

Comparison of pharmacokinetics and safety of fixed-dose combination of SKI306X and aceclofenac versus separate tablets in healthy subjects

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Received 11 Nov 2017

Revised 11 Dec 2017

Accepted 11 Dec 2017

Keywords

JOINS,
aceclofenac,
fixed-dose combination

pISSN: 2289-0882

eISSN: 2383-5427

JOINS (SKI306X) is an herbal anti-arthritic medicine that is widely used with aceclofenac for treating osteoarthritis in Korea. A fixed-dose combination (FDC) tablet containing SKI306X and aceclofenac was developed to improve patient compliance. This study aimed to compare the pharmacokinetics (PK) and safety of the FDC tablet with those of co-administered SKI306X and aceclofenac in healthy subjects. In this randomized, open-label, two-way crossover, single-dose study, the FDC tablet (SKI306X 300 mg/aceclofenac 100 mg) (test) was given or co-administration of 300 mg of SKI306X and 100 mg of aceclofenac (reference) was performed followed by a 7-day wash-out period. Blood samples were collected before and after drug administration to evaluate aceclofenac PK parameters, and safety was assessed throughout the study. A total of 54 healthy male subjects were enrolled in and completed the study. T_{max} and $t_{1/2}$ of aceclofenac of the FDC tablet were similar to those of aceclofenac co-administered with SKI306X (T_{max} : test 2.96 h and reference 2.14 h; $t_{1/2}$: test 3.46 h and reference 4.04 h). The geometric mean ratios (90% confidence intervals) of C_{max} and AUC_{last} (T/R) were 0.85 (0.81 to 0.91) and 1.03 (1.01 to 1.06) respectively; these results were within the predefined range (0.8 to 1.25). There was only one drug-related adverse event (dizziness) occurred after administration of the FDC tablet; however, it was mild in severity and resolved without any complications. The FDC tablet was well tolerated and exhibited an absorption rate and extent comparable to those of SKI306X and aceclofenac administered simultaneously.

Introduction

Osteoarthritis (OA) is a degenerative joint disease that is characterized by a slow loss of cartilage, resulting in erosions to the subchondral bone.[1] OA is prevalent among the elderly worldwide

and risk factors for OA include older age and obesity.[2] In Korean people aged 50 years or older, the prevalence of radiographic OA was 33.3% and 12.4% had symptoms.[2] Current treatments for OA usually focus on alleviation of pain using acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and herbal anti-arthritic medicines. Although NSAIDs are most widely used as first-line treatment for pain control,[3] NSAID mono-therapy is generally insufficient to control the pain. Therefore, most patients take two or more drugs, including NSAIDs.[4] However, it is difficult to take several drugs properly, especially in the elderly, and efficacy may be lower than desired. The development of fixed-dose combination (FDC) tablets is needed to im-

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Reviewer

This article was reviewed by peer experts who are not TCP editors.

prove compliance in patients with OA.

Aceclofenac, a cyclooxygenase (COX) inhibitor, is the most frequently prescribed NSAID for OA treatment in Korea.[5] JOINS (SKI306X, SK Chemicals Co., Seongnam, Korea) is a mixture of extracts from *Clematis mandshurica*, *Trichosanthes kirilowii*, and *Prunella vulgaris* at a 1:2:1 weight ratio that has demonstrated efficacy for pain control in OA.[1] SKI306X has been widely used in combination with aceclofenac in Korea for pain control in OA.[6] Even though the active moiety of SKI306X and its metabolites has not been established and its pharmacokinetic (PK) characteristics are unknown,[7] SKI306X has demonstrated efficacy in pain control and protective effects in articular cartilage through its anti-inflammatory and immunomodulatory actions without notable side effects.[1,7-9] In addition, SKI306X did not influence the PK and safety of aceclofenac when it was concomitantly administered.[7] Based on these facts, an FDC tablet containing aceclofenac and SKI306X was developed. The aim of the study was to evaluate the PK of aceclofenac and the safety of the FDC tablet compared to those of the co-administration of aceclofenac and SKI306X in healthy adults.

Methods

Ethics

This study was conducted at Clinical Trials Center of Severance Hospital, Yonsei University College of Medicine (Seoul, Republic of Korea). The protocol was approved by the Institutional Review Board (IRB number: 4-2013-0892) prior to the start of the study, and the study was performed according to the Declaration of Helsinki and Korean Good Clinical Practice Guidelines. All participants provided written and signed informed consents.

Subjects

The healthy Korean subjects that participated in this study ranged in age from 19 to 50 years, weighed at least 55 kg, and had a body mass index (BMI) between 18.5 and 25.0 kg/m². Subjects were screened using questionnaires, physical examinations, laboratory tests, 12-lead electrocardiography (ECG), and a medical history review to make sure they were healthy. Volunteers who were hypersensitive to the components of the investigational product or the same class of medicines (*Clematis mandshurica*, *Trichosanthes kirilowii*, *Prunella vulgaris*, aceclofenac, diclofenac), or had a medical history of asthma, urticaria, or allergic reaction to aspirin or other NSAIDs (including COX-2 inhibitors) were excluded from this study. Apart from the scheduled treatments with the investigational products, study participants were not allowed to take any medications or herbal products during the study.

Sample Size

Because there was no PK data of SKI306X, only the PK data of

aceclofenac was taken into account for sample size calculation. From the result of previously reported bioequivalence study[10] of aceclofenac 100 mg tablets conducted on Korean adults, the within-subject coefficient of variation (CV_w) of maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve up to the last measurable concentration (AUC_{last}) was 24.85 % and 10.26%, respectively. Use the biggest CV_w (24.85%) and its point estimation of 1.085, at significance level of 0.05 and a power of 80%, the required sample size was obtained as 40. Considering the dropout rate of 25%, the number of subjects of this study was targeted at 54.

Study Design

This was a randomized, open-label, two-way crossover, single-dose study. A total of 54 subjects were randomized into one of two sequence groups. Participants in the sequence 'T-R' group received the FDC tablet that contained 300 mg of SKI306X and 100 mg of aceclofenac once (treatment T) in period 1, then co-administration of 300 mg of SKI306X and 100 mg of aceclofenac (Airtal tablet, Daewoong Pharmaceutical Co., Ltd., Seongnam, Korea) in separate tablets once (treatment R) in period 2. Participants in the sequence 'R-T' group received treatment R in period 1, then treatment T in period 2. Each treatment period was separated by a 7-day washout period. All participants were administered treatments T or R with 120 mL water under fasting conditions. For PK evaluation, peripheral venous blood samples were collected prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, and 12 hours after study drug administration on Day 1 in each period. All plasma samples were stored at or below -70°C until analysis.

Plasma Aceclofenac Assay

Because SKI306X is a natural herbal product consisting of various ingredients, its major active component is still unclear and infeasible for assay. Therefore, only aceclofenac has been performed PK analysis. The concentration of aceclofenac in plasma was analyzed using a validated liquid chromatography (LC) assay (Shiseido Nanospace SI-2, Shiseido, Japan) together with tandem mass spectrometry (MS/MS; API 4000, AB SCIEX, USA). Plasma samples were thawed from -70°C to room temperature and vortexed for at least 10 seconds. Thereafter, 200 µL of the vortexed plasma samples was added to 10 µL of flufenamic acid as the internal standard solution (1 µg/mL in 50% methanol) and 600 µL of acetonitrile. After centrifugation, 100 µL of supernatant was diluted with 400 µL of 50% acetonitrile, then 2 µL of the supernatant from the resultant solution was injected directly into the LC/MS/MS. The mobile phase was used at a flow rate of 0.2 mL/min and the lower limit of quantification (LLOQ) was 50 ng/mL. The calibration curve was linear over the concentration range of 50–30,000 ng/mL (correlation coefficient [r²] = 0.999). The precision of the assay was less than 15% (less than 20% for concentration of LLOQ) and the accuracy was within the range of 80–120%.

Pharmacokinetics Analysis

All PK parameters were assessed with the non-compartmental method using Phoenix WinNonlin®, version 6.3 (Pharsight, Sunnyvale, CA, USA). The C_{max} and the time to reach the C_{max} (T_{max}) were obtained from real time observed data, and the AUC_{last} that was obtained using the linear trapezoidal rule. The terminal elimination rate constant (λ_z) was estimated using log-linear regression analysis. The elimination half-life ($t_{1/2}$) and apparent plasma clearance (CL/F) were calculated from the equations $t_{1/2} = \ln(2) / \lambda_z$ and $CL/F = \text{dose} / AUC_{in\beta}$ respectively. The primary parameters were the AUC_{last} and the C_{max} of aceclofenac; the secondary parameters were the $AUC_{in\beta}$, the t_{max} and the half-life ($t_{1/2}$) of aceclofenac.

Safety Assessment

Adverse events (AEs) were assessed throughout the study by monitoring vital signs (systolic and diastolic blood pressure, pulse rate, body temperature), physical examination, laboratory tests, 12-lead ECG, and self-reporting. Any undesirable sign, symptom, or medical condition that occurred after the administration of the study drug was recorded, regardless of its suspected relationship to the study medication. AEs were analyzed descriptively.

Statistical Analysis

Statistical analysis for PK parameters was carried out using the per protocol set as PK analysis set in which the subjects had no significant protocol violation and completed this study. Subjects who received at least one dose of the investigational products in this study were considered as the safety set for safety statistical analysis.

All PK parameters were analyzed descriptively, and were expressed as the mean \pm standard deviation (SD). The primary PK parameters (C_{max} and AUC_{last}) were converted to the natural logarithm scale and evaluated by analysis of variance using a mixed-effects model. To compare the PK parameters, the point estimates (with 90% confidence intervals) of the geometric mean ratios (treatment T/treatment R) were also estimated for the log-scaled C_{max} and AUC_{last} . If the 90% confidence intervals of the geometric mean ratios were within 80-125%, the two investigational products were considered bioequivalent. [11] Analysis for demographic data and PK parameters was performed using the SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, NC, USA) and Phoenix Win-

Nonlin®, version 6.3, respectively. Statistical significance was defined as $p < 0.05$.

Results

Study Participants

A total of 54 subjects were enrolled and 27 were randomly assigned to each treatment sequence group (Fig.1). All subjects completed the study. There were no statistical differences in age, body weight, or BMI among the sequence groups ($p \geq 0.05$, Table 1).

Pharmacokinetics Parameters

The mean plasma concentrations of aceclofenac over time after treatment with the FDC tablet (T) and co-administration

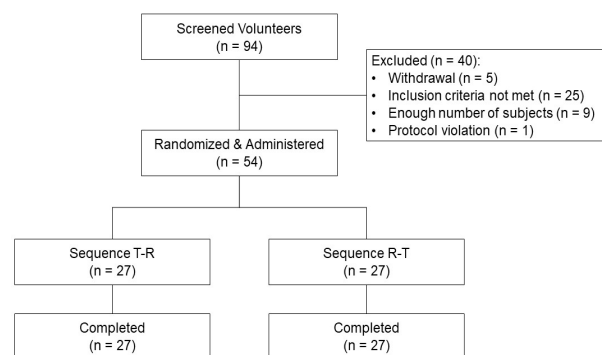


Figure 1. Subject disposition. Abbreviations: Sequence T–R, a fixed-dose combination tablet of SKI306X 300 mg /aceclofenac 100 mg once (treatment T) was administered first in period 1, then co-administration of 300 mg of SKI306X and 100 mg of aceclofenac as individual tablets once (treatment R) in period 2; Sequence R–T, treatment R first in period 1, then treatment T in period 2.

Table 1. Demographics and baseline characteristics of the study population

Variables	Sequence		Total (n = 54)	p-value
	T–R (n = 27)	R–T (n = 27)		
Age (years)	27.1 \pm 3.7 (21.0–35.0)	26.8 \pm 5.7 (20.0–45.0)	26.9 \pm 4.7 (20.0–45.0)	0.32
Body weight (kg)	69.1 \pm 7.5 (59.5–92.3)	66.4 \pm 5.8 (57.0–80.6)	67.8 \pm 6.8 (57.0–92.3)	0.19
Body mass index (kg/m ²)	22.7 \pm 1.6 (20.1–24.9)	22.1 \pm 1.6 (19.2–24.8)	22.4 \pm 1.6 (19.2–24.9)	0.28

Notes: The data are expressed as the mean \pm SD (min–max). Abbreviations: Sequence T–R, a fixed-dose combination tablet of SKI306X 300 mg /aceclofenac 100 mg once (treatment T) was administered first in period 1, then co-administration of 300 mg of SKI306X and 100 mg of aceclofenac as individual tablets once (treatment R) in period 2; Sequence R–T, treatment R first in period 1, then treatment T in period 2. The p-values between the two groups in each part were calculated using the Wilcoxon rank sum test. There were no statistically significant differences in age, body weight, and body mass index.

(R) were displayed in Figure 2. All calculated PK parameters of aceclofenac are listed in Table 2. The PK parameters of the FDC tablet were similar to those of the aceclofenac–SKI306X combination therapy. The point estimate (with 90% CI) of the geometric mean ratios (T/R) of the C_{max} and AUC_{last} were 0.85 (0.81 to 0.91) and 1.03 (1.01 to 1.06), respectively.

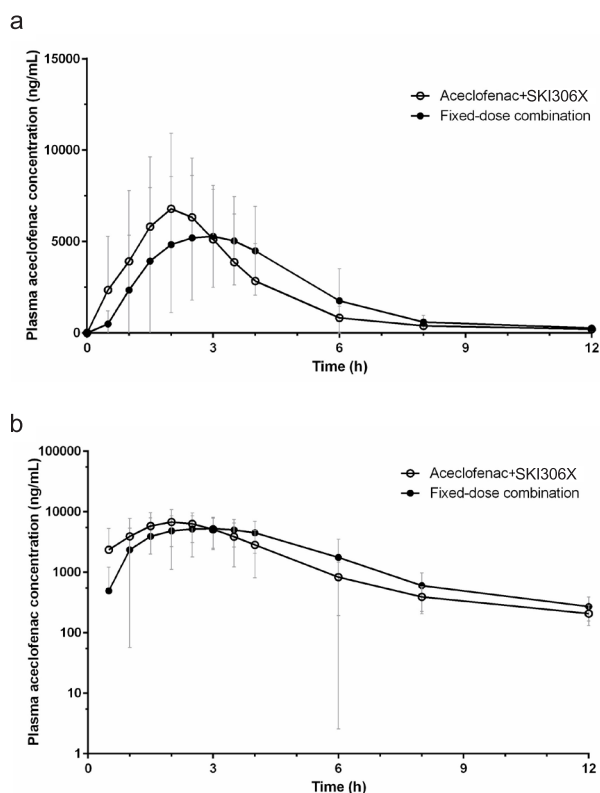


Figure 2. Mean (SD) plasma concentration-time profiles of aceclofenac (a: linear scale, b: semi-logarithmic scale).

Table 2. Pharmacokinetic parameters of aceclofenac after the administration of a fixed-dose combination tablet that included 300 mg of SKI306X and 100 mg of aceclofenac once (treatment T) and co-administration of a SKI306X 300 mg and an aceclofenac 100 mg once (treatment R) in healthy volunteers

PK parameters	T (n = 54)	R (n = 54)	Geometric Mean Ratio (T/R)	
			Point estimate	90% confidence interval
C_{max} (ng/mL)	8640.06 ± 1970.84	10197.71 ± 2573.55	0.85	0.81–0.91
AUC_{last} (ng·h/mL)	23992.71 ± 4814.39	23207.96 ± 4632.36	1.03	1.01–1.06
AUC_{inf} (ng·h/mL)	25312.82 ± 5194.40	24401.10 ± 4975.88		
$t_{1/2}$ (h)	3.46 ± 0.64	4.04 ± 0.62		
T_{max} (h)	2.75 (1.00–6.00)	2.00 (0.50–6.00)		
CL/F (L/h)	4.11 ± 0.79	4.27 ± 0.87		

Notes: The values are presented as the mean ± SD, except for the t_{max} , which is presented as the median (range). Abbreviations: PK, pharmacokinetic; C_{max} , maximum plasma concentration of the drug; AUC_{last} , area under the plasma concentration-time curve from the dosing time to the last measurable concentration; AUC_{inf} , AUC from the dosing time extrapolated to infinity; $t_{1/2}$, elimination half-life; T_{max} , time to C_{max} ; CL/F, apparent total clearance.

Safety

There were total of three AEs reported in this study (one in the co-administration group, two in the FDC group, Table 3). No serious drug-induced AEs were reported. A drug-related AE (dizziness) was reported once in one subject after receiving the FDC tablet; however, it was mild and the participant recovered without any complications. No significant changes in vital signs, clinical laboratory results, or ECG were observed.

Discussion

OA is one of the most common causes of chronic disability in the elderly owing to the associated pain and altered joint function.[12] The main goal of OA management is to minimize pain with analgesics.[4] Among the analgesics, aceclofenac and SKI306X have been used to control pain in Korea. An FDC tablet including aceclofenac and SKI306X was developed to improve medication compliance and efficacy.[13] If PK and safety

Table 3. Summary of adverse events

System Organ Class	Treatment	
	T	R
Gastrointestinal disorders		
Diarrhea	1 (1.85)	0
Infections and infestations		
Acute tonsillitis	0	1 (1.85)
Nervous system disorders		
Dizziness*	1 (1.85)	0

Notes: The data are expressed as the number (%) of adverse events. *Dizziness is considered as drug-related AE. Abbreviations: T, treatment group administered a fixed-dose combination tablet that included 300 mg of SKI306X and 100 mg of aceclofenac once; R, treatment group administered 300 mg of SKI306X and 100 mg of aceclofenac concomitantly once.

profiles of FDC were comparable to those of co-administration, FDC can become a suitable option for treating elderly OA patients.

Aceclofenac, a widely used NSAID, had a clinical efficacy for knee OA similar to that of diclofenac and piroxicam in a randomized, double-blind trial.[14] *In vivo*, aceclofenac blocked prostaglandin E2 production via COX-1 and COX-2 inhibition after being metabolized to 4'-hydroxyaceclofenac, diclofenac, and 4'-hydroxydiclofenac in human inflammatory cells.[10,15] Aceclofenac is absorbed rapidly after oral administration and is effective within 30 minutes of ingestion.[10] The C_{max} is reached after approximately 1 to 3 hours and the $t_{1/2}$ is approximately 4 hours.[10,16]

SKI306X is used commonly in Korea for pain control in OA. [17] It has demonstrated efficacy in pain control and protective effects in articular cartilage[1,8,9] In a randomized, double-blinded study in which the efficacy and safety of SKI306X were compared with those of diclofenac in patients with OA, SKI306X demonstrated efficacy statistically comparable to that of diclofenac and was well tolerated.[18] In addition, SKI306X did not influence the PK and safety of aceclofenac in co-administration.[7]

The FDC tablet containing aceclofenac and SKI306X was developed to improve patient adherence based on the results of previous PK interaction study.[7] In this study, the PK results demonstrated that the FDC tablet was pharmacokinetically bioequivalent to the co-administration of aceclofenac and SKI306X. The 90% confidence intervals of the geometric mean ratios of C_{max} and AUC_{last} for aceclofenac were within the predetermined range of 0.80-1.25, which is generally accepted as bioequivalent.[11] In addition, the FDC tablet with aceclofenac and SKI306X was well tolerated. All AEs that occurred during the study were mild in severity and resolved without any sequelae.

Since SKI306X is a natural herbal product, it is not feasible to conduct PK analysis on SKI306X. Comparison of aceclofenac PK was the only option to show comparability between the FDC tablet and the co-administration of separate tablets in this study. Because there were technical challenges in determining major active constituents of this natural herbal product, we could not evaluate whether aceclofenac can affect the PK of SKI306X. However, although there was no PK data about SKI306X, we could have a better understanding through clinical efficacy studies with FDC tablet in OA patients in the future.

Conclusions

In conclusion, the FDC tablet of aceclofenac and SKI306X was well tolerated and exhibited an absorption rate and extent comparable to those after the co-administration of aceclofenac and SKI306X.

Acknowledgments

This study was conducted from 2013 to 2014. Because the clinical trial registry was not a mandatory condition at that

time, this study was not registered in any public site. However, this study was conducted through a thorough IRB review, and performed according to the Declaration of Helsinki and Korean Good Clinical Practice Guidelines.

This study was sponsored by SK Chemicals Co., Ltd, Seongnam, Republic of Korea and supported by a grant from the Korean Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health and Welfare, Republic of Korea (HI14C1062). We thank the staff at the Clinical Trials Center of Severance Hospital for their generous cooperation.

Conflicts of interest

-Authors: Jeong Hoon Kim is an employee of SK Chemicals Co., Ltd. The other authors have no conflicts of interest to disclose.

-Reviewers: Nothing to declare

-Editors: Nothing to declare

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