

Comparative Pharmacokinetics and Safety of Imrecoxib, a Novel Selective Cyclooxygenase-2 Inhibitor, in Elderly Healthy Subjects

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Background: Imrecoxib is a novel and moderately selective cyclooxygenase-2 inhibitor with properties of anti-inflammation and alleviating pain, which is widely applied in osteoarthritis patients. The pharmacokinetic data supporting imrecoxib's rational use in elderly population are not available.

Purpose: The study aims to investigate the pharmacokinetics of imrecoxib and its main metabolites and explore the safety of imrecoxib in elderly healthy subjects.

Methods: A total of 19 healthy subjects including 10 non-elderly and 9 elderly subjects received single dose of 100 mg imrecoxib under fasting condition. Pharmacokinetics, safety and tolerability profiles were assessed.

Results: After oral administration of single dose of 100 mg imrecoxib, it was absorbed into plasma with median time to reach peak concentration (T_{max}) around 2 hours. The concentration–time curves of imrecoxib (M0) showed higher interindividual variability in elderly subjects compared with non-elderly subjects. Peak concentration (C_{max}) of M0, its hydroxyl metabolite M1 and carboxylated metabolite M2 in plasma increased by 39%, 21% and 17%, and area under concentration–time curve from time 0 to time t (AUC_{0-t}) of M0, M1 and M2 in plasma increased by 34%, 13% and 27%, respectively, in elderly subjects compared with non-elderly subjects. The 90% CIs of geometric mean ratios of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of M0, M1 and M2 between the two groups were not located within 80–125%, indicating C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were not completely equivalent between non-elderly and elderly healthy subjects. However, comparison of pharmacokinetic data of M0, M1 and M2 between the two groups showed no significant difference ($P>0.05$). Imrecoxib was well tolerated in both non-elderly and elderly healthy subjects, especially with favorable gastrointestinal and cardiovascular safety profiles.

Conclusion: Pharmacokinetic and safety profiles of imrecoxib in elderly healthy subjects indicated that no dose adjustment should be required for elderly population.

Keywords: cyclooxygenase-2 inhibitor, imrecoxib, pharmacokinetics, safety, elderly

Introduction

Osteoarthritis (OA) is a chronic degenerative musculoskeletal disorder and is a common factor resulting in pain and disability especially in the elderly.^{1–4} Advancing age is considered to be the main risk for the development of OA^{2–4} and the prevalence of OA in worldwide has increased dramatically over the past decades.⁵ Many available evidences indicate that oral non-steroidal anti-inflammatory drugs (NSAIDs) are the preferred pharmacological approaches of OA,^{1,4} which mainly target on inhibiting cyclooxygenase (COX) to inhibit the inflammatory response and relief pain.^{6,7}

COX includes two isoenzymes COX-1 and COX-2. According to the selectivity to COX, oral NSAIDs can be divided into non-selective inhibitors of both COX-1 and COX-2 and selective inhibitors of COX-2.^{6,8,9} Non-selective COX inhibitors have properties of anti-inflammation and alleviating pain through inhibiting COX-2, but simultaneously

increase the risk of gastrointestinal reactions due to inhibiting COX-1.^{6,8,10} Selective COX-2 inhibitors can retain the physiological gastrointestinal protective effects of COX-1, thus reducing the incidence of gastrointestinal reactions.^{6,8,10} Therefore, non-selective COX inhibitors are recommended for patients without contraindications including gastrointestinal diseases, hepatic and renal insufficiency, but selective COX-2 inhibitors, such as celecoxib can be considered for patients at higher risk of gastrointestinal comorbidities in view of multiple clinical practice guidelines.^{1,4,6}

It is worth noting that excessive inhibition of COX-2 will result in the imbalance between functions of prostacyclin (PGI₂) and thromboxane A₂ (TXA₂), so long-term application of COX-2 inhibitors increases the risk of cardiovascular adverse events, which is also the main reason for withdrawal of rofecoxib worldwide in 2004.^{11,12} Therefore, ideal selective COX-2 inhibitor should not be too highly selective for COX-2, and should regulate the inhibitory activities of COX-2 and COX-1 within a certain range, maintaining the balance between functions of PGI₂ and TXA₂.¹³

Imrecoxib is an innovative and moderately selective COX-2 inhibitor with the similar pharmacological effects as celecoxib.^{14–16} Imrecoxib exhibits anti-inflammatory effect through moderate inhibition of COX-2 mRNA expression,¹⁷ and is widely used in orthopedics especially for knee OA.¹⁶ Phase II and III clinical studies have shown that imrecoxib can significantly improve the clinical symptoms of patients with knee OA, and the efficacy is similar to celecoxib.^{14,15} Imrecoxib is catalyzed to hydroxyl metabolite M1 and then oxidized to carboxyl metabolite M2 in human.^{18–20} The major metabolic process of imrecoxib is shown in Figure 1.^{18,21}

The proportion of aged population is remarkably increasing worldwide.²² Due to the deterioration of different tissues and organs caused by advancing age, it is necessary to pay attention to the changes of drug pharmacokinetics and pharmacodynamics in elderly population and avoid inappropriate drug use.^{23–27} Several former studies have investigated the pharmacokinetics of imrecoxib in healthy subjects, patients with impaired renal function and patients with hepatic impairment.^{21,28} However, no research has explored pharmacokinetics, safety and tolerability of imrecoxib in the elderly, which hinders the evidenced-based clinical application of imrecoxib in elderly patients. Therefore, the purpose of our study was to provide the evidences for rational use of imrecoxib in elderly population for the first time by comparing the pharmacokinetic characteristics of imrecoxib and its main metabolites (M1 and M2), safety and tolerability of imrecoxib in elderly and non-elderly subjects.

Subjects and Methods

Study Design

This study was a single-center, single-dose, open-label, parallel-controlled Phase I clinical trial, which planned to enroll 20 healthy Chinese subjects (10 subjects in non-elderly and elderly group, respectively). The whole flowchart of the study is shown in Figure 2.

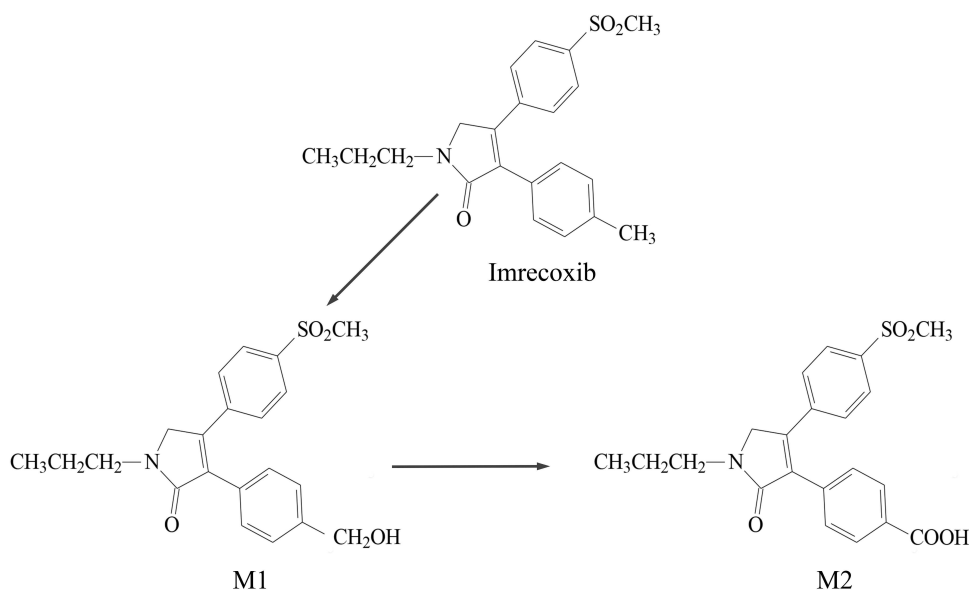


Figure 1 The major metabolic process of imrecoxib.

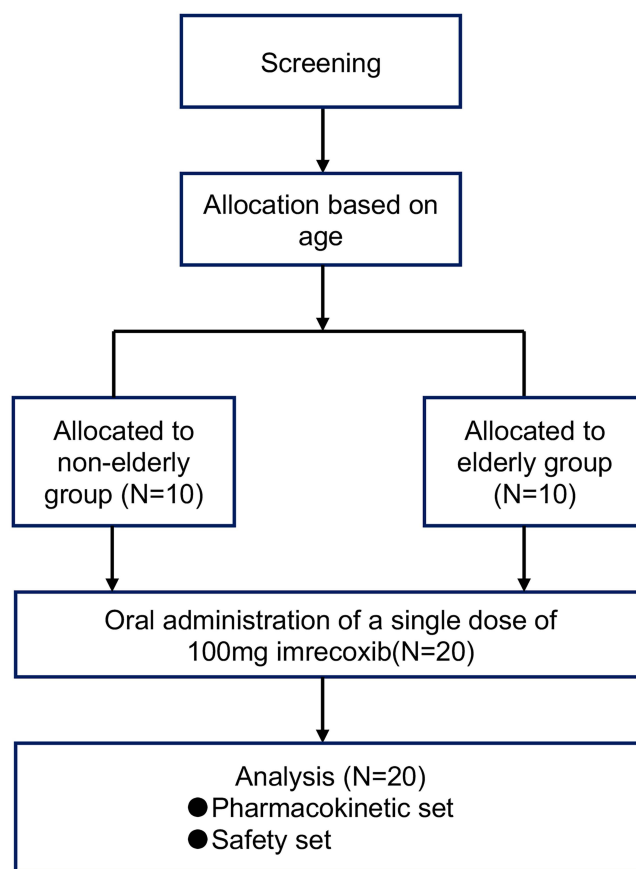


Figure 2 The flowchart of the study.

The study was performed according to the ICH-GCP guidelines and the Declaration of Helsinki. The study protocol and informed consent forms (ICFs) were approved by the Independent Ethics Committee of West China Hospital, Sichuan University (No. 2015–79). All subjects provided written ICFs before any related procedure of the study performed. Meanwhile, the study has been registered in the World Health Organization International Clinical Trials Registry Platform (ChiCTR2100051644).

Study Population

Healthy Chinese subjects (male:female 1:1) aged from 18 to 85 years with a body mass index between 19 and 28 kg/m² were eligible for recruitment. Subjects aged ≥ 18 , < 65 years were allocated to non-elderly group (Group A), while subjects aged ≥ 65 , ≤ 85 years were allocated to elderly group (Group B). Non-elderly subjects with any clinically significant abnormality in medical history, physical examination, laboratory tests (hematology, blood biochemistry, urinalysis, hepatitis B surface antigen, hepatitis C antibody, HIV antibody, syphilis antibody, tests for alcohol, smoking and drugs abuse), 12-lead electrocardiogram (ECG), chest X-ray, abdominal ultrasound were excluded. For elderly group, subjects with well-controlled chronic diseases which might not affect the observational indicators of the study were eligible.

Other main exclusion criteria included: subjects with allergic history of imrecoxib and ingredients contained in imrecoxib or history of cardiovascular, hepatic, renal, gastrointestinal, immune, hematologic, endocrine, metabolic, cancer, neuropsychiatric or any other diseases that might influence drug absorption, distribution, metabolism, or excretion; exposure to any investigational medication including placebo within 30 days.

Drug Administration and Pharmacokinetic Sampling

All eligible subjects were admitted to the Phase I clinical trial center ward of West China Hospital, Sichuan University on Day-1, and fasted for 10 hours overnight after meal. In the morning on Day 1, each subject received a single dose of

100 mg imrecoxib tablet orally with 240 mL of water under fasting condition 4 hours before dosing and water intake was not permitted 1 hour before dosing.

Blood samples (~3mL) for pharmacokinetic analysis were collected. Sampling timepoints were: within 60 minutes before dosing and 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours after dosing. All blood samples were collected in ethylene diamine tetraacetic acid (EDTA) anticoagulation tubes and centrifuged (3000 rpm/minute for 10 minutes, 4°C) within 30 minutes of collection. Separated plasma samples were pipetted into 3 tubes (350 µL/tube) and were stored at -70°C until assayed.

The researched imrecoxib tablets were manufactured by Jiangsu Hengrui Pharmaceuticals Co., Ltd. (Jiangsu, China). Unit strength: 100 mg.

Safety and Tolerability Assessment

All subjects were under medical supervision in the Phase I clinical trial center ward of West China Hospital, Sichuan University, during the drug administration and sampling phase until 72 hours after dosing.

Tolerability was evaluated by monitoring Adverse Events (AEs), physical examinations, laboratory tests (hematology, blood biochemistry, and urinalysis) and 12-lead ECG. All laboratory tests were performed at the clinical laboratory of West China Hospital, Sichuan University, which was authenticated by College of American Pathologists (CAP).

Assay of Imrecoxib and Metabolites

Concentrations of imrecoxib (M0), M1 and M2 in plasma were measured by Liquid Chromatography coupled with Tandem Mass Spectrometry (LC-MS/MS) method. LC was performed with ACQUITY I Class UPLC liquid chromatography system (Waters Corporation, Milford, MA, USA) equipped with Eclipse Plus C18 column (100×4.6 mm, 3.5µm) (Agilent Technologies Corporation, Palo Alto, CA, USA) and mass spectrometric was performed with Triple Quad 5500 mass spectrometer (Applied Biosystems Inc., Foster City, CA, USA).

Imrecoxib (M0), M1, M2 and internal standard (IS) BAP385 were supplied by Jiangsu Hengrui Pharmaceuticals Co., Ltd. (Jiangsu, China). For M1 and IS measurements, each 100 µL plasma sample was spiked with 25 µL methanol-water, 25 µL IS (3 ng/mL BAP385) and 300 µL acetonitrile, respectively. After vortexing for 1 minute and centrifugation for 5 minutes, 100 µL supernatant was added with 50 µL 5 mM ammonium acetate containing 0.1% formic acid and then 20 µL sample was loaded for LC-MS/MS analysis. The mobile phase included a mixture of methyl alcohol: 5 mM ammonium acetate containing 0.1% formic acid at 60:40 ratio (v/v). For imrecoxib (M0), M2 and IS measurements, each 100 µL plasma sample was spiked with 25 µL methanol-water, 25 µL IS (1 ng/mL BAP385) and 300 µL acetonitrile, respectively. The mix solution was vortexed for 1 minute and centrifuged for 5 minutes and then 10 µL supernatant was taken for LC-MS/MS analysis. The mobile phase included a mixture of methyl alcohol: 5 mM ammonium acetate containing 0.1% formic acid at 65:35 ratio (v/v). The flow rate and column temperature were all at 0.7 mL/min and 40°C, respectively.

The transitions for multiple reaction monitoring (MRM) mode were at m/z 370.2→278.2 (imrecoxib), 386.2→278.2 (M1 and IS) and 400.2→236.2 (M2). The MS parameters were optimized for detection: ion source gas, 50 psi; curtain gas, 30 psi; collision gas, 8 psi; declustering potential, 80 V; corona discharge current, 3 µA; source temperature, 500°C; spray voltage, 5000 V. The collision 32, 29 and 40 V were selected for imrecoxib (M0), M1 and IS, and M2, respectively. Data was analyzed through Analyst 1.6.2 quantitative software (Applied Biosystems Inc., Foster City, CA, USA).

Pharmacokinetic and Statistical Analysis

Pharmacokinetic parameters of imrecoxib (M0), M1 and M2 were calculated by Phoenix WinNonlin Version 6.4 (Pharsight Corporation, Mountain View, CA, USA) using non-compartmental method.

Pharmacokinetic parameters in the study included peak concentration (C_{max}), time to reach C_{max} (T_{max}), plasma area under concentration–time curve from time 0 to the last measurable concentration (AUC_{0-t}), plasma area under concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$), elimination half-life ($t_{1/2}$), volume of distribution/bioavailability (Vz/F) and clearance/bioavailability (CL/F).

SPSS Version 11.5 (IBM Corporation, Chicago, IL, USA) and SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) were performed for statistical analyses of the pharmacokinetic parameters and safety data, respectively. Independent-samples *t*-test (normal distribution data) or independent-samples nonparametric-tests (abnormal distribution data) were used to determine significant differences between the two groups. All statistical tests were 2-tailed and $P < 0.05$ was statistically significant for all analyses in the study. Geometric means of C_{\max} and AUC of imrecoxib (M0), M1 and M2 were calculated. C_{\max} and AUC between the two groups were considered to be equivalent if the 90% confidence intervals (CIs) of geometric mean ratios of C_{\max} and AUC were located within 80–125%.

Results

Study Population

The study initially planned to enroll 20 subjects and a total of 28 subjects were screened, among whom 19 subjects including 10 non-elderly subjects (5 male and 5 female) and 9 elderly subjects (4 male and 5 female) were enrolled into the study after being evaluated for eligibility. All enrolled subjects completed the study in accordance with protocol and were included in the pharmacokinetic and safety analysis set. Two subjects in the elderly group had hypertension medical history and used amlodipine besylate tablets and nifedipine sustained release tablets to control blood pressure, respectively. Other detailed demographics of the subjects are shown in Table 1.

Assay Validation

Typical chromatograms of imrecoxib (M0), M1, M2 and IS are shown in Figure 3. The calibration curves of imrecoxib (M0), M1 and M2 were linear over the range of 0.100–40.0 ng/mL, 0.200–80.0 ng/mL and 2.00–800 ng/mL, respectively. The intra-day relative standard deviation (RSD) values of quality control (QC) samples at different concentrations (low, medium and high levels) of imrecoxib (M0), M1 and M2 were <6.2%, <4.3% and <5.0%, respectively. The relative error (RE) values of QC samples at different concentrations (low, medium and high levels) of imrecoxib (M0), M1 and M2 were -7.1%~3.9%, -9.4%~-8.1%, and -5.4%~0.0%, respectively.

Pharmacokinetic Properties

The individual and mean plasma concentration–time curves of imrecoxib (M0), M1 and M2 in the non-elderly group and elderly group after dosing 100 mg imrecoxib are presented in Figure 4. After single oral administration, imrecoxib was absorbed into plasma with median time of 2 hours to reach peak concentration, and the interindividual concentration–time curves of imrecoxib (M0) were more variable in elderly subjects (Figure 4A and B) and the mean concentration–time curves showed that the exposures of imrecoxib (M0) were increased in elderly subjects compared with non-elderly subjects (Figure 4C). The detailed results and comparison of pharmacokinetic parameters between the two groups are shown in Table 2.

Independent-samples *t*-test was used to compare pharmacokinetic parameters between the two groups, except for T_{\max} which was analyzed through Mann–Whitney *U*-test. The T_{\max} of M2 in elderly subjects was prolonged than that of

Table 1 Demographics of Enrolled Subjects

Characteristic	Non-Elderly Group (N=10)	Elderly Group (N=9)	Total (N=19)
Age (years)	33.0±8.5	67.4±1.9	49.3±18.7
Gender (male/female)	5/5	4/5	9/10
Weight (kg)	59.25±6.61	61.67±4.24	60.39±5.60
Height (m)	1.618±0.083	1.586±0.074	1.603±0.078
BMI (kg/m ²)	22.679±2.293	24.614±2.371	23.596±2.472
Medical history (yes/no)	0/10	2/7	2/17
Concomitant treatment (yes/no)	0/10	2/7	2/17

Note: All data are shown as mean ± standard deviation (Mean ± SD), except for gender, medical history and concomitant treatment which are presented as proportions.

Abbreviation: BMI, body mass index.

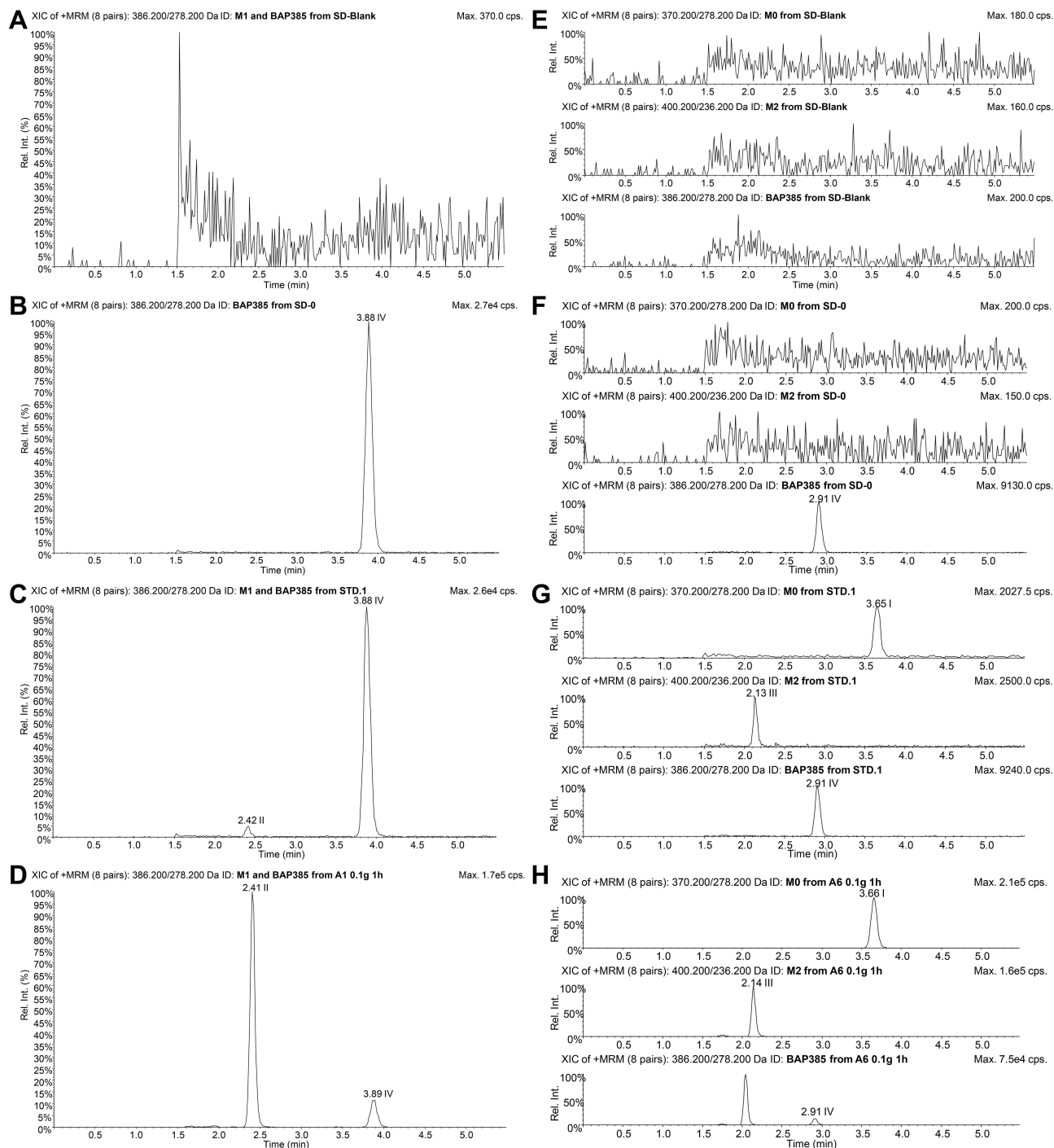


Figure 3 Typical chromatograms of imrecoxib (M0), M1, M2 and IS. (A–D) Chromatograms of M1 and IS in (A) blank plasma; (B) blank plasma containing IS; (C) blank plasma containing M1 and IS at their LLOQ values; and (D) the plasma sample collected 1h after an oral administration of 100 mg imrecoxib. (E–H) Chromatograms of M0, M2 and IS in (E) blank plasma; (F) blank plasma containing IS; (G) blank plasma containing M0, M2 and IS at their LLOQ values; and (H) the plasma sample collected 1h after an oral administration of 100 mg imrecoxib. Peaks I–IV shows imrecoxib (M0), M1, M2 and IS (BAP385), respectively.

Abbreviations: IS, internal standard; LLOQ, lower limit of quantitation.

non-elderly subjects ($P < 0.05$), while other results of pharmacokinetic parameters of imrecoxib (M0), M1 and M2 in plasma between the two groups were not significantly different ($P > 0.05$).

Subsequently, the ratio of geometric mean and its 90% CI of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of imrecoxib (M0), M1 and M2 between the two groups were calculated. As presented in Table 3, the geometric mean of C_{max} of imrecoxib (M0),

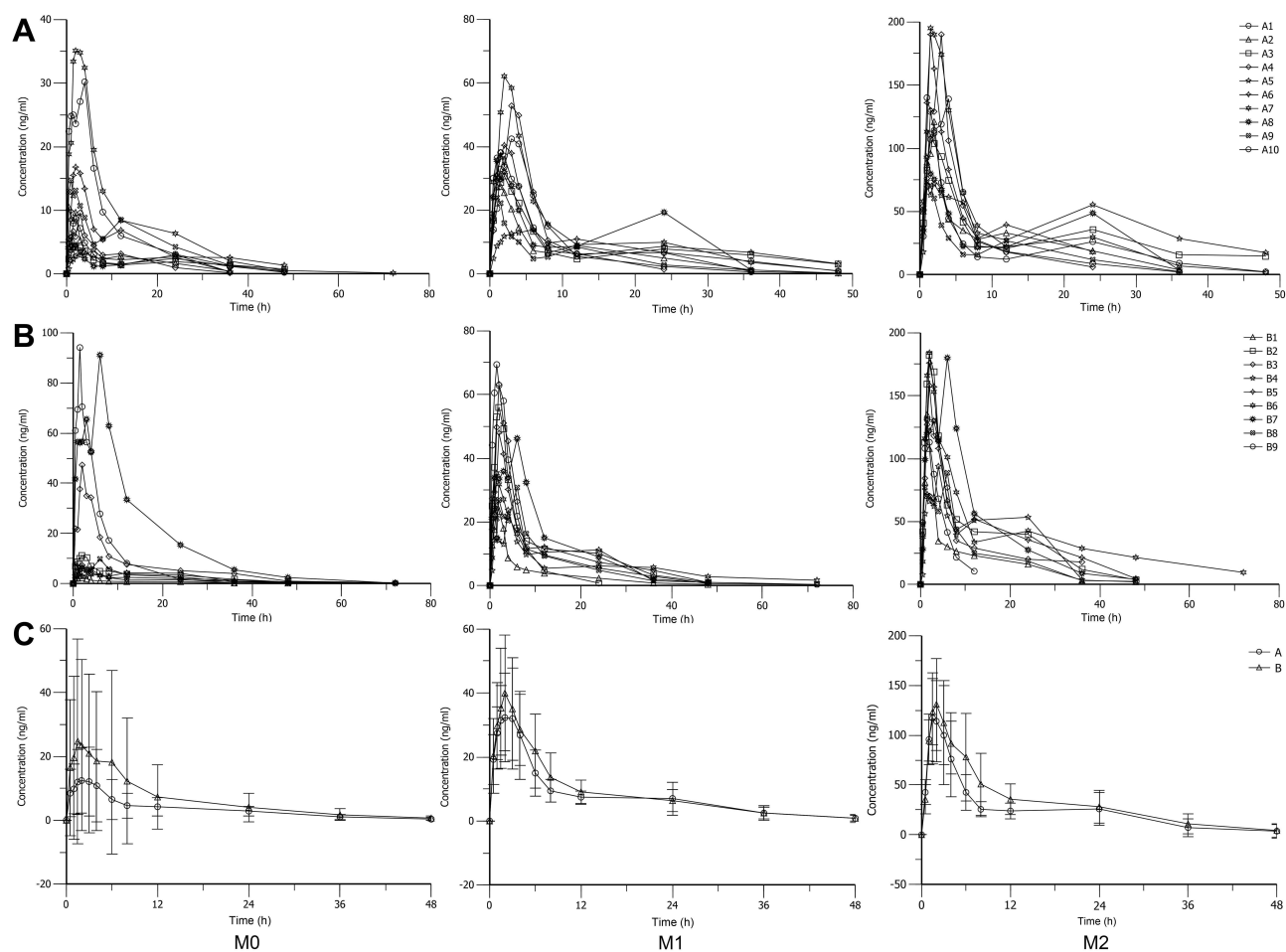


Figure 4 Individual and mean plasma concentration-time curves of imrecoxib (M0, M1 and M2. **(A)** The individual plasma concentration-time curves of M0, M1 and M2 in the non-elderly group (A1–A10). **(B)** The individual plasma concentration-time curves of M0, M1 and M2 in the elderly group (B1–B9). **(C)** The mean plasma concentration-time curves of M0, M1 and M2 in the non-elderly group **(A)** and elderly group **(B)**.

M1 and M2 in plasma increased by 39%, 21% and 17%, and the AUC_{0-t} of imrecoxib (M0), M1 and M2 in plasma increased by 34%, 13% and 27%, respectively, in elderly subjects in comparison with non-elderly subjects. The 90% CIs of geometric mean ratios of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of imrecoxib (M0), M1 and M2 in plasma between the two groups were not located within 80–125%, indicating the C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were not completely equivalent between non-elderly and elderly healthy subjects.

Safety and Tolerability

The numbers and types of adverse events (AEs) are summarized in Table 4. Overall, 2 subjects (20.0%) in non-elderly group reported a total of 4 AEs, and 2 subjects (22.2%) in elderly group reported a total of 2 AEs. The increased blood glucose was regarded as adverse drug reaction (ADR) among AEs in non-elderly group. Increased aspartate transaminase and blood bilirubin were 2 AEs happened in elderly group, which were all considered to be ADRs.

All the AEs were mild in severity and recovered without any medical intervention. No concomitant gastrointestinal, cardiovascular or renal side effects which may be occurred by inhibiting cyclooxygenase enzymes were observed.

Discussion

Based on the conception of “moderate inhibition of COX-2” which aimed to balance the functions of PGI_2 and TXA_2 , imrecoxib is developed and approved in clinical use.^{14–16,29} Our study initially explored the impacts of age on the

Table 2 Results of Plasma Pharmacokinetics of Imrecoxib (M0), M1 and M2

Analyze	Pharmacokinetic	Non-Elderly Group Mean ± SD (CV%)	Elderly Group Mean ± SD (CV%)	P value
M0	C _{max} (ng/mL)	13.9±10.8(77.2)	30.7±37.5(122.2)	0.226
	*T _{max} (h)	2.00(0.500–6.00)	2.00 (4.32–28.9)	0.427
	AUC _{0-t} (h*ng/mL)	163±110(67.5)	309±370(119.7)	0.283
	AUC _{0-∞} (h*ng/mL)	173±107(61.9)	315±368(116.9)	0.293
	t _{1/2} (h)	10.9±6.07(55.7)	13.0±7.31(56.3)	0.508
	V _z /F (L)	12,300±8780(71.4)	17,400±20,000(114.5)	0.495
	CL/F (L/h)	765±366(47.9)	789±784(99.4)	0.935
	M1	C _{max} (ng/mL)	36.6±14.0(38.1)	44.2±16.6(37.5)
*T _{max} (h)		2.00(1.00–6.00)	2.00 (1.50–6.00)	0.643
AUC _{0-t} (h*ng/mL)		370±97.1(26.2)	427±123(28.9)	0.275
AUC _{0-∞} (h*ng/mL)		393±103(26.1)	443±126(28.4)	0.355
t _{1/2} (h)		9.25±4.38(47.3)	11.5±5.77(50.4)	0.349
V _z /F (L)		3482±1445(41.5)	4064±2205(54.3)	0.501
CL/F (L/h)		273±83(30.4)	255±121(47.5)	0.696
M2		C _{max} (ng/mL)	130±47.5(36.6)	148±37.5(25.4)
	*T _{max} (h)	1.50(1.00–3.00)	2.00 (1.50–6.00)	0.042 [#]
	AUC _{0-t} (h*ng/mL)	1180±340(28.9)	1580±662(41.8)	0.130
	AUC _{0-∞} (h*ng/mL)	1300±449(34.5)	1740±734(42.2)	0.129
	t _{1/2} (h)	9.65±4.02(41.7)	12.3±8.15(66.2)	0.395
	V _z /F (L)	1094±281(25.7)	1029±496(48.2)	0.724
	CL/F (L/h)	85±29(34.1)	71±40(56.3)	0.399

Notes: All values are presented as Mean ± SD (coefficient of variation%, CV%), except *T_{max} which is median (range). [#]Difference between the two groups is considered as statistically significant when P < 0.05.

Abbreviations: C_{max}, peak concentration; T_{max}, time to reach C_{max}; AUC_{0-t}, plasma area under concentration–time curve from time 0 to the last measurable concentration; AUC_{0-∞}, plasma area under concentration–time curve from time 0 to infinity; t_{1/2}, elimination half-life; V_z/F, volume of distribution/bioavailability; CL/F, clearance/bioavailability; SD, standard deviation.

Table 3 Geometric Mean Ratio and Its 90% CI of Main Pharmacokinetic Parameters of Imrecoxib (M0), M1 and M2

Analyze	Pharmacokinetic	Geometric Mean		Geometric Mean Ratio (%)	
		Group A (N=10)	Group B (N=9)	B/A	90% CI
M0	C _{max} (ng/mL)	10.8	15.0	139	(60.9, 317)
	AUC _{0-t} (h*ng/mL)	137	183	134	(67.4, 265)
	AUC _{0-∞} (h*ng/m)	148	193	130	(67.5, 250)
M1	C _{max} (ng/mL)	34.0	41.3	121	(87.5, 169)
	AUC _{0-t} (h*ng/mL)	358	406	113	(87.9, 146)
	AUC _{0-∞} (h*ng/m)	380	421	111	(85.8, 144)
M2	C _{max} (ng/mL)	122	143	117	(89.6, 153)
	AUC _{0-t} (h*ng/mL)	1130	1440	127	(93.2, 174)
	AUC _{0-∞} (h*ng/m)	1230	1580	128	(91.3, 179)

Notes: Group A: non-elderly group. Group B: elderly group. C_{max} and AUC between the two groups are considered to be equivalent if the 90% CIs of geometric mean ratios of C_{max} and AUC are located within 80–125%.

Abbreviations: C_{max}, peak concentration; AUC_{0-t}, plasma area under concentration–time curve from time 0 to the last measurable concentration; AUC_{0-∞}, plasma area under concentration–time curve from time 0 to infinity; CIs, confidence intervals.

pharmacokinetics of imrecoxib (M0) and its main metabolites (M1 and M2), and evaluated the safety and tolerability of imrecoxib in healthy elderly subjects, thus offering references for clinical use of imrecoxib in elderly population.

Imrecoxib undergoes strong first-pass metabolism after oral administration in human, and prototype drug (M0) mainly generates hydroxyl metabolite M1 and carboxylated metabolite M2 under the catalysis of various liver enzymes

Table 4 Summarization of All the Adverse Events

	Non-Elderly Group (N=10)				Elderly Group (N=9)			
	Incidence (%)	Severity Grade			Incidence (%)	Severity Grade		
		I	II	III		I	II	III
All adverse events	2(20.0%)	2	0	0	2(22.2%)	2	0	0
Acute upper respiratory infection	1(10.0%)	1	0	0	0(0.0%)	0	0	0
White blood cell increased	1(10.0%)	1	0	0	0(0.0%)	0	0	0
Aspartate transaminase increased	0(0.0%)	0	0	0	1(11.1%)	1	0	0
Blood bilirubin increased	0(0.0%)	0	0	0	1(11.1%)	1	0	0
Blood glucose increased	1(10.0%)	1	0	0	0(0.0%)	0	0	0
Fibrinogen decreased	1(10.0%)	1	0	0	0(0.0%)	0	0	0

including CYP2C9, CYP2D6 and CYP3A4.^{18,29} Finally, imrecoxib mainly excretes in the urine in the form of M2 and its glucuronic acid conjugates.^{29–31} Both M1 and M2 also have moderate COX-1/COX-2 selectivity.¹⁹

Previous study had revealed that imrecoxib showed linear dynamic characteristics in healthy subjects following oral administration of single dose of 30, 60, 90 and 200mg imrecoxib, respectively.²⁹ Imrecoxib (M0) and M1 had similar pharmacokinetic properties, but the concentration of M2 in plasma was more than about 8 times than those of imrecoxib (M0) and M1.²⁹ However, the concentration of imrecoxib (M0), M1 and M2 showed moderate interindividual differences.²⁹ The T_{max} of imrecoxib (M0), M1 and M2 were about 2 hours.²⁹ We found similar results in the study that after receiving a single dose of 100 mg imrecoxib under fasting condition, it was absorbed into plasma with median time of 2 hours to reach peak concentration, and the individual concentration–time curves of imrecoxib were variable in non-elderly subjects, which was more apparent in elderly subjects.

Our study demonstrated that the C_{max} of imrecoxib (M0), M1 and M2 in plasma increased by 39%, 21% and 17%, and AUC_{0-t} of imrecoxib (M0), M1 and M2 in plasma increased by 34%, 13% and 27%, respectively, in elderly subjects compared with non-elderly subjects after oral administration of 100 mg imrecoxib. The C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were not completely equivalent between non-elderly and elderly subjects. The results of main pharmacokinetic parameters including C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, V_z/F and CL/F of imrecoxib (M0) exhibited higher interindividual variability in elderly subjects compared with nonelderly subjects. However, the differences of pharmacokinetics between elderly and non-elderly subjects were not statistically significant, except for the T_{max} of M2 between the two groups.

The reasons may be as follows: drug absorption may slow down because of decreased gastrointestinal motility, reduced integrity of the mucosa, decreased blood flow to digestive tract and increased gastric PH due to decreased gastric acid secretions in elderly population,²⁶ meanwhile, the blood flow in renal decreases in elderly population, thus increasing exposure of drug, prolonging half-life of drug and slowing renal elimination of drug in the body,^{23,32} which might explain increased exposures of imrecoxib and its metabolites and prolonged T_{max} of M2 in elderly subjects; with increase of age, the activities of cytochrome enzymes including CYP2C9, CYP2C19, CYP3A4, CYP3A5 and CYP1A2 gradually decrease²³ and imrecoxib is substrate of CYP2C9 and CYP3A4,²⁰ so imrecoxib's metabolism is more susceptible to age,²⁷ which also might lead to an increased plasma concentration of imrecoxib and its metabolites at the same dose compared with non-elderly population; besides, the activity of liver metabolizing enzymes varies greatly among different individuals especially for the elderly, which may be the reason for the larger interindividual variability of pharmacokinetics in elderly subjects.^{23,27}

In summary, although the exposures of imrecoxib and its metabolites were increased in the elderly population, the changes showed no statistical differences, indicating no significant impacts of age on the pharmacokinetics of imrecoxib, so dose adjustment is not necessary in the elderly. However, studies had found that patients with renal insufficiency showed a markedly increased exposure of M2 and the CL significantly reduced compared to healthy subjects, implying the dosage of imrecoxib should be reduced for patients with renal insufficiency.^{28,33} Therefore, it should be emphasized that the dosage of imrecoxib should be appropriately adjusted for elderly patients accompany with chronic diseases significantly affecting drug absorption, distribution, metabolism, or excretion in clinical practice.

The half maximal inhibitory concentration of COX-1 ($IC_{50COX-1}$)/ $IC_{50COX-2}$ value of rofecoxib is above 213, while $IC_{50COX-1}/IC_{50COX-2}$ value of imrecoxib is 6.39 that is 77% of celecoxib, implying lower incidences of adverse events comparable to celecoxib.^{17,29,34} Available studies had verified the favorable efficacy and safety profiles of imrecoxib for the management of inflammation, pain and fever in patients with OA.^{16,35,36}

Phase IV clinical trial further verified clinical efficacy and safety of imrecoxib, especially its gastrointestinal and cardiovascular safety. They found that imrecoxib could effectively and safely manage knee OA with low incidence of adverse events, few gastrointestinal adverse events and no serious cardiovascular adverse events, which was worthy of promotion for the treatment of OA.¹⁶

In our study, increased blood glucose in non-elderly subjects, increased aspartate transaminase and blood bilirubin in elderly group were considered to be ADRs. All the AEs were mild in severity and recovered without any medical intervention. So, imrecoxib administered by oral was well tolerated in both non-elderly and elderly healthy subjects, especially with favorable gastrointestinal, cardiovascular and renal safety profiles.

The study also has some limitations. Two subjects in the elderly group had hypertension medical history and, respectively, used amlodipine besylate tablets and nifedipine sustained release tablets to control blood pressure. Since there were no reports regarding the impacts of amlodipine and nifedipine on the pharmacokinetics of imrecoxib, so results of the two subjects had not been ruled out and were included in the pharmacokinetic and safety analysis set. More studies are needed to further determine the effects of common geriatric diseases and commonly used drugs on the pharmacokinetics and pharmacodynamics of imrecoxib. In addition, the sample size in the study was relatively small, which might have certain impact on the statistical power, and we will plan to expand sample size to explore the pharmacokinetic profiles of imrecoxib in different human populations.

Conclusion

Although the exposures of imrecoxib and its main metabolites in elderly subjects increased compared with those of healthy subjects, the differences showed no statistical significance. Meanwhile, imrecoxib was well tolerated for elderly people. We suggest that no dose adjustment should be required for elderly population. It is noteworthy that the appropriate dosage of imrecoxib for elderly patients with chronic diseases significantly affecting drug absorption, distribution, metabolism, or excretion deserves further investigation.

Data Sharing Statement

The data in the study are available by contacting the corresponding author upon reasonable request for research purpose.

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Disclosure

All authors have no conflicts of interest to declare in this work.

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