety in 2001. JOINS is indicated for the relief of pain in OA and rheumatoid arthritis. In a randomized, double-blind trial of JOINS in patients with knee OA, the efficacy of JOINS for pain relief was proven non-inferior compared to that of diclofenac. It was also demonstrated that the incidence of drug-related adverse events (AEs) was significantly lower than that observed for diclofenac.[8] In a cartilage explant culture study, JOINS inhibited proteoglycan (PG) degradation and significantly protected the knee joint of rabbits to an extent similar to that shown in the collagenase-induced OA model (control group).[9] Furthermore, in animal studies, JOINS significantly protected against the damage due to diclofenac-induced gastric ulcerations.[10]

Unlike NSAIDs, JOINS has different mechanisms of action for protecting the knee joint that relieve symptoms of OA and show gastrointestinal AEs, which are common in patients using NSAIDs. Thus, co-administration of JOINS with NSAIDs is expected to be a more effective OA treatment. According to the UBIST data (2012), in 77.6% of the cases of JOINS co-prescribed with NSAIDs, no remarkable side effects were observed. Thus, the anti-arthritis efficacy and protection against NSAID-induced side effects of JOINS co-administered with NSAIDs have already been demonstrated by the actual prescribing practice according to the data of the Korean Health Insurance Review and Assessment service. A fixed-dose combination of JOINS 300 mg and aceclofenac 100 mg may benefit the medical practice as it may improve compliance. However, before conducting clinical trials to assess the efficacy of this fixed-dose combination treatment, a study of the potential drug-drug interactions between both drugs is needed. Therefore, the objective of this study was to investigate the effect of JOINS on the pharmacokinetic (PK) profiles of aceclofenac in healthy male adults.

Method

This study was conducted at the Clinical Trials Center (CTC) of Yonsei University Severance Hospital (Seoul, Korea), and the protocol was approved by the Institutional Review Board (IRB) at Severance Hospital. It was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice standards. Written informed consents were obtained from all subjects before study enrollment.

The investigational drugs were JOINS 300 mg (SK Chemical Co. Ltd., Seongnam, Korea) and aceclofenac 100 mg (Daewoong Pharmaceuticals Co. Ltd., Seoul, Korea). To assess potential PK drug interactions, it was recommended that the subjects receive the following approved maximum dose of both drugs: 200 mg per day (100 mg twice daily) of aceclofenac and 600 mg per day (200 mg thrice daily) of JOINS. In anticipation of developing a fixed-dose combination of aceclofenac and JOINS in a future study, the study was designed such that the subjects received JOINS 300 mg twice daily instead of the approved regimen of JOINS 200 mg thrice daily.

Study Population

Healthy male volunteers aged 20 to 50 years with a body mass index between 18.5 and 25 kg/m² were recruited for this study, and were screened according to the following inclusion criteria: volunteers in clinically good health conditions according to standard laboratory tests (hematology, blood chemistry, immune-serum levels, and urinary) and 12-lead electrocardiogram (ECG). Volunteers who experienced hypersensitivity reactions or allergy to the study drugs (NSAID class drugs including aceclofenac, JOINS, or their additives), or had any other disease or medical history of abnormality were excluded from the study.

Study Design

This study was an open-label, multiple-dose, one-sequence, two-period study. All subjects received aceclofenac 100 mg alone twice daily for 3 days (Days 1 to 3), followed by aceclofenac 100 mg and JOINS 300 mg in combination twice daily for 8 days (Days 4 to 11) (Fig. 1)

All subjects visited the Clinical Trials Center of the Severance Hospital twice (8 a.m. and 8 p.m.) on Day 1 and on 8 a.m. on Day 2, and received aceclofenac 100 mg with 240 mL water. The subjects started taking each meal at least 30 min before administration of the study drugs and finished eating within 20 min.

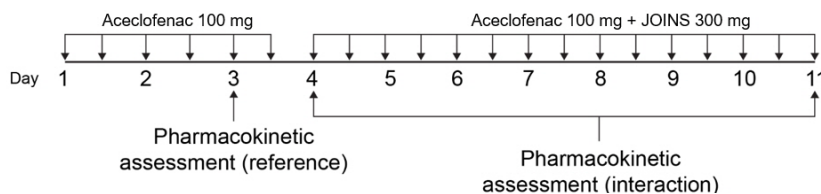


Figure 1. Study design.

The subjects were hospitalized by 6 p.m. on Day 2 and were required to abstain from strenuous exercise, having a snack, smoking, and consuming alcohol- and xanthine-containing drinks during the entire study days. All eligible subjects received aceclofenac 100 mg twice daily (8 a.m. and 8 p.m.) on Day 2 and Day 3.

Subjects received aceclofenac 100 mg plus JOINS 300 mg with 240 mL water at 8 a.m. and 8 p.m. on Day 4 under fasting conditions. Afterward, the subjects were discharged; they revisited the hospital on Day 5 to 10 to receive aceclofenac 100 mg with JOINS 300 mg twice daily (8 a.m. and 8 p.m.). By 6 p.m. on Day 10, the subjects were re-hospitalized and followed the same pre-determined time schedule as that during the first hospitalization.

The subjects who completed all study schedules returned for a follow-up visit within 7 days (± 2 days).

Sample Size Calculation

The intra-subject coefficients of variation (CV_w) for the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve up to the last measurable concentration (AUC_{last}) of aceclofenac 100 mg were assumed to be 24.85% and 10.26%, respectively, based on the results of a previous study.[11] Using the greatest CV_w , 24.85% and its point estimate, 1.085, at a 0.05 significance level with 90% power, the required sample size was calculated to be 54 subjects. The total sample size was estimated to be 64 subjects, assuming a drop-out rate of 15%.

Sample Collection and Bioanalytical Methods

The time to C_{max} (t_{max}) and half-life ($t_{1/2}$) of aceclofenac were 0.66–1.7 h and 1.4–5.4 h, respectively, according to the results of previous PK studies.[11–13] Blood samples were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, and 12 h after administration (12 times per day) on the basis of the t_{max} , $t_{1/2}$ and administration interval (12 h). Blood samples were collected on Day 3 when the steady state of aceclofenac was achieved, and on Day 4 and Day 11 when aceclofenac and JOINS were co-administered. Additionally, blood samples were collected at 8 a.m. on Day 5, 7 and 9 before drug administration to assess the C_{trough} of each day. A total of 39 samples were collected per subject. A washout period was not included in this study.

Plasma samples for the determination of the aceclofenac concentrations were analyzed by Biocore Co. Ltd., Seoul, South Korea. A validated LC-MS/MS plasma assay with a lower limit of quantification of 0.3 $\mu\text{g/mL}$ for aceclofenac was used. This method had adequate linearity ($r > 0.9950$) within the concentration ranges of 0.3 to 100 $\mu\text{g/mL}$. The inter-assay variability was determined with a coefficient of variation of 3 different control samples containing nominal concentrations of 0.9, 5.0, and 80 $\mu\text{g/mL}$ aceclofenac.

Pharmacokinetics Analysis

PK analysis was performed using the Per Protocol Set in which the subjects completed all study schedules. The primary endpoints were the AUC within a dosing interval (τ) at steady state ($AUC_{\tau,ss}$) and the C_{max} at steady state ($C_{max,ss}$) of aceclofenac. The secondary endpoints were the AUC extrapolated to infinity at steady state ($AUC_{inf,ss}$), the time to reach $C_{max,ss}$ ($t_{max,ss}$), $t_{1/2}$, the minimum plasma concentration at steady state ($C_{min,ss}$), the average plasma concentration at steady state ($C_{avg,ss}$), and fluctuation [$(C_{max,ss} - C_{min,ss})/C_{avg,ss}$] of aceclofenac.

Safety Analysis

Safety analysis was performed for the safety set of subjects who received at least one dose of the study drug. All AEs were reported. The safety profile evaluations were based on vital signs, physical examinations, 12-lead ECGs, and clinical laboratory tests.

Statistical Analysis

The PK parameters were evaluated by a non-compartment method using the Phoenix® WinNonlin® software version 6.3 (Pharsight, Mountain View, CA, USA). The $AUC_{\tau,ss}$ and $C_{max,ss}$ were transformed to a natural log scale. Using the log-transformed data, a mixed effect model with subjects (nested in sequence) as a random effect was developed to compare the PK values between the treatment conditions. The GMRs of aceclofenac combined with JOINS to aceclofenac alone were calculated to determine whether its 90% CIs were entirely contained within the range of 0.8–1.25. Safety profile analyses were evaluated using descriptive statistics. At the discretion of the investigator, inferential tests (such as repeated ANOVA and McNemar's test) were performed on measurements considered clinically significant, if necessary.

Results

Study Subjects

A total of 90 healthy volunteers were enrolled for screening and 64 volunteers participated in the study on the basis of the inclusion and exclusion criteria. Sixty-one subjects (95.3%) completed the study schedule and 3 subjects (4.7%) dropped out because of consent withdrawal (2 subjects) and loss to follow-up (1 subject). All subjects were male. The mean (standard deviation, SD) age, weight, height, and BMI are shown in Table 1.

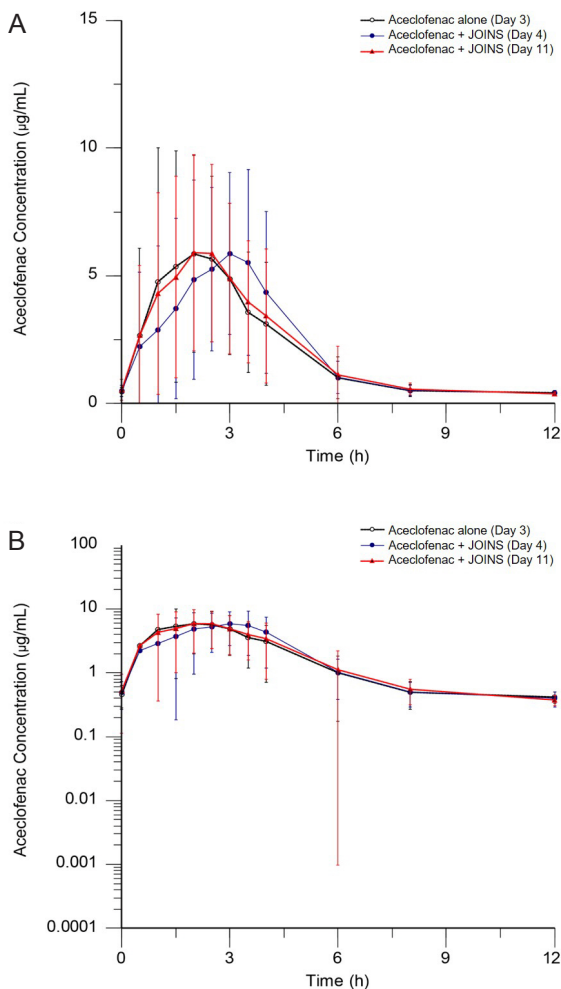
Pharmacokinetics

The mean plasma concentration-time profiles of aceclofenac with or without JOINS are shown in Figure 2. The PK parameters are summarized in Table 2. The $AUC_{\tau,ss}$ and $C_{max,ss}$ of aceclofenac administered alone were not significantly different from that of aceclofenac co-administered with JOINS. The other PK values, i.e., $C_{min,ss}$ and $C_{avg,ss}$, were also similar between

Table 1. Characteristics of the study participants*

Characteristics		Total (N = 64)
Age (years)	Mean (SD)	27.8 (5.0)
	Min	20.0
	Max	45.0
Weight (kg)	Mean (SD)	70.2 (7.3)
	Min	55.5
	Max	90.2
Height (cm)	Mean (SD)	176.1 (6.0)
	Min	161.9
	Max	191.5
BMI (kg/m ²)	Mean (SD)	22.6 (1.6)
	Min	19.2
	Max	24.9

*All subjects were male.

**Figure 2.** Mean (SD) plasma concentration-time profiles of aceclofenac with or without JOINS (upper graph: linear, lower graph: log-linear). Treatment: aceclofenac 100 mg alone (Day 3), aceclofenac 100 mg with JOINS 300 mg (Day 4 and Day 11), $\tau = 12$ h.

the two treatment conditions. The t_{max} at Day 4 was slightly different from that at Day 3 or 11. However, the non-parametric test revealed no significant difference in the t_{max} of aceclofenac between the two treatment conditions.

The GMRs of aceclofenac co-administered with JOINS to aceclofenac alone are shown in Table 2. The GMRs of the $AUC_{\tau,ss}$ of aceclofenac with to without JOINS (D4/D3 and D11/D3) were 0.9858 and 1.0015, respectively. The GMRs of $C_{max,ss}$ of aceclofenac with JOINS to without JOINS (D4/D3 and D11/D3) were 0.9166 and 0.9093, respectively. The predose plasma concentrations ($\mu\text{g/mL}$) of aceclofenac on Day 5, Day 7, and Day 9 were 0.096, 0.211 and 0.124, respectively.

Safety and Tolerability

During the study days, 31 AEs were reported in 26 subjects: 6 subjects (7 cases) who received aceclofenac alone and 22 subjects (24 cases) who received aceclofenac combined with JOINS. AEs were significantly less frequent in the aceclofenac alone group than in the aceclofenac-JOINS co-administration group ($p = 0.001$, McNemar's test). One subject suffered from a serious AE (SAE) caused by a traffic accident (TA), which was not related to the study drug. Drug-related AEs (dyspepsia, aphthous stomatitis, and abdominal discomfort) occurred in 4 subjects (4 cases) who received aceclofenac alone and in 9 subjects (9 cases) who received aceclofenac combined with JOINS. There was no statistically significant difference in drug-related AE profiles between aceclofenac administered alone and aceclofenac co-administered with JOINS ($p = 0.132$, McNemar's test), and no occurrence of any significant changes in vital signs, physical examination results, 12-lead ECGs, and clinical lab tests.

Discussion

To develop a fixed-dose combination of aceclofenac and JOINS, a drug-drug interaction study is needed. Therefore, here, we explored potential PK interactions between aceclofenac 100 mg and JOINS 300 mg affecting the PK properties in healthy male volunteers. Because JOINS is a special natural herbal product consisting of various natural ingredients, the mechanism of action underlying its specific effects is unknown. Further, the specific drug ingredients and their metabolites have not been explored before. These reasons preclude assessment of the PK profiles of JOINS. However, to assess the PK effects of JOINS on aceclofenac, the present study was designed as an open-label, multiple-dose, one-sequence, two-period study.

The full PK blood sampling was performed on Day 3, 4 and 11. To evaluate the PK properties of aceclofenac administered alone at steady state, blood samples were collected 48 hours after the first dosing (Day 3), which was five times the maximum $t_{1/2}$ of aceclofenac (5.4 h). Since the $t_{1/2}$ of aceclofenac 100 mg in the present study (1.9–2.1 h) was lower than that reported by other studies,[11–13] it was postulated that the steady state concentration would be achieved by Day 3. To our knowledge, thus far, the PK of JOINS has not been reported. To assign enough time

Table 2. Comparison of the pharmacokinetics of aceclofenac with and without JOINS

Parameter	Arithmetic mean \pm SD			Geometric mean ratio (90% CI) ^a	
	Day 3	Day 4	Day 11	Day 4/Day 3	Day 11/Day 3
$t_{max,ss}$ (h)*	2.00 (0.50, 6.00)	3.00 (0.50, 6.00)	2.00 (0.50, 6.00)	-	-
AUC _{0-12h,ss} (h· μ g/mL)	22.25 \pm 4.55	22.01 \pm 4.91	22.34 \pm 4.95	0.9858 (0.9593–1.0130)	1.0015 (0.9745–1.0291)
$C_{max,ss}$ (μ g/mL)	10.98 \pm 3.00	10.01 \pm 2.48	9.90 \pm 2.42	0.9166 (0.8578–0.9795)	0.9093 (0.8510–0.9717)
$C_{min,ss}$ (μ g/mL)	0.18 \pm 0.20	0.13 \pm 0.19	0.18 \pm 0.20	-	-
$C_{avg,ss}$ (μ g/mL)	1.91 \pm 0.37	1.89 \pm 0.40	1.92 \pm 0.40	-	-

Treatment: aceclofenac 100 mg only (Day 3), aceclofenac 100 mg with JOINS 300 mg (Day 4 and Day 11), \square = 12 h. *The data are presented as the median [min, max]. SD, standard deviation; CI, confidence interval; t_{max} , time to C_{max} ; AUC_{0-12h}, the area under the concentration-time curve during the dosing interval; AUC_{inf}, AUC from dosing time extrapolated to infinity; C_{max} , the maximum concentration of drug; C_{min} , the minimal drug concentration; C_{avg} , the average drug concentration during the dosing interval, ^aAssessment of the mean difference of 'Day 4 minus Day 3' and 'Day 11 minus Day 3' based on log-transformed data (WinNonlin[®])

to investigate the induction of drug metabolism, a 7-day period of co-administering aceclofenac with JOINS was chosen, and blood samples were collected 7 days after the first dosing (Day 11). Since aceclofenac and JOINS are to be used as a long-term therapy in OA patients, evaluating the PK profiles of both drugs at steady state with multiple dosing schedules is appropriate.

The aceclofenac PK parameters found in this study were comparable to those obtained in previous studies.[11,12] The present study also showed that the AUC_{0-12h,ss} and $C_{max,ss}$ of aceclofenac at steady state were comparable to those of aceclofenac co-administered with JOINS. The 90% CI GMRs of the AUC_{0-12h,ss} and $C_{max,ss}$ of aceclofenac were within the range of 0.8–1.25. These results indicated that the PK of aceclofenac was not changed by JOINS.

The multiple dosing schedule of aceclofenac with or without JOINS was well tolerated in this study population. The frequency of AEs was significantly higher in the aceclofenac-JOINS co-administration group than that in the aceclofenac alone group. However, all AEs were mild in severity (except in 1 case), and there were no significant differences in the severity of AEs between the two groups. Further, there was no statistically significant difference in adverse drug reactions between the two groups.

Overall, the present study indicates that the co-administration of JOINS with aceclofenac does not affect the systemic exposure to aceclofenac. Moreover, JOINS does not inhibit the metabolism of aceclofenac by cytochrome P450 2C9. Therefore, we conclude that the co-administration of aceclofenac with JOINS does not influence the PK and safety profiles of aceclofenac.

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Conflict of interest

The authors have no conflict of interest to disclose.

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