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PHARMACOKINETICS

Absence of ethnic differences in the pharmacokinetics of moxifloxacin, simvastatin, and meloxicam among three East Asian populations and Caucasians

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AIM

To examine whether strict control of clinical trial conditions could reduce apparent differences of pharmacokinetic (PK) parameters among ethnic groups.

METHODS

Open-label, single dose PK studies of moxifloxacin, simvastatin and meloxicam were conducted in healthy male subjects from three East Asian populations (Japanese, Chinese and Koreans) and one Caucasian population as a control. These three drugs were selected because differences in PK parameters have been reported, even though the backgrounds of these East Asian populations are similar. Moxifloxacin (400 mg) was administered orally to 20 subjects, and plasma and urine levels of moxifloxacin and its metabolite (M2) were measured. Simvastatin (20 mg) was given to 40 subjects, and plasma levels of simvastatin and simvastatin acid were measured. Meloxicam (7.5 mg) was given to 30 subjects and its plasma concentration was determined. Intrinsic factors (polymorphism of *UGT1A1* for moxifloxacin, *SLCO1B1* for simvastatin, and *CYP2C9* for meloxicam) were also examined.

RESULTS

AUC_{inf} values for moxifloxacin, simvastatin and meloxicam showed no significant differences among the East Asian groups. C_{max} values of moxifloxacin and simvastatin, but not meloxicam, showed significant differences. There were no significant differences of data for M2 or simvastatin acid. Genetic analysis identified significant differences in the frequencies of relevant polymorphisms, but these differences did not affect the PK parameters observed.

CONCLUSIONS

Although there were some differences in PK parameters among the three East Asian groups, the present study performed under strictly controlled conditions did not reproduce the major ethnic differences observed in previous studies.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- There have been several reports about ethnic differences in pharmacokinetics (PK) among Asian populations, although their genetic background is rather similar.
- Such ethnic differences in drug responses need to be considered in global clinical trials, requiring independent trials in various countries.

WHAT THIS STUDY ADDS

- This was the first PK study conducted simultaneously at multinational sites in East Asia under a strict protocol.
- For three drugs with previously reported differences, there were no major differences in PK parameters among East Asian groups (and Caucasians).
- These results provide the basis for interpreting pharmacokinetic data from East Asian countries.

Introduction

In the drug development process, efficient performance of clinical trials is a critical factor for reducing both time and cost. Global clinical trials represent one approach to improving efficiency, but sometimes ethnic differences in drug responses need to be considered and such differences may require independent clinical trials in various countries [1, 2]. This issue is also a major problem for regulatory agencies. From an ethical viewpoint, it is problematic that repeating clinical trials in different countries leads to an increase in the number of participants required.

Ethnic differences in drug responses are caused not only by intrinsic factors such as genetic differences (genetic polymorphism of metabolic enzymes or transporters) or differences in body weight [3], but also by extrinsic factors such as environmental differences (diet, habits, climate, etc.) [3–5]. There is considerable evidence of genetic similarity among different East Asian populations [6–8]. For example, the frequencies of genetic variants of several drug metabolizing enzymes (CYP2C9 [8–10], CYP2C19 [6, 8, 10, 11], CYP2D6 [6, 8, 12] and CYP3A4 [6, 8]), drug transporters (P-glycoprotein [13] and SLCO1B1 [6]), and hormone receptors (adrenergic receptors [14]) are similar among East Asian populations, whereas these frequencies show larger differences between East Asians and Caucasians [6, 15–17].

Because extrinsic factors, such as diet and beverages, also influence drug responses, such factors may lead to pharmacokinetic (PK) and pharmacodynamic differences even among East Asian countries [1, 5, 8, 18]. It has been reported that some drugs show ethnic differences in PK parameters among East Asian populations [19–23], although the mechanisms underlying these differences have not been clarified.

The aim of the present study was to examine whether strict control of clinical trial conditions such as intake of food and beverages could reduce differences in the PK parameters of drugs that were previously reported to show marked differences among various ethnic groups, including East Asians (Chinese, Koreans and Japanese) and Caucasians. For this purpose, we surveyed East Asian and Caucasian PK data on more than 40 drugs and found 17 drugs with differences among East Asian populations or differences between East Asians and Caucasians. Among these drugs, we chose moxifloxacin, simvastatin, and meloxicam, as large ethnic differences in their PK parameters have been reported and the reasons for such differences have not been clarified. To investigate relevant intrinsic factors, polymorphism of genes for major metabolic enzymes or transporters was also examined, including polymorphism of *UGT1A1* for moxifloxacin, *SLCO1B1* for simvastatin and *CYP2C9* for meloxicam.

Methods

Subjects and study sites

Healthy male Japanese, Chinese, Korean and Caucasian subjects (aged 20 to 35 years, body mass index (BMI) of 18.5 to <30.0 and body weight of 50.0 to 100.0 kg at screening) were enrolled in open-label, single-dose PK studies of moxifloxacin, simvastatin and meloxicam. All subjects were healthy on the basis of their medical histories. They did not have a present or past history of organopathy, such as heart disease (including QTc prolongation) or lung, liver or kidney disease; hypersensitivity or allergies to drugs or foods, etc.; or drug or alcohol abuse (ethanol intake ≤50 g/day). They were normal based on prestudy physical examination, electrocardiography, and clinical laboratory tests. The study sites were Kitasato University (Tokyo, Japan), Seoul National University (Seoul, Korea), Peking University First Hospital (Beijing, China), and SNBL Clinical Research Center (Baltimore, USA). Ethnicity of the subjects was defined as follows. Subjects who were citizens living in Japan, China or Korea were defined as Japanese, Chinese or Korean, respectively. Their parents and grandparents had also been citizens living in the same countries. The male Caucasian subjects were recruited in the USA, and their ancestors were from Northern Europe according to their own declaration. The number of subjects enrolled in each study was calculated from the variance of previously published data as the number required to confirm or exclude the hypothesis that ethnic differences in PK existed among these populations, amounting to a maximum of 20% for moxifloxacin or meloxicam and 40% for simvastatin. All of the subjects gave written informed consent prior to commencement of the studies. The ethics committees or Institutional Review Boards of Kitasato University, Seoul National University, Peking University First Hospital, SNBL Clinical Research Center and related institutes approved the conduct of these PK studies. Approval numbers or dates for Kitasato University, Seoul National University, Peking University First Hospital and SNBL Clinical Research Center were respectively as follows: 09612, H-1001-022-306, 2010–03 and 1/26/2010 for the moxifloxacin study; 10616, H-1006-109-322, 2010–13 and 6/29/2010 for the

simvastatin study; 10618, H-1010-009-334, 2010–20 and 11/9/2010 for the meloxicam study. All of the studies were registered in the UMIN Clinical Trials Registry, with the registration numbers being UMIN000002968 for the moxifloxacin study, UMIN000003644 for the simvastatin study, and UMIN000004173 for the meloxicam study. This study was conducted according to the tenets of the Declaration of Helsinki and the ICH regulations on Good Clinical Practice.

PK studies

Demographic characteristics of the subjects in each study are presented in Table 1. The mean body weight (BW) and body mass index (BMI) [and creatinine clearance (CCr) for the moxifloxacin study] were calculated for each group and were analyzed by analysis of variance (ANOVA). Data on C_{max}, AUC_{48}, AUC_{inf} and CL/F were adjusted for a BW of 70 kg using the following equation (example for C_{max}): C_{max}(corrected) = C_{max}(uncorrected) × (BW/70). Dunnett's test was also employed for comparisons between the Japanese subjects and the other ethnic groups. All analyses were carried out using JMP9.3 software (SAS Institute Japan, Tokyo, Japan). Before enrolment in each study, subjects underwent a health check and were confirmed to be healthy (in particular, hepatic and renal function were confirmed to be within the normal range). Current smokers (or those who had stopped <6 months previously) were excluded from the studies, as were persons who drank >50 g of alcohol daily, those who abused recreational drugs, and those who had participated in another clinical trial within the previous 4 months. Each subject fasted overnight and received a single dose of the test drug orally with 150 mL of water on the morning of day 1 in the fasting state. In all three studies, total dietary calories and nutrients were matched in each study site (although the details of the menu were decided by the dietician at each site to fit the tastes of each ethnic group) to exclude the influence of diet on drug metabolism. In the simvastatin and meloxicam studies, subjects were prohibited from taking grapefruit juice or foods containing grapefruit, caffeine-containing drinks including green tea, and other supplements and health foods for two weeks prior to the study. In all three studies, subjects were prohibited from taking any drugs, supplements or health foods from one week prior to the study until discharge from hospital. Subjects were only allowed to drink water for 4 hours after administration of each drug, and water hardness (< 100 mg/L) was also matched among the study sites to exclude possible interactions between drugs and minerals in the water [24, 25]. In each study, a single batch of the test drug was used to avoid variation of bioavailability between different batches.

In the moxifloxacin study, the target was to enrol 20 subjects at each study site. A dose of 400 mg of moxifloxacin was administered to each subject. Blood samples were taken from the forearm before and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 36 and 48 h after dosing [the total blood volume collected was 115.0 mL (Japanese), 106.0 mL (Chinese), 107.0 mL (Koreans) and 130.5 mL (Caucasians)], while urine was collected over four time periods until 48 h after dosing (0–6, 6–12, 12–24 and 24–48 h).

Table 1

Demographic characteristics of the healthy male subjects

Drug		Japanese	Chinese	Korean	Caucasian	ANOVA
Moxifloxacin	*n*	20	20	19	20	NT
	Age (years)	23.0 ± 3.9	29.2 ± 4.2	25.7 ± 3.6	28.0 ± 4.8	NT
	BW (kg)	63.8 ± 6.7	68.9 ± 5.9	72.9 ± 9.9*	77.0 ± 12.4*	$P = 0.0002$
	BMI (kg/m^2)	21.6 ± 1.9	24.6 ± 1.5*	23.3 ± 2.4	24.2 ± 3.0*	$P = 0.0005$
	CCr (mL/min)[1]	122.1 ± 19.3	118.7 ± 17.5	125.8 ± 20.6	101.5 ± 14.4*	$P = 0.0003$
Simvastatin	*n*	40	40	40	40	NT
	Age (years)	25.0 ± 4.0	31.5 ± 2.9	23.5 ± 2.7	25.7 ± 4.0	NT
	BW (kg)	63.6 ± 7.5	65.9 ± 8.4	67.9 ± 9.4	77.5 ± 10.3*	$P < 0.0001$
	BMI (kg/m^2)	21.6 ± 2.4	23.5 ± 2.4*	22.5 ± 2.6	24.9 ± 2.8*	$P < 0.0001$
Meloxicam	*n*	30	30	29	30	NT
	Age (years)	24.6 ± 3.0	31.3 ± 2.5	24.2 ± 2.1	26.5 ± 4.1	NT
	BW (kg)	64.7 ± 9.6	67.0 ± 9.3	69.7 ± 7.7	77.8 ± 13.0*	$P < 0.0001$
	BMI(kg/m^2)	22.1 ± 3.0	23.5 ± 2.6	22.3 ± 1.9	24.9 ± 3.1*	$P = 0.0003$

Data are expressed as the mean ± SD. NT = not tested. BW = body weight. BMI = body mass index. CCr = creatinine clearance. Creatinine clearance was calculated using the Cockcroft-Gault formula. *Significantly different ($P < 0.05$) from Japanese by Dunnett's test. The mean ± SD of BW and BMI (also CCr for moxifloxacin) in the four groups showed statistical differences by ANOVA, so Dunnett's test was carried out for comparison with Japanese. All of these parameters were different in Caucasians, and some were different in Chinese and Koreans.

In the simvastatin study, 40 subjects were recruited at each study site, and a dose of 20 mg was administered. Blood samples were taken before and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 h after dosing [the total blood volume collected was 127.0 mL (Japanese), 122.0 mL (Chinese), 119.0 mL (Koreans) and 142.5 mL (Caucasians)].

In the meloxicam study, 30 subjects were scheduled for enrolment at each site, and a dose of 7.5 mg was administered. Blood samples were taken before and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60 and 72 h after dosing [the total blood volume collected was 125.0 mL (Japanese), 120.0 mL (Chinese), 117.0 mL (Koreans) and 140.5 mL (Caucasians)].

All of the study drugs were purchased in China and sent to the other participating countries to ensure use of the same drug batches. Moxifloxacin was a product of Bayer HealthCare Pharmaceuticals (Germany), simvastatin was from Merck & Co., Inc. (USA), and meloxicam was from Boehringer Ingelheim GmbH (Germany).

Genotyping

DNA for genotyping was prepared from whole blood samples of each subject. Genotyping of the Japanese, Korean and Caucasian subjects was carried out by the National Institute of Health Sciences (NIHS) (Tokyo, Japan), while genotyping of the Chinese subjects was performed by Biomedical Research, Ltd. at the Jiaxing Pharmacokinetics and Bioanalysis Center (Shanghai, China). In the moxifloxacin study, we determined the genotypes of *UGT1A1* by full sequencing of known activity-reducing alleles **6* and **28* according to the method described previously [26], because this drug is metabolized by UGT1A1 [27, 28]. For the simvastatin study, genotyping of activity-reducing *SLCO1B1* (521 T > C, V174A) was performed using the TaqMan SNP Genotyping Assay (Life Technologies Japan Ltd., Tokyo, Japan) [29]. Meloxicam is metabolized to an inactive form by CYP2C9, so genotyping of activity-reducing polymorphisms *CYP2C9*2* and *CYP2C9*3* was performed using a TaqMan SNP Genotyping Assay in the meloxicam study [29].

Analysis of the drugs and metabolites

Drug concentrations were assayed in plasma and urine samples by validated high-performance liquid chromatography with tandem mass spectrometry (LC/MS/MS) methods.

In the moxifloxacin study, the plasma and urine concentrations of moxifloxacin and its main metabolite (moxifloxacin glucuronide: M2) were measured according to the method reported by Raju *et al.* [27]. All assays for the moxifloxacin study were performed at the Pharma Research Center for Preclinical Pharmacokinetics of Bayer HealthCare AG (Wuppertal, Germany).

For simvastatin, the plasma concentrations of two forms of the parent compound (the lactone and open acid forms) and their metabolites were measured according to the method reported by Zhang *et al.* [30]. All assays for the simvastatin study were performed at the SNBL Analytical Center in Japan.

Meloxicam was assayed according to the method of Yuan *et al.* [31] at the SNBL Analytical Center in Japan (Wakayama, Japan). The details of each assay validation are presented in the Supplementary Materials.

PK parameters and statistical analysis

The following PK parameters were calculated using WinNonlin, version 5.2.1 (Pharsight Corporation, St. Louis, MO, USA) and model-independent compartmental analysis: the time of the maximum drug concentration (T_{max}), the elimination half-life ($T_{1/2}$), the maximum serum concentration (C_{max}), the area under the concentration *vs.* time curve (AUC) from time 0 to the last time of sampling ($AUC_{0\text{-}tn}$) or infinity (AUC_{inf}), the total clearance (CL), and the mean residence time (MRT). For moxifloxacin, the urinary recovery (%) (Σ(urinary concentration × urine volume)/dose × 100) and renal clearance (Σ(urinary concentration × urine volume)/AUC_{inf}) were also calculated. For statistical analyses, data on some parameters (C_{max}, AUC_{48}, AUC_{inf} and CL/F) were adjusted for a BW of 70 kg. Two-sided confidence intervals were calculated for pairwise differences in the mean values of each parameter between the Japanese group and the other three ethnic groups. ANOVA and Dunnett's test were used to assess the significance of differences in C_{max} and AUC_{inf} among the four ethnic groups. The influence of each of the alleles investigated on PK parameters was also analysed by Student *t*-test using AUC_{inf} data for each genotype group, but not each ethnic group. These analyses were carried out using JMP9.3 software (SAS Institute Japan, Tokyo, Japan).

Safety analysis

For all studies, safety data were obtained during hospitalization. For safety analysis, symptoms and objective findings, vital signs, body weight and laboratory data (haematology tests, biochemistry tests and urinalysis) were evaluated by the investigators.

At all participating sites, each study was conducted over a three-month period. The studies of simvastatin and meloxicam were conducted more than six months after the study of moxifloxacin.

Results

Moxifloxacin study

Twenty subjects each were enrolled in the Japanese, Chinese and Caucasian arms of the study, while there were 19 subjects in the Korean arm. BW was significantly different between the Japanese and Caucasian subjects, as well as the Japanese and Korean subjects. BMI showed a significant difference between the Japanese and Caucasian subjects, as well as the Japanese and Chinese subjects. CCr was also significantly different by ANOVA, but only a difference between Japanese and Caucasians was confirmed by Dunnett's test (Table 1). Figure 1 (A, B) shows the plasma profile of moxifloxacin and its metabolite M2 in each of the ethnic groups, while the BW-adjusted PK plasma and urine parameters of moxifloxacin and M2 for each population are listed in Table 3 and displayed in Figure 2 (A–D). ANOVA revealed significant differences in C_{max} and AUC_{inf} for the parent compound among the four groups (both $P < 0.0001$). C_{max} also showed differences between Japanese and the other ethnic groups (Chinese: $P = 0.0024$, Koreans: $P < 0.0001$, Caucasians: $P = 0.0087$) by Dunnett's test, but AUC_{inf} only showed a significant difference

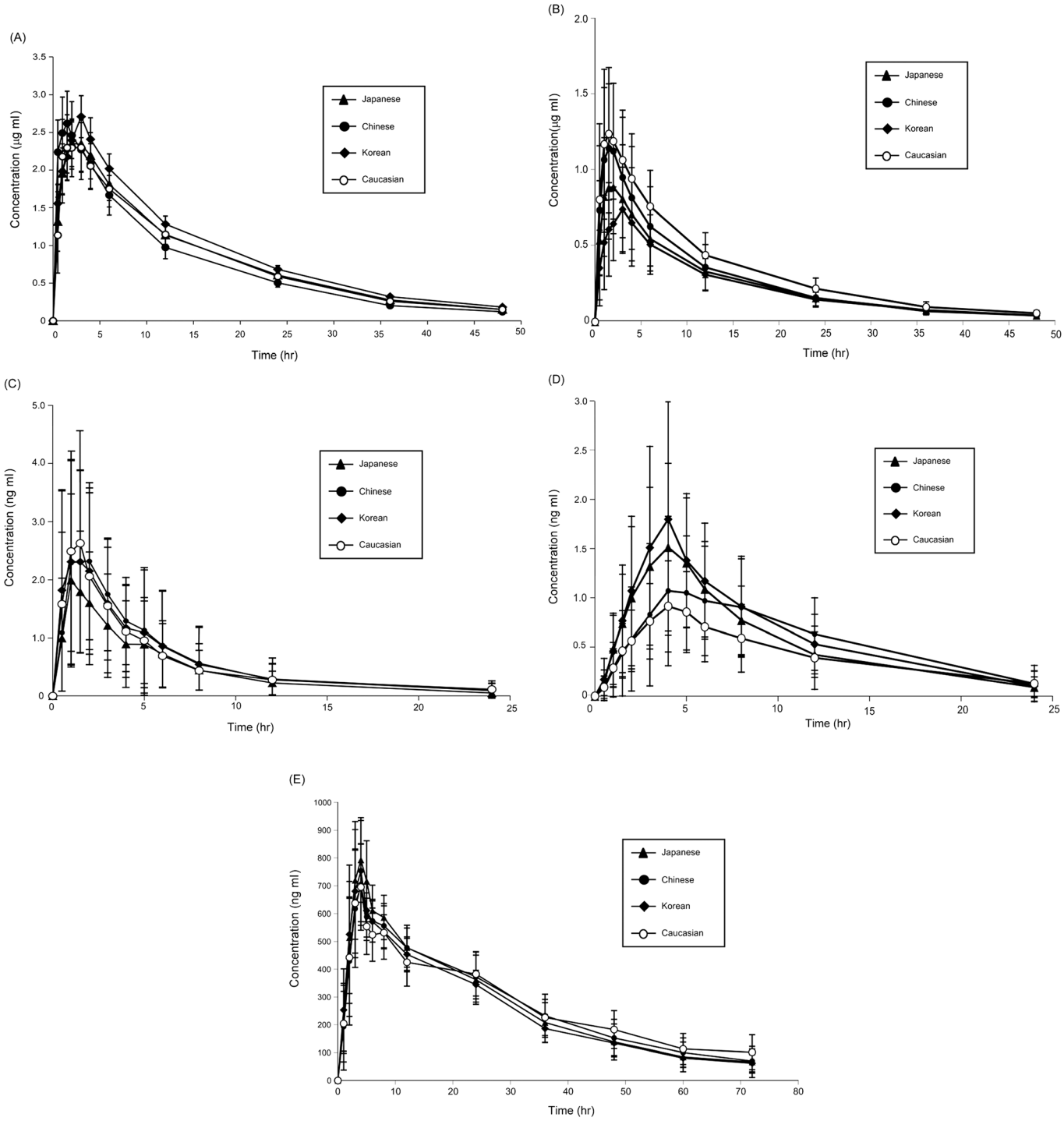

Figure 1

Plasma concentration vs. time profile of (A) moxifloxacin, (B) M2 (moxifloxacin glucuronate), (C) simvastatin, (D) simvastatin acid and (E) meloxicam. Symbols and bars display the mean and SD of each group, respectively

between the Japanese and Korean groups by Dunnett's test (P = 0.0007). ANOVA also identified significant differences in the C_{max} and AUC_{inf} of M2 among the ethnic groups (P = 0.0002 and $P < 0.0001$, respectively). However, both parameters only showed a significant difference between Japanese and Caucasians by Dunnett's test (P = 0.0007 and $P < 0.0001$). Table 3 lists the urinary recovery and renal clearance data for moxifloxacin and M2. Both the urinary recovery and renal clearance of moxifloxacin (P = 0.0118 and $P < 0.0001$, respectively) and the urinary recovery of M2 (P = 0.0182) showed differences among the ethnic groups by ANOVA, but Dunnett's test only identified differences between Chinese and Japanese subjects for moxifloxacin (P = 0.0140 for the urinary recovery and $P < 0.0001$ for renal clearance).

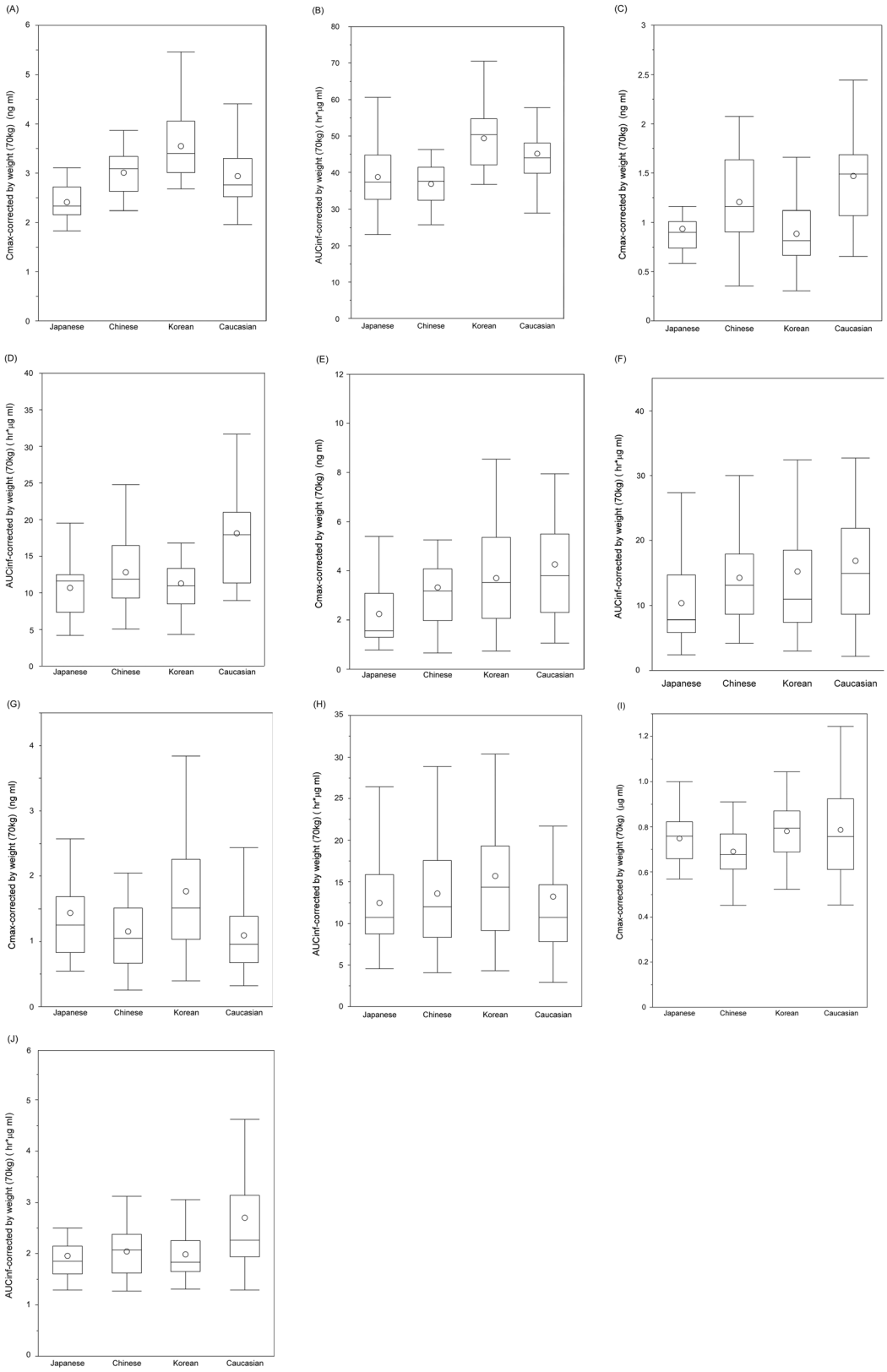

Figure 2

Comparison of the C_{max} and AUC_{inf} of each drug adjusted by BW (70 kg). (A) C_{max} of moxifloxacin, (B) AUCinf of moxifloxacin, (C) C_{max} of M2, (D) AUC_{inf} of M2, (E) C_{max} of simvastatin, (F) AUC_{inf} of simvastatin, (G) C_{max} of simvastatin acid, (H) AUCinf of simvastatin acid, (I) C_{max} of meloxicam and (J) AUC_{inf} of meloxicam

We also categorized the subjects according to their *UGT1A1* genotypes and calculated the mean of each pharmacokinetic parameter for each genotype group: **6* carriers, **28* carriers, and wild-type (**1*). Figure 3 (A) shows that **6* carriers had a significantly lower AUC_{inf} of M2 compared with the other genotypes (**1/*28* and **28/*28*: $P = 0.0008$, **1/*1*: $P < 0.0001$). However, metabolism of moxifloxacin itself was not influenced by variation of the *UGT1A1* genotype (C_{max}: $P = 0.4106$, AUC_{inf}: $P = 0.3045$, by ANOVA). The **6* allele of *UGT1A1* showed a higher frequency among East Asians than Caucasians (Table 2), suggesting that the lower frequency of the **6* allele in Caucasians may have been responsible for the larger AUC_{inf} of M2. The frequency of **28* was higher in Caucasians, but this did not cause an ethnic difference because the AUC of M2 did not differ between the **28* and **1/*1* populations. Concerning safety, 14 adverse events (AEs) were reported in 12 subjects and four events were considered to be related to the study drug (urticaria: one event in a Japanese subject, dizziness: two events in Korean subjects, and headache: one event in a Caucasian subject). All of these events were mild, except for one moderate episode of headache. There were no reports of QT prolongation.

Simvastatin study

Forty subjects were enrolled from each ethnic group. BW was significantly different between Japanese and Caucasians, while BMI showed a significant difference between Japanese and Caucasians as well as between Japanese and Chinese (Table 1). Figure 1 (C, D) displays the plasma profile of simvastatin and simvastatin acid in each ethnic group, while the BW-adjusted PK parameters of simvastatin and simvastatin acid for each ethnic group are listed in Table 3 and shown in Figure 2 (E–H). There were significant differences in the C_{max} and AUC_{inf} of simvastatin among the four groups by ANOVA ($P = 0.0004$ and 0.0328, respectively). Dunnett's test detected a significant difference in C_{max} between Japanese and Koreans ($P = 0.0001$), as well as between Japanese and Caucasians ($P = 0.0066$), but AUC_{inf} only showed a difference between Japanese and Caucasians ($P = 0.0127$). The C_{max} of simvastatin acid also showed significant differences among the ethnic groups by ANOVA ($P = 0.0002$), but there was no significant difference between Japanese subjects and any of the other ethnic groups by Dunnett's test. AUC_{inf} values of simvastatin did not show any ethnic differences by ANOVA ($P = 0.3215$) (Table 3). We also examined the influence of *SLCO1B1* genotype on the AUC_{inf} of simvastatin acid because it is a substrate of SLCO1B1. The frequency of variant alleles of *SLCO1B1* (c.521 T > C, V174A) was higher in Caucasians than in East Asians (Table 2). We used Student's *t*-test to examine whether heterozygous variation affected the mean AUC_{inf} and C_{max} values among all subjects. This analysis revealed that both the AUC_{inf} and C_{max} of simvastatin acid were significantly different between subjects with the wild-type allele and subjects with variant alleles (both $P < 0.0001$) [note: AUC_{inf} is shown in Figure 3 (B)]. These results suggested that the ratio of *SLCO1B1* variants in a study population could influence PK parameters. Regarding safety, ten AEs were reported in nine subjects, but only one event was related to the study drug (mild diarrhoea in a Korean subject).

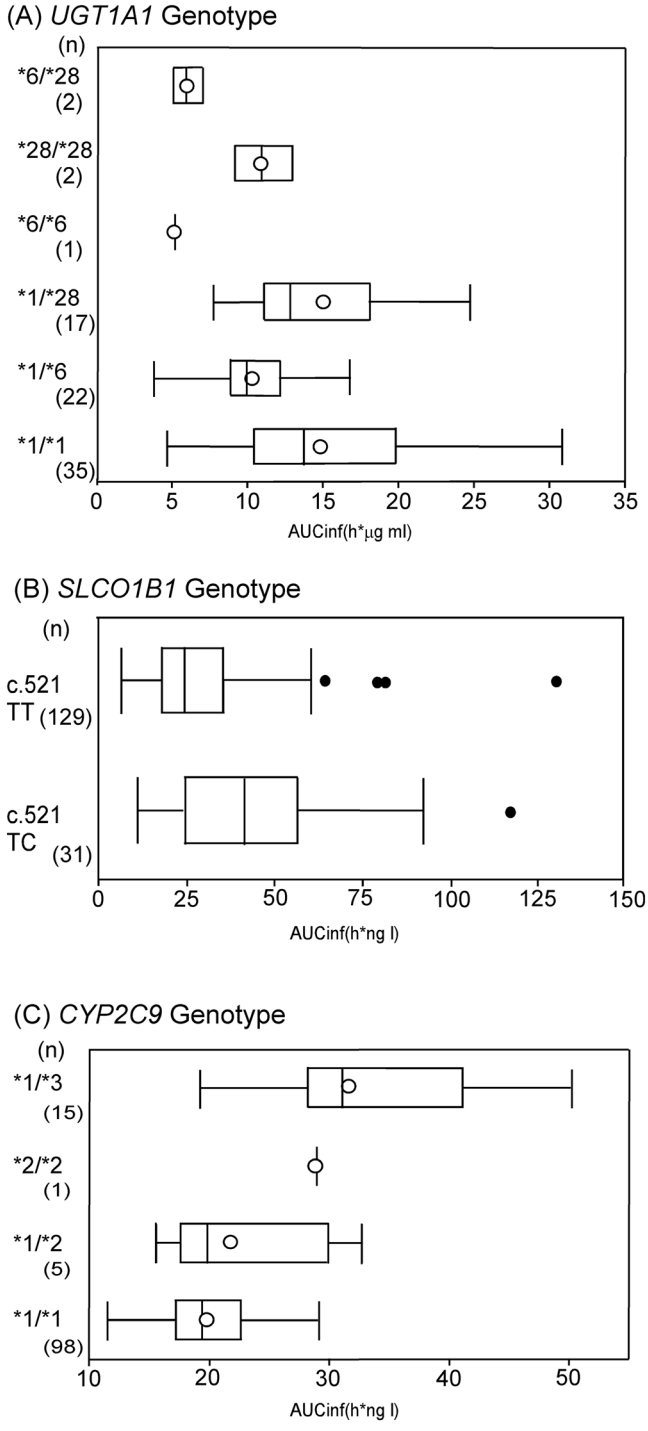

Figure 3

Comparison of the AUC_{inf} of each drug stratified by genotype (box-and-whisker plot without outliers (dots)). M2 (moxifloxacin glucuronate) in each *UGT1A1* genotype group. Simvastatin acid in each *SLCO1B1* genotype group. Meloxicam in each *CYP2C9* genotype group. Boxes display the 25th to 75th percentile range, while the centre line indicates the median value, open circles indicate the mean, and closed circles indicate the outliers of each group. AUC_{inf} is shown on the x-axis

Table 2

Genotype distribution [positive subject number/tested subject number (population allele frequency)]

Drug	Enzyme/Transporter	Genotype	Japanese	Chinese	Korean	Caucasian
Moxifloxacin	*UGT1A1*	*1/*1	10/20 (0.50)	6/20 (0.30)	9/19 (0.47)	10/20 (0.50)
		*1/*6	7/20 (0.35)	8/20 (0.40)	6/19 (0.32)	1/20 (0.05)
		*6/*6	0/20 (0.00)	1/20 (0.05)	0/19 (0.00)	0/20 (0.00)
		*6/*28	0/20 (0.00)	1/20 (0.05)	1/19 (0.05)	0/20 (0.00)
		*1/*28	3/20 (0.15)	3/20 (0.15)	3/19 (0.16)	8/20 (0.40)
		*28/*28	0/20 (0.00)	1/20 (0.05)	0/19 (0.00)	1/20 (0.05)
Simvastatin	*SLCO1B1c.521 T > C*	TT	32/40 (0.80)	36/40 (0.90)	35/40 (0.88)	26/40 (0.65)
		TC	8/40 (0.20)	4/40 (0.10)	5/40 (0.13)	14/40 (0.35)
		CC	0/40 (0.00)	0/40 (0.00)	0/40 (0.00)	0/40 (0.00)
Meloxicam	*CYP2C9*	*1/*1	26/30 (0.87)	27/30 (0.90)	25/29 (0.86)	20/30 (0.67)
		*1/*2	0/30 (0.00)	1/30 (0.03)	0/29 (0.00)	5/30 (0.17)
		*2/*2	0/30 (0.00)	0/30 (0.00)	0/29 (0.00)	1/30 (0.03)
		*1/*3	4/30 (0.13)	3/30 (0.10)	4/29 (0.14)	4/30 (0.13)

Allele frequency of each enzyme/transporter polymorphism is as follows (Japanese/Korean/Chinese/Caucasian)[6]: *UGT1A1* *6 (0.155/0.220/0.205/0.003), *28 (0.110/0.115/0.127/0.340). *SLCO1B1 521 T >* C: (0.139/0.136/0.127/0.161). *CYP2C9* *2 (ND/ND/0.001/0.140), *3 (0.029/0.036/0.037/0.064).

Table 3

Body weight adjusted (70kg) pharmacokinetic parameters of each drug and its metabolites and comparison by statistical analysis [mean ± S.D. (%CV)]

		Japanese	Chinese	Korean	Caucasian	ANOVA*
Moxifloxacin	T_{max} (h)	1.7 ± 1.0 (58.8)	1.2 ± 0.6 (50.0)	1.7 ± 1.0 (58.8)	1.6 ± 0.8 (50.0)	C_{max}: $P < 0.0001$*
	$T_{1/2}$ (h)	12.3 ± 1.3 (10.6)	11.8 ± 1.5 (12.7)	12.7 ± 1.3 (10.2)	12.2 ± 1.7 (13.9)	AUC_{inf}: $P < 0.0001$*
	C_{max} (ng/mL)	2.41 ± 0.36 (14.9)	3.01 ± 0.48 (15.9)**	3.55 ± 0.69 (19.4)**	2.94 ± 0.64 (21.8)**	Urine excretion rate: $p = 0.0118$*
	AUC_{48} (h*μg/mL)	36.0 ± 8.0 (22.2)	34.7 ± 5.0 (14.4)	45.7 ± 7.1 (15.5)**	41.9 ± 8.0 (19.1)**	
	AUC_{inf} (h*μg/mL)	38.8 ± 9.5 (24.5)	36.9 ± 5.9 (16.0)	49.4 ± 8.5 (17.2)**	45.2 ± 10.0 (22.1)	Renal clearance: $p < 0.0001$*
	CL/F (L/h)	10.90 ± 2.63 (24.1)	11.13 ± 1.92 (17.3)	8.32 ± 1.42 (17.1)**	9.20 ± 1.79 (19.5)**	
	MRT_{48} (h)	14.1 ± 1.1	12.9 ± 0.8	14.2 ± 1.0	13.9 ± 0.9	
	Urinary recovery rate (%)	21.0 ± 3.3 (15.7)	24.5 ± 3.7 (15.1)**	21.1 ± 4.5 (21.3)	22.6 ± 3.2 (14.2)	
	Renal clearance (parent (g)/ AUC) (L/h)	2.03 ± 0.33 (16.3)	2.65 ± 0.45 (17.0)**	1.79 ± 041 (22.9)	2.24 ± 039 (17.4)	
Moxifloxacin-glucuronide (M2)	T_{max} (h)	1.6 ± 0.8 (50.0)	1.4 ± 0.6 (42.9)	2.0 ± 0.9 (45.0)	1.5 ± 0.6 (24.0)	C_{max}: $P = 0.0002$*
	$T_{1/2}$ (h)	11.2 ± 1.5 (22.3)	10.6 ± 1.1 (10.4)	11.8 ± 1.3 (11.0)	11.3 ± 1.1 (9.7)	AUC_{inf}: $P < 0.0001$*

(continues)

Table 3

(Continued)

		Japanese	Chinese	Korean	Caucasian	ANOVA*
	C_{max} (ng/mL)	0.94 ± 0.36 (38.3)	1.21 ± 0.45 (37.2)	0.88 ± 0.34 (40.0)	1.47 ± 0.56 (14.8)**	Urine excretion rate: $p = 0.0182$*
	AUC_{48} (h*μg/mL)	10.2 ± 3.5 (34.3)	12.3 ± 4.7 (38.2)	10.6 ± 4.1 (38.7)	17.2 ± 7.0 (40.7)**	
	AUC_{inf} (h*μg/mL)	11.7 ± 3.6 (30.8)	12.8 ± 4.8 (21.1)	11.3 ± 4.4 (38.9)	18.1 ± 7.5 (41.4)**	Renal clearance: $p = 0.5331$
	CL/F (L/h)	42.7 ± 18.2 (42.6)	36.1 ± 14.9 (41.3)	41.8 ± 19.5 (46.7)	25.7 ± 10.2 (39.7)**	
	MRT_{48} (h)	12.7 ± 1.0	11.8 ± 0.9	13.4 ± 0.9	12.6 ± 0.9	
	Urinary recovery rate (%)	13.2 ± 4.8 (36.4)	13.3 ± 4.6 (34.6)	11.4 ± 4.2 (36.8)	16.8 ± 5.9 (35.1)	
	Renal clearance (parent (g)/AUC) (L/h)	6.46 ± 1.04 (16.1)	6.01 ± 1.01 (16.8)	6.21 ± 1.17 (18.8)	6.07 ± 0.98 (16.1)	
Simvastatin	T_{max} (h)	1.94 ± 1.36 (70.1)	2.00 ± 1.32 (66.0)	1.81 ± 1.35 (74.6)	1.55 ± 1.10 (71.0)	C_{max}: $P = 0.0004$*
	$T_{1/2}$ (h)	4.4 ± 2.0 (45.5)	5.7 ± 3.4 (59.6)	5.1 ± 3.5 (68.6)	6.3 ± 5.3 (84.1)	AUC_{inf}: $P = 0.0328$*
	C_{max} (ng/mL)	2.24 ± 1.46 (65.2)	3.33 ± 2.11 (63.4)	3.70 ± 1.94 (52.4)**	4.26 ± 2.76 (64.8)**	
	AUC_{72} (h*μg/mL)	9.4 ± 5.7 (60.6)	13.0 ± 6.8 (52.3)	13.2 ± 9.1 (68.9)	14.6 ± 8.2 (56.2)**	
	AUC_{inf} (h*μg/mL)	10.3 ± 6.3 (61.2)	14.3 ± 7.4 (51.7)	15.2 ± 14.1 (92.8)	16.9 ± 11.0 (65.1)**	
	CL/F (mL/h)	2,708 ± 1,632 (60.3)	1,548 ± 727 (47.0)**	2,138 ± 1,453 (68.0)	1,886 ± 1,667 (88.4)**	
	MRT (h)	4.88 ± 2.03 (41.6)	5.41 ± 2.39 (44.2)	4.85 ± 2.37 (48.9)	5.08 ± 2.47 (48.6)	
Simvastatin acid	T_{max} (h)	4.30 ± 0.97 (22.6)	5.55 ± 2.02 (36.4)	4.28 ± 0.96 (15.4)	4.62 ± 1.60 (35.1)	C_{max}: $P = 0.0002$*
	$T_{1/2}$ (h)	5.2 ± 2.0 (47.6)	6.3 ± 3.9 (61.9)	5.8 ± 3.9 (67.2)	7.8 ± 4.5 (57.7)	AUC_{inf}: $P = 0.3215$
	C_{max} (ng/mL)	1.44 ± 0.78 (54.2)	1.16 ± 0.63 (54.3)	1.77 ± 0.96 (54.2)	1.09 ± 0.51 (46.8)	
	AUC_{72} (h*μg/mL)	11.1 ± 5.6 (50.5)	11.7 ± 6.4 (54.7)	13.4 ± 6.6 (49.3)	10.2 ± 6.3 (61.8)	
	AUC_{inf} (h*μg/mL)	12.5 ± 6.0 (48.0)	13.6 ± 6.9 (50.7)	15.7 ± 9.1 (58.0)	13.2 ± 9.8 (74.2)	
	CL/F (mL/h)	2,006 ± 993 (49.5)	1,687 ± 1,012 (60.0)	1,623 ± 806 (49.7)	2,078 ± 1,156 (55.6)	
	MRT (h)	7.21 ± 1.71 (23.7)	8.78 ± 1.89 (21.5)	7.37 ± 1.79 (24.3)	8.05 ± 2.14 (26.6)	
Meloxicam	T_{max} (h)	4.0 ± 1.0 (25.0)	4.1 ± 0.9 (22.0)	3.9 ± 1.1 (28.2)	3.7 ± 0.6 (16.2)	C_{max}: $P = 0.0529$
	$T_{1/2}$ (h)	19.7 ± 7.1 (36.0)	19.7 ± 5.5 (27.9)	19.8 ± 4.8 (24.2)	25.8 ± 8.9 (34.5)	AUC_{inf}: $P = 0.0003$*
	C_{max} (ng/mL)	748.3 ± 131.8 (17.6)	689.7 ± 115.6 (16.8)	779.2 ± 130.7 (16.8)	785.3 ± 196.4 (25.0)	
	AUC_{72} (h*μg/mL)	17.4 ± 3.4 (19.5)	18.3 ± 3.8 (20.8)	17.9 ± 3.2 (17.9)	21.8 ± 6.5 (29.8)**	
	AUC_{inf} (h*μg/mL)	19.6 ± 6.0 (30.6)	20.4 ± 5.2 (25.5)	19.9 ± 4.5 (22.6)	27.0 ± 11.8 (43.7)**	
	CL/F (mL/h)	409.1 ± 96.0 (23.5)	391.7 ± 101.7 (26.0)	393.9 ± 80.3 (20.4)	317.1 ± 102.9 (32.5)**	
	MRT_{72} (h)	22.6 ± 3.1 (13.7)	23.9 ± 3.1 (13.0)	22.9 ± 2.6 (11.4)	25.5 ± 2.8 (11.0)	

The number of Japanese, Chinese, and Caucasian subjects was 20 each in the moxifloxacin study and there were 19 Korean subjects. There were 40 subjects for each population in the simvastatin study, while there were 30 Japanese, Chinese and Caucasians each and 29 Koreans in the meloxicam study. *Significant difference ($p < 0.05$) among four ethnic groups by ANOVA (analysis of variance). **Significant difference ($p < 0.05$) vs. Japanese by Dunnett's test.

Meloxicam study

Thirty subjects were enrolled from each ethnic group, apart from the Korean arm of the study which had only 29 subjects. BW and BMI were significantly different between the Japanese and Caucasian subjects (Table 1). Figure 1 (E) shows the plasma profile of meloxicam in each ethnic group, while Table 3 and Figure 2 (I, J) list the PK parameters adjusted by BW. There was a significant difference in AUC_{inf} among the

four ethnic groups by ANOVA ($P = 0.0003$), but Dunnett's test only showed a difference between Japanese and Caucasians ($P = 0.0006$). C_{max} did not differ among the ethnic groups according to ANOVA ($P = 0.0529$), although there have been previous reports of marked ethnic differences [31–33]. We also investigated the genotype of *CYP2C9*, the enzyme responsible for inactivation of meloxicam (Table 2). As reported previously [6], the frequency of **2* heterozygotes was higher in Caucasians than East Asians. However, the frequency of **3* heterozygotes was similar among the four ethnic groups in this study, even though it was previously reported to be higher in Caucasians. When differences among three genotypes (wild-type (**1/*1*), *1/*2*, and **1/*3*) were analyzed by ANOVA, there was no significant difference in C_{max} ($P = 0.1785$), but there was a difference in AUC_{inf} ($P < 0.0001$). A difference in AUC_{inf} between **1/*1* and **1/*3* was also revealed by Dunnett's test ($P < 0.0001$). *CYP2C9***2/*2* showed higher AUC_{inf} than the wild-type although there was only one carrier of **2/*2*. Concerning safety, 23 AEs were reported in 18 subjects, and eight events were related to the study drug (uric acid increased, white blood cell count decreased, and haemoglobin decreased in one Chinese subject each; maculopapular rash, systemic skin rash, and irritating rash in one Korean subject each; and skin pruritus in two Korean subjects). All of these events were mild.

In all three studies, no major ethnic differences in PK parameters were detected, even though there were some statistical differences in the parameters.

Discussion

Moxifloxacin is a new quinolone [34] for which PK studies have been conducted in several regions [35, 36] and large differences in PK parameters have been reported between Japanese and Chinese or German subjects. In the present study, the mean AUC_{inf} and C_{max} of the parent compound showed significant differences among East Asian groups by ANOVA, but there was only a difference between Japanese and Koreans by Dunnett's test. The reason for this difference between Japanese and Koreans is not clear. As there was no difference between Chinese and Japanese subjects, extrinsic factors that were not controlled in this study, such as capsaicin or other spices, may have been responsible [37]. The differences in the urine excretion rate and renal clearance of moxifloxacin between Chinese and Japanese subjects might also have been caused by unknown extrinsic factors. The AUC_{inf} of M2 was larger in Caucasians than in the three East Asian populations, and this finding was considered to be related to a difference in the frequency of the *UGT1A1*6* genotype. Concerning the **28/*28* population, only one Chinese subject and one Caucasian subject had this polymorphism. Theoretically, they should have had higher AUC values of M2, but the AUC_{inf} and C_{max} values of both subjects were within the range for the **1/*28* population. Since the **28/*28* population was very small, data for the **28/*28* and **1/*28* populations are combined in Figure 3 (A). These results indicate that variations in the genotypes of metabolizing enzymes could potentially lead to ethnic differences in PK parameters for specific metabolites. However, the effect was not strong enough to significantly reduce clearance of the parent compound in our study of moxifloxacin.

There have been many reports of large ethnic differences between Asians and Caucasians in the PK parameters of statins [38, 39]. Accordingly, we investigated simvastatin, as its maximum approved dose in the USA is four times higher than in Japan (package insert data), and the doses approved in China and Korea are also different from Japan. Our study identified differences in the C_{max} of simvastatin between Japanese and Koreans, as well as between Japanese and Caucasians, but there were no differences in AUC_{inf} values among the East Asian groups. Even though the frequency of *SLCO1B1* genotypes differed, the AUC_{inf} of simvastatin acid was not significantly different among the four ethnic groups. Several other genetic factors have been reported to affect the AUC of simvastatin, including SLCO1B3, MRP2 and BCRP transporters [39, 40], but SLCO1B1 has the strongest influence on statin metabolism. Even though there were some differences in *SLCO1B1* polymorphism among the four ethnic groups in the present study, these differences were not as large as those reported previously [6]. This discrepancy may have been caused by the lower frequency of *SLCO1B1 521C* in our Caucasian population, which minimized the difference between Caucasians and Asians.

Meloxicam is a nonsteroidal anti-inflammatory drug that is metabolized to its inactive form by CYP2C9. Therefore, it could be expected that the AUC of meloxicam would be larger in Caucasians than East Asians as the frequency of both *CYP2C9*2* and **3* is higher in the general Caucasian population [6]. On the other hand, there have been reports that the AUC of meloxicam was higher in Chinese than in Japanese and Caucasians [24–26]. Accordingly, we also chose this drug to examine ethnic differences among East Asian populations. While we found no significant difference in C_{max} among the four ethnic populations, AUC_{inf} showed a difference between Japanese and Caucasians. With regard to *CYP2C9* genotype, the **1/*3* and the **2/*2* reduce CYP2C9 activity markedly and were associated with a larger AUC_{inf} of meloxicam, whereas the **1/*2* causes less reduction of CYP2C9 activity. In the present study, the prevalence of the **3* allele was similar among the four populations, but the **2/*2* genotype carrier was involved in Caucasians, and this may help to explain the difference in AUC values between Japanese and Caucasians.

There were some differences in BW-adjusted PK parameters, especially for moxifloxacin. In all three studies, the Japanese subjects were smaller than those in the other ethnic groups, but BW-adjusted data also showed differences. We controlled the study conditions as tightly as possible, especially for possible extrinsic factors, so these differences might have been diminished if the number of subjects had been larger. The reasons for the differences revealed by our PK studies are not clear. There have been some reports about inter-individual and intra-individual variability or inter-occasion variability [41, 42], and the present results may reflect such variability due to the influence of unknown intrinsic or extrinsic factors.

Concerning the reasons for the discrepancies between our present results and previous reports, we can suggest the following possibilities. First, the previous studies were rather small and the genetic profile of the subjects was quite different. In this

context, Oishi *et al*. have stated that reported differences in the PK parameters of tolterodine that were found in small-scale Japanese and Korean studies are responsible for misperceptions about ethnic differences [19]. Second, various extrinsic factors (such as the diet, mineral content of water, drug lot, etc.) have been suggested as potential causes of differences in PK parameters, and controlling such factors could be important for reducing apparent differences. In particular, food intake is known to influence the gastric emptying time of drugs and foods may contain ingredients that affect gut metabolizing enzymes/transporters, so that drug–food interactions in the gastrointestinal tract might influence PK [43, 44]. Moreover, we controlled the nutrients and calories of each meal, but not the menu, allowing the study sites to provide meals appropriate to each ethnic group. Third, other factors such as the sources or dosages of drugs, the drug batches, analytical techniques and timing of PK sample collection might have differed among the studies in the drug archive. Since most of the data were obtained from the literature or internal reports of companies, we could not perform precise comparison between archival data and our results. Early phase global studies are usually performed by matching the conditions of the subjects to some extent. If the diet and other extrinsic factors were more strictly controlled, so-called ethnic differences might be reduced. Extrinsic impacts could be minimized and true ethnic differences could be better characterized if extrinsic factors were more strictly controlled in future studies.

This present study was only conducted on male subjects and gender differences in PK parameters have been reported for some drugs [45], so different results may have been obtained in women. However, most drugs have a similar PK profile in both genders, so we think that our results can be extrapolated to other drugs, including drugs under development.

In conclusion, the present studies of moxifloxacin, simvastatin and meloxicam showed no major differences in PK parameters among male subjects from three East Asian populations and Caucasians when extrinsic factors were strictly controlled, and our findings also indicated that pharmacogenetic variations made an important contribution to the residual differences observed. Our findings suggest that drug development could be accomplished more efficiently if clinical trials are performed under appropriately controlled conditions.

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Conflict of Interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; S.K. has received research grants from Mitsubishi-Tanabe Pharma Co. and lecture fees from Eisai Co., Ltd. in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

T.H., I-J.J., C.Y. and M.K. performed the clinical studies as primary investigators at each institution. M.To., N.K. and Y. S. performed genetic analysis, M.Ta. performed statistical analysis, and T.H., M.To., H.W. and Y.Y. contributed to the design of these clinical studies. T.H., M.To. and S.K. were mainly involved in writing the manuscript. All authors edited and commented on the manuscript. S.K. conceived, designed, and supervised the studies.

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