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

Ling Yang, Qi Shen, Chao Hu, Ying Wang, Xiaohong Zhu, Shiqing Shu, Zhu Luo

Clinical Trial Center, National Medical Products Administration Key Laboratory for Clinical Research and Evaluation of Innovative Drugs, West China Hospital Sichuan University, Chengdu, People’s Republic of China

*These authors contributed equally to this work

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\text{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\text{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\text{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\text{max}, AUC\text{0-t} and AUC\text{0-∞} of M0, M1 and M2 between the two groups were not located within 80–125%, indicating C\text{max}, AUC\text{0-t} and AUC\text{0-∞} 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.\textsuperscript{1–4} Advancing age is considered to be the main risk for the development of OA\textsuperscript{2–4} and the prevalence of OA in worldwide has increased dramatically over the past decades.\textsuperscript{5} Many available evidences indicate that oral non-steroidal anti-inflammatory drugs (NSAIDs) are the preferred pharmacological approaches of OA,\textsuperscript{1,4} which mainly target on inhibiting cyclooxygenase (COX) to inhibit the inflammatory response and relief pain.\textsuperscript{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.\textsuperscript{5,8,9} 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. Selective COX-2 inhibitors can retain the physiological gastrointestinal protective effects of COX-1, thus reducing the incidence of gastrointestinal reactions. 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.

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. 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.

Imrecoxib is an innovative and moderately selective COX-2 inhibitor with the similar pharmacological effects as celecoxib. Imrecoxib exhibits anti-inflammatory effect through moderate inhibition of COX-2 mRNA expression, and is widely used in orthopedics especially for knee OA. 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. Imrecoxib is catalyzed to hydroxyl metabolite M1 and then oxidized to carboxyl metabolite M2 in human. The major metabolic process of imrecoxib is shown in Figure 1.

The proportion of aged population is remarkably increasing worldwide. 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. Several former studies have investigated the pharmacokinetics of imrecoxib in healthy subjects, patients with impaired renal function and patients with hepatic impairment. 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.
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, 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 (Cmax), time to reach Cmax (Tmax), plasma area under concentration–time curve from time 0 to the last measurable concentration (AUC0-t), plasma area under concentration–time curve from time 0 to infinity (AUC0-∞), elimination half-life (t1/2), 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 \( C_{\text{max}} \) and AUC of imrecoxib (M0), M1 and M2 were calculated. \( C_{\text{max}} \) and AUC between the two groups were considered to be equivalent if the 90% confidence intervals (CIs) of geometric mean ratios of \( C_{\text{max}} \) 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 \( T_{\text{max}} \) which was analyzed through Mann–Whitney \( U \)-test. The \( T_{\text{max}} \) 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.
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 $C_{\text{max}}$, $\text{AUC}_{0-\text{t}}$ and $\text{AUC}_{0-\infty}$ of imrecoxib (M0), M1 and M2 between the two groups were calculated. As presented in Table 3, the geometric mean of $C_{\text{max}}$ of imrecoxib (M0),

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.
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.\textsuperscript{14–16,29} Our study initially explored the impacts of age on the
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 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\textsubscript{max} (ng/mL) | 13.9±10.8(77.2) | 30.7±37.5(122.2) | 0.226 |
|         | t\textsubscript{max} (h) | 2.00(0.500–6.00) | 2.00 (4.32–28.9) | 0.427 |
|         | AUC\textsubscript{0-0} (h*ng/mL) | 163±110(67.5) | 309±370(119.7) | 0.283 |
|         | AUC\textsubscript{0-∞} (h*ng/mL) | 173±107(61.9) | 315±368(116.9) | 0.293 |
|         | t\textsubscript{1/2} (h) | 10.9±6.07(55.7) | 13.0±7.31(56.3) | 0.508 |
|         | V\textsubscript{z}/F (L) | 765±366(47.9) | 789±784(99.4) | 0.935 |
| M1      | C\textsubscript{max} (ng/mL) | 36.6±14.0(38.1) | 44.2±16.6(37.5) | 0.294 |
|         | t\textsubscript{max} (h) | 2.00(1.00–6.00) | 2.00 (1.50–6.00) | 0.643 |
|         | AUC\textsubscript{0-0} (h*ng/mL) | 370±97.1(26.2) | 427±123(28.9) | 0.275 |
|         | AUC\textsubscript{0-∞} (h*ng/mL) | 393±103(26.4) | 443±126(28.4) | 0.355 |
|         | t\textsubscript{1/2} (h) | 9.25±4.38(47.3) | 11.5±5.77(50.4) | 0.349 |
|         | V\textsubscript{z}/F (L) | 3482±1445(41.5) | 4064±2205(54.3) | 0.501 |
| M2      | C\textsubscript{max} (ng/mL) | 130±47.5(36.6) | 148±37.5(25.4) | 0.376 |
|         | t\textsubscript{max} (h) | 1.50(1.00–3.00) | 2.00 (1.50–6.00) | 0.042 |
|         | AUC\textsubscript{0-0} (h*ng/mL) | 1180±340(28.9) | 1580±662(41.8) | 0.130 |
|         | AUC\textsubscript{0-∞} (h*ng/mL) | 1230±449(34.1) | 1740±734(42.2) | 0.129 |

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

**Abbreviations:** C\textsubscript{max}, peak concentration; t\textsubscript{max}, time to reach C\textsubscript{max}; AUC\textsubscript{0-0}, plasma area under concentration–time curve from time 0 to the last measurable concentration; AUC\textsubscript{0-∞}, plasma area under concentration–time curve from time 0 to infinity; t\textsubscript{1/2}, elimination half-life; Vz/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\textsubscript{max} (ng/mL) | 10.8 | 15.0 | 139 (60.9, 317) |
|         | AUC\textsubscript{0-0} (h*ng/mL) | 137 | 183 | 134 (67.4, 265) |
|         | AUC\textsubscript{0-∞} (h*ng/mL) | 148 | 193 | 130 (67.2, 250) |
| M1      | C\textsubscript{max} (ng/mL) | 34.0 | 41.3 | 121 (87.5, 169) |
|         | AUC\textsubscript{0-0} (h*ng/mL) | 358 | 406 | 113 (87.9, 146) |
|         | AUC\textsubscript{0-∞} (h*ng/mL) | 380 | 421 | 111 (85.8, 144) |
| M2      | C\textsubscript{max} (ng/mL) | 122 | 143 | 117 (89.6, 153) |
|         | AUC\textsubscript{0-0} (h*ng/mL) | 1130 | 1440 | 127 (93.2, 174) |
|         | AUC\textsubscript{0-∞} (h*ng/mL) | 1230 | 1580 | 128 (91.3, 179) |

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

**Abbreviations:** C\textsubscript{max}, peak concentration; AUC\textsubscript{0-0}, plasma area under concentration–time curve from time 0 to the last measurable concentration; AUC\textsubscript{0-∞}, plasma area under concentration–time curve from time 0 to infinity; CI, confidence interval.
including CYP2C9, CYP2D6 and CYP3A4. Finally, imrecoxib mainly excretes in the urine in the form of M2 and its glucuronic acid conjugates. Both M1 and M2 also have moderate COX-1/COX-2 selectivity.

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. 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. However, the concentration of imrecoxib (M0), M1 and M2 showed moderate interindividual differences. The T_{\text{max}} of imrecoxib (M0), M1 and M2 were about 2 hours. 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_{\text{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_{\text{max}}, AUC_{0-t} and CL were not completely equivalent between non-elderly and elderly subjects. The results of main pharmacokinetic parameters including C_{\text{max}}, AUC_{0-t}, 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 nonelderly subjects were not statistically significant, except for the T_{\text{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, 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, which might explain increased exposures of imrecoxib and its metabolites and prolonged T_{\text{max}} of M2 in elderly subjects; with increase of age, the activities of cytochrome enzymes including CYP2C9, CYP2C19, CYP3A4, CYP3A5 and CYP1A2 gradually decrease and imrecoxib is substrate of CYP2C9 and CYP3A4, so imrecoxib’s metabolism is more susceptible to age, 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.

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. 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 \( (\text{IC}_{50}^{\text{COX-1}}) \)/IC\(_{50}^{\text{COX-2}}\) value of rofecoxib is above 213, while IC\(_{50}^{\text{COX-1}}\)/IC\(_{50}^{\text{COX-2}}\) 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 imparts 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.

**Acknowledgments**

We would like to thank the support from Jiangsu Hengrui Pharmaceuticals Co., Ltd. (Jiangsu, China) and express our appreciation to colleagues from Shanghai Institute of Materia Medica for LC-MS/MS assays. We would like to acknowledge all the study nurses in Phase I clinical trial center ward of West China Hospital, Sichuan University for blood sampling. We would like to acknowledge all the human subjects for participation in the study.

**Funding**

This work was funded by Jiangsu Hengrui Pharmaceuticals Co., Ltd. (Jiangsu, China).

**Disclosure**

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

**References**

1. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, Hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27(11):1578–1589. doi:10.1016/j.joca.2019.06.011
2. Tang X, Wang S, Zhan S, et al. The prevalence of symptomatic knee osteoarthritis in China: results from the China health and retirement longitudinal study. *Arthritis Rheumatol*. 2016;68(3):648–653. doi:10.1002/art.39465
3. Ren Y, Hu J, Tan J, et al. Incidence and risk factors of symptomatic knee osteoarthritis among the Chinese population: analysis from a nationwide longitudinal study. *BMC Public Health*. 2020;20(1):1491. doi:10.1186/s12889-020-09611-7
4. Rafanan BS, Valdecasas BF, Lim BP, et al. Consensus recommendations for managing osteoarthritic pain with topical NSAIDs in Asia-Pacific. *Pain Manag*. 2018;8(2):115–128. doi:10.2217/pmt-2017-0047
5. Long H, Liu Q, Yin H, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the global burden of disease study 2019. *Arthritis Rheumatol*. 2022;74(7):1172–1183. doi:10.1002/art.42809
6. Davies NM, McLachlan AJ, Day RO, Williams KM. Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet*. 2000;38(3):225–242. doi:10.2165/00003088-20003803-00003
7. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340(24):1888–1899. doi:10.1056/nejm199907153402402
8. Tacconelli S, Capone ML, Patrignani P. Clinical pharmacology of novel selective COX-2 inhibitors. *Curr Pharm Des*. 2004;10(6):589–601. doi:10.2174/1381612043453108
9. Vane JR, Botting RM. Mechanism of action of aspirin-like drugs. *Semin Arthritis Rheum*. 1997;26(Suppl 1):2–10. doi:10.1016/s0049-0722(97)80046-7
10. Meng Q, Zhang Z, Li F, et al. The prescription patterns and safety profiles of oral non-steroidal anti-inflammatory drugs in China: an 8-year real-life analysis. *Ann Palliat Med*. 2021;10(2):2224–2237. doi:10.21037/apm-20-2356
11. Lenzer J. FDA advisers warn: COX 2 inhibitors increase risk of heart attack and stroke. *BMJ*. 2005;330(7489):440. doi:10.1136/bmj.330.7489.440
12. McGgettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296(13):1633–1644. doi:10.1001/jama.296.13.jrv60011
13. Pitt B, Pepine C, Willerson JT. Cyclooxygenase-2 inhibition and cardiovascular events. *Circulation*. 2002;106(2):167–169. doi:10.1161/01.01.000005261.58465.62
14. Jianlin H, Jieruo G, Yunfeng P, et al. A multicenter, double-blind and randomized controlled Phase II trial of imrecoxib in treatment of knee osteoarthritis. *Clin Pharm J*. 2011;42(22):1740–1745. Chinese.
15. Dong X, Fengchen Z, Jieruo G, et al. A multicenter double blind and randomized controlled Phase III trial of imrecoxib in treatment of knee osteoarthritis. *Chin J Allergy Clin Immunol*. 2018;4(03):205–210. Chinese. doi:10.3969/j.issn.1673-8705.2018.03.008
16. Xizi Z, Wenzhe Z, Fengchen Z. A multicenter open-labeled phase IV trial of imrecoxib in the treatment of knee osteoarthritis. *Chin J Rheumatol*. 2016;20(11):730–733. Chinese. doi:10.1080/0049825060051377
17. Chen XH, Bai JY, Shen F, Bai AP, Guo ZR, Cheng GF. Imrecoxib: a novel and selective cyclooxygenase 2 inhibitor with anti-inflammatory effect. *Acta Pharmacol Sin*. 2004;25(7):927–931.
18. Hou X, Zhou J, Yu S, et al. Differences in the in vivo and in vitro metabolism of imrecoxib in humans: formation of the rate-limiting aldehyde intermediate. *Drug Metab Dispos*. 2018;46(9):1320–1328. doi:10.1124/dmd.118.081182
19. Feng Z, Chu F, Guo Z, Sun P. Synthesis and anti-inflammatory activity of the major metabolites of imrecoxib. *Bioorg Med Chem Lett*. 2009;19(8):2270–2272. doi:10.1016/j.bmcl.2009.02.090
20. Li Q, Huang HH, Dong Y, Zhong DF. 采用重组人CYP酶研究艾瑞昔布的体外羟基化代谢 [Investigation on the hydroxylation metabolism of imrecoxib in vitro by using recombinant human CYPs]. *Yao Xue Xue Bao*. 2005;40(10):912–915. doi:10.3321/j.issn:0513-4870.2005.10.010. Chinese.
21. Hou X, Dai X, Yang Y, Zhang Y, Zhong D, Chen X. Simultaneous determination of imrecoxib and its two active metabolites in plasma of hepatic impairment patients by liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Sci Life Sci*. 2019;1122–1123:58–63. doi:10.1016/j.jchromb.2019.05.018
22. Cho SJ, Stout-Delgado HW. Aging and Lung Disease. *Annu Rev Physiol*. 2020;82:433–459. doi:10.1146/annurev-physiol-021119-034610
23. Koren G, Nordon G, Radinsky K, Shalev V. Clinical pharmacology of old age. *Expert Rev Clin Pharmacol*. 2019;12(8):749–755. doi:10.1080/17512333.2019.1632188
24. Thürmann PA. Pharmacodynamics and pharmacokinetics in older adults. *Curr Opin Anaesthesiol*. 2020;33(1):109–113. doi:10.1097/aco.0000000000000814
25. Maher D, Ailabouni N, Mangoni AA, Wiese MD, Reeve E. Alterations in drug disposition in older adults: a focus on geriatric syndromes. *Expert Opin Drug Metab Toxicol*. 2021;17(1):41–52. doi:10.1080/17425525.2021.1839413
26. Reeve E, Wiese MD, Mangoni AA. Alterations in drug disposition in older adults. *Expert Opin Drug Metab Toxicol*. 2015;11(4):491–508. doi:10.1517/17425525.2015.1004310
27. Klots U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev*. 2009;41(2):67–76. doi:10.1080/03602530902722679
28. Pei Q, Xie JL, Huang J, et al. Pharmacokinetic study of imrecoxib in patients with renal insufficiency. *Eur J Clin Pharmacol*. 2019;75(10):1355–1360. doi:10.1007/s00228-019-02698-x
29. Zongru G. Discovery of imrecoxib. *Chin J New Drugs*. 2012;21(03):223–230. Chinese.
30. Xu HY, Xie ZY, Zhang P, et al. Role of rat liver cytochrome P450 3A and 2D in metabolism of imrecoxib. *Acta Pharmacol Sin*. 2006;27(3):372–380. doi:10.1111/j.1745-7254.2006.00265.x
31. Xu H, Zhang Y, Sun Y, et al. Metabolism and excretion of imrecoxib in rat. *Xenobiotica*. 2006;36(5):441–455. doi:10.1080/00989250600595524
32. Khan MS, Roberts MS. Challenges and innovations of drug delivery in older age. *Adv Drug Deliv Rev*. 2018;135:3–38. doi:10.1016/j.addr.2018.09.003
33. Li Y, Wang J, Huang J, et al. Dose investigation of imrecoxib in patients with renal insufficiency based on modelling and simulation. *Eur J Pharm Sci*. 2020;152:105449. doi:10.1016/j.ejps.2020.105449
34. Shen F, Bai AP, Guo ZR, Cheng GF. Inhibitory effect of 3,4-diaryl-3-pyrrolin-2-one derivatives on cyclooxygenase 1 and 2 in murine peritoneal macrophages. *Acta Pharmacol Sin*. 2002;23(8):762–768.
35. Jianlin H, Yunpeng F, Yu-qiong W, Hui S, Jieruo G. Phase I clinical tolerability of imrecoxib. *Chin Pharm J*. 2011;46(21):1670–1673. Chinese.
36. Jiang Y, Qi L, Liu J, et al. Analogic efficacy of imrecoxib for postoperative pain following oral surgery: a prospective randomized, active-controlled, non-inferiority trial. *Ann Transl Med*. 2021;9(6):469. doi:10.21037/atm-21-264
