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Original Article

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Exploration of pharmacokinetic differences between East Asians and Caucasians: insights from pharmacokinetic studies in healthy subjects

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ABSTRACT

Interethnic differences in the pharmacokinetics of drugs result from a complex interplay of environmental, genetic, and demographic factors. Identifying ethnic differences in pharmacokinetics is challenging due to the multifaceted contributions of the underlying factors. To address these challenges, this paper reviews 9 pharmacokinetic studies meeting the following criteria: (A) Conducted at Seoul National University Hospital from 2013 to 2022 as a single-center study. (B) Pharmacokinetic studies involving both East Asians (Korean, Japanese, or Chinese) and Caucasians. (C) Study drugs were administered orally. (D) Raw data was provided for reanalysis. This retrospective analysis aimed to investigate the existence of ethnic differences in drug exposure and understand the possible factors contributing to these variabilities. Pharmacokinetic, demographic, and clinical laboratory test data were analyzed to assess potential pharmacokinetic differences between East Asians and Caucasians. This assessment involved calculating the geometric mean ratio of dose-normalized area under the time-concentration curve (AUC) and dose- and weight-normalized AUC, along with their 90% confidence intervals. Additionally, pharmacological information, including metabolic pathways, was gathered from the investigational brochure or the respective country's drug label. Among 9 studies, 4 studies demonstrated approximately 1.3 to 1.8 times higher drug exposure in East Asians compared to Caucasians. These drugs were primarily eliminated through hepatic metabolism, with less than 5% excreted unchanged in the urine. Two drugs were metabolized by hepatic cytochrome P450 3A4, one by glutathione S-transferase, and specific metabolic pathways for another drug were not identified. Further research is needed to assess the causes of ethnic variability in these drugs.

Keywords: Ethnicity; Pharmacokinetic Genetic Variants; Race Factors

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Conflict of Interest
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- Reviewers: Nothing to declare
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INTRODUCTION

Ethnicity is one of the crucial variables that contribute to the interindividual variability in the pharmacokinetics of drugs, and this variability can result in a lack of efficacy or adverse reactions [1]. To address this issue, the International Conference on Harmonization (ICH) published a guidance, "Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data," in 1998 to facilitate evaluating the impact of ethnic factors on drugs' pharmacokinetics, pharmacodynamics, as well as its efficacy and safety at a particular dosage regimen.

The ICH guidance lists extrinsic and intrinsic ethnic factors that can affect the pharmacokinetics and pharmacodynamics of drugs. Extrinsic factors refer to elements associated with the environment and culture of a specific region, such as medical practice, exposure to pollution, socio-economic status, and compliance with prescribed medications. Intrinsic factors are those related to an individual's physiological characteristics, including genetic polymorphism, age, gender, body weight, and organ dysfunction. Smoking, alcohol use, and dietary habits are examples that fall into both extrinsic and intrinsic factors [2].

Understanding pharmacokinetic variability among ethnicities becomes critical, particularly when drugs show non-linear pharmacokinetics, steep dose response curves, a narrow therapeutic dose range, are metabolized through a single pathway, or are metabolized by enzymes with genetic polymorphisms [2]. A comprehensive pharmacokinetic comparison among ethnic populations can provide valuable insights to determine the need for further pharmacodynamic and clinical evaluations. However, identifying ethnic differences in pharmacokinetics is challenging due to the multifaceted contribution of various extrinsic and intrinsic factors, further complicated by their mutual influence [1,3,4]. There is a significant challenge in quantifying their impact on pharmacokinetics and discerning their subsequent influence on drug response.

Research that considers all ethnic factors and quantifies their impact is limited because it requires large and diverse populations. To overcome this limitation, this paper reviews pharmacokinetic data from clinical studies conducted on East Asians (Chinese, Koreans, and Japanese) and Caucasians. These studies were conducted on healthy subjects at a single center, and multiple methods were implemented to provide a more controlled environment. With these data, we investigated differences in drug exposure between East Asians and Caucasians, focusing on understanding the possible factors contributing to these variabilities.

METHODS

Study selection

This retrospective analysis included the studies meeting the following criteria:
(A) Conducted at Seoul National University Hospital from 2013 to 2022 as a single-center study. (B) Pharmacokinetic studies involving both East Asians (Korean, Japanese, or Chinese) and Caucasians. (C) Study drugs were administered orally. (D) Raw data was provided for reanalysis.

All studies were conducted in accordance with the Good Clinical Practice Guidelines and the principles outlined in the Declaration of Helsinki. Informed consent was waived for this study by the Institutional Review Board of the Seoul National University Hospital (Seoul, Korea) due to the retrospective nature of this research.

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Ways to control confounding factors

The subjects included in each study were restricted to individuals with specific characteristics, aiming to control for intrinsic factors affecting the pharmacokinetics of the study drugs. East Asians are defined as individuals who were born in East Asia, have lived outside of East Asia for less than 10 years, and have parents and grandparents of East Asian origin. Caucasians are individuals who were born in Europe, have lived outside of Europe for less than 10 years, and have parents and grandparents of European origin. Subjects aged between 19 and 50 years with a body mass index ranging from 18.0 to 30.0 kg/m^2 were able to participate in the studies. Previous medical history, physical examination, vital signs, 12-lead electrocardiography, and clinical laboratory tests such as hematology, blood chemistry, urinalysis, and serology (negative for hepatitis B surface antigen, anti-hepatitis C virus antibody, human immunodeficiency virus serology, and syphilis rapid plasma reagin test) were comprehensively evaluated. Subjects with abnormal results or clinically relevant concomitant diseases were excluded from the studies.

Restrictions on concomitant medication, food, and activity were also implemented to control extrinsic factors affecting the pharmacokinetics of the study drugs. Generally, the use of concomitant medications, herbal medication, and health supplements was not allowed. In cases of adverse events requiring treatment, concomitant medication was allowed after assessing the possibility of interactions with the study drug. Alcohol, caffeine, and grapefruit-containing foods and drinks were prohibited 72 hours before entering the study and throughout the study period. Excessive smoking (more than 10 cigarettes/day) and alcohol consumption (more than 30 g/day) were prohibited until the study ended. During the study period, subjects were restricted from consuming any foods or drinks not provided by the study site. Subjects were instructed to fast overnight for at least 10 hours before the scheduled dosing time. The drugs were administered with a specified volume of water (150 mL or 240 mL). After administration of the study drug, standardized meals were provided at a predetermined time (4 and 10 hours after drug administration). Subjects were directed to maintain an upright posture of at least 45 degrees for 4 hours following drug administration. Excessive physical activity, such as competitive sports, was to be avoided during the study.

Data for analysis

The area under the time-concentration curve (AUC) extrapolated to infinity (AUC_{inf}), the maximum concentration (C_{max}), and the terminal half-life following a single administration were extracted for each study. For study drugs administered multiple times, AUC within a dosing interval (AUC_{tau}), C_{max}, and the terminal half-life at steady state were also retrieved. AUC was calculated by the linear-up/log-down trapezoidal method. If a study included various dose groups, the dose groups that received the exact dosage for both ethnicities were selected for analysis. Demographic data, including sex, age, body weight, and height, were collected alongside clinical laboratory test results, including alanine transaminase (ALT), aspartate transaminase (AST), creatinine, and estimated glomerular filtration rate (eGFR). Data retrieval was restricted to subjects who completed the study without major deviations that could impact the pharmacokinetic results. Pharmacological information for each study drug was obtained from the investigational brochure, and for authorized drugs, the respective country's drug label was also used.

Comparison between ethnicities

Dose-normalized AUC (AUC_{dose}) was calculated by dividing the AUC (AUC_{inf} following a single administration and AUC_{tau} following multiple administrations) by the administered dose (mg).

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Dose- and weight-normalized AUC ($AUC_{dose,bwt}$) was calculated by dividing the AUC by the dose (mg) normalized with the subject's body weight (kg).

$$AUC_{dose} = \frac{AUC}{Dose}$$

$$AUC_{dose,bwt} = \frac{AUC}{Dose/Body\ Weight}$$

In studies with 2 dose groups, AUC_{dose} and $AUC_{dose,bwt}$ in each ethnicity were combined for reanalysis if the independent *t*-test or Mann-Whitney test showed no significant difference among the dose groups in each ethnicity. In studies with more than 2 dose groups, the dose proportionality of AUC in each ethnicity was evaluated by regression analysis using the power model. When dose proportionality in AUC was confirmed, AUC_{dose} and $AUC_{dose,bwt}$ of all dose groups were combined in each ethnicity for reanalysis. Otherwise, the data was separately analyzed for each dose group. A generalized linear model (ethnicity as a fixed effect) was used to estimate the effect of ethnicity on the AUC_{dose} and $AUC_{dose,bwt.}$ The geometric mean ratio (GMR) of East Asians to Caucasians, along with its 90% confidence interval (CI), was calculated. Ethnic difference in pharmacokinetics was concluded if the 90% CI of the GMR did not include 1. Other pharmacokinetic parameters were compared between ethnicities using arithmetic mean values by each dose group.

Demographic data (sex, age, height, and body weight) and baseline clinical laboratory results (ALT, AST, creatinine, and eGFR) of East Asians and Caucasians were separately summarized using descriptive statistics, including the arithmetic mean and standard deviation. Independent *t*-tests or Mann-Whitney tests were used to evaluate differences in demographics between the 2 ethnicities. For all analyses, statistical significance was determined at a 2-sided *p*-value of less than 0.05. SAS® software version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

RESULTS

Selected study for analysis

A total of 9 studies meeting the study selection criteria were included in the analysis (**Fig. 1**). Pharmacokinetic, demographic, clinical laboratory test data, and pharmacologic characteristics of the study drugs were reanalyzed (**Table 1**, **Supplementary Table 1**). While some clinical

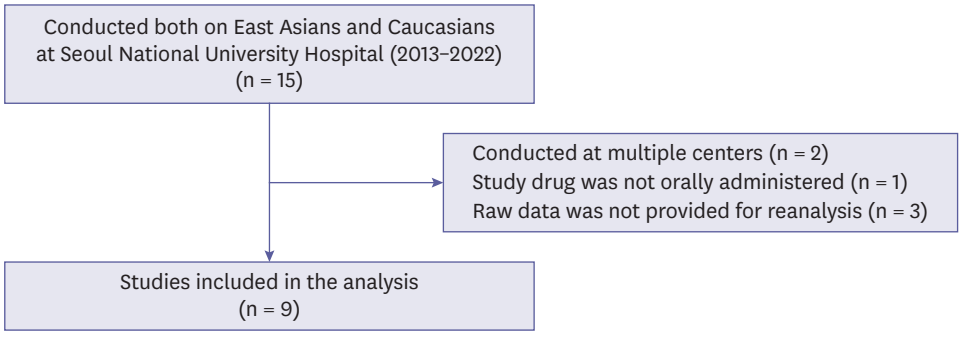

Figure 1. Flow chart of study selection.

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Table 1. The pharmacological information of study drugs and the number of subjects analyzed

Study No.	Mechanism of action	f_e (%)	Metabolic pathway	Dose (mg)	No. of subjects	
					East Asians	Caucasians
1	Potassium-competitive acid blocker	4.1	CYP3A4	50	6	8
				75	6	8
				100	6	8
2	Sodium-glucose cotransporter-2 inhibitor	< 2	CYP3A4	0.3	22	8
3	Persistent or late inward sodium current (I_{Na}) inhibitor	5–6	CYP3A4	375	23	24
				750	24	24
4	Poly ADP ribose polymerase inhibitor	36–76	CYP3A4	80	24	12
5	Voltage-gated sodium channel blocker	61.8	UGT	400	8	8
				1,600	8	8
6	Epidermal growth factor receptor tyrosine kinase inhibitor	< 5*	GST	240	12	12
7	Epidermal growth factor receptor tyrosine kinase inhibitor	< 0.3	GST	200	16	8
				300	16	8
8	Isoflavane	< 5*	Hydroxylation, Oxidation	480	7	8
9	Uric acid transporter 1 inhibitor	< 0.3	Glucuronidation, Sulfation	1	6	6
				3	6	6
				10	5	6

f_e, fraction excreted unchanged in the urine; CYP3A4, cytochrome P450 3A4; UGT, uridine 5'-diphospho-glucuronosyltransferase; GST, glutathione S-transferase.
*Data from ^{14}C radio-labeled study in rat.

laboratory test values differed statistically between ethnicities, the absolute values remained within the normal range without significant implications.

Among studies with 2 dose groups (Study No. 3, No. 5, and No. 7), there were no statistically significant differences in AUC_{dose} and $AUC_{dose,bwt}$ between dose groups for both ethnicities in Study No. 3 and No. 7. However, significant differences were noted in Study No. 5. Consequently, AUC_{dose} and $AUC_{dose,bwt}$ were combined for reanalysis across the dose groups in Study No. 3 and No. 7, while they were analyzed separately for each dose group in Study No. 5. In studies with 3 dose groups (Study No. 1 and No. 9), AUC_{dose} and $AUC_{dose,bwt}$ were combined for reanalysis across the dose groups, as dose proportionality was confirmed for both East Asians and Caucasians (**Supplementary Tables 2** and **3**).

Pharmacokinetics

Among the 9 studies meeting the study selection criteria, 4 studies (Study No. 1, No. 2, No. 6, and No. 8) showed ethnic differences in pharmacokinetics after a single administration. Notably, all 4 studies showed higher drug exposure in East Asians compared to Caucasians. After a single administration, the GMR of AUC_{dose} for these study drugs ranged from 1.3223 to 1.8369 (**Fig. 2A**, **Supplementary Table 4**), and the GMR of $AUC_{dose,bwt}$ ranged from 1.3186 to 1.7738 (**Fig. 2B**, **Supplementary Table 4**). Among 3 studies involving multiple administrations, AUC_{dose} was higher in East Asians compared to Caucasians in Study No. 3 and No. 8 (**Fig. 3A**, **Supplementary Table 5**). As there were differences in demographics between ethnicities in Study No. 3 (**Supplementary Table 1**), the difference in $AUC_{dose,bwt}$ after multiple administrations was observed only in Study No. 8 (**Fig. 3B**, **Supplementary Table 5**).

All 4 study drugs that showed pharmacokinetic differences between East Asians and Caucasians were primarily eliminated through hepatic metabolism, with less than 5% excreted unchanged in the urine. Two of them were metabolized by hepatic cytochrome P450 (CYP) 3A4, one by glutathione S-transferase (GST), and the specific metabolic pathways for the remaining one were not identified (**Table 1**).

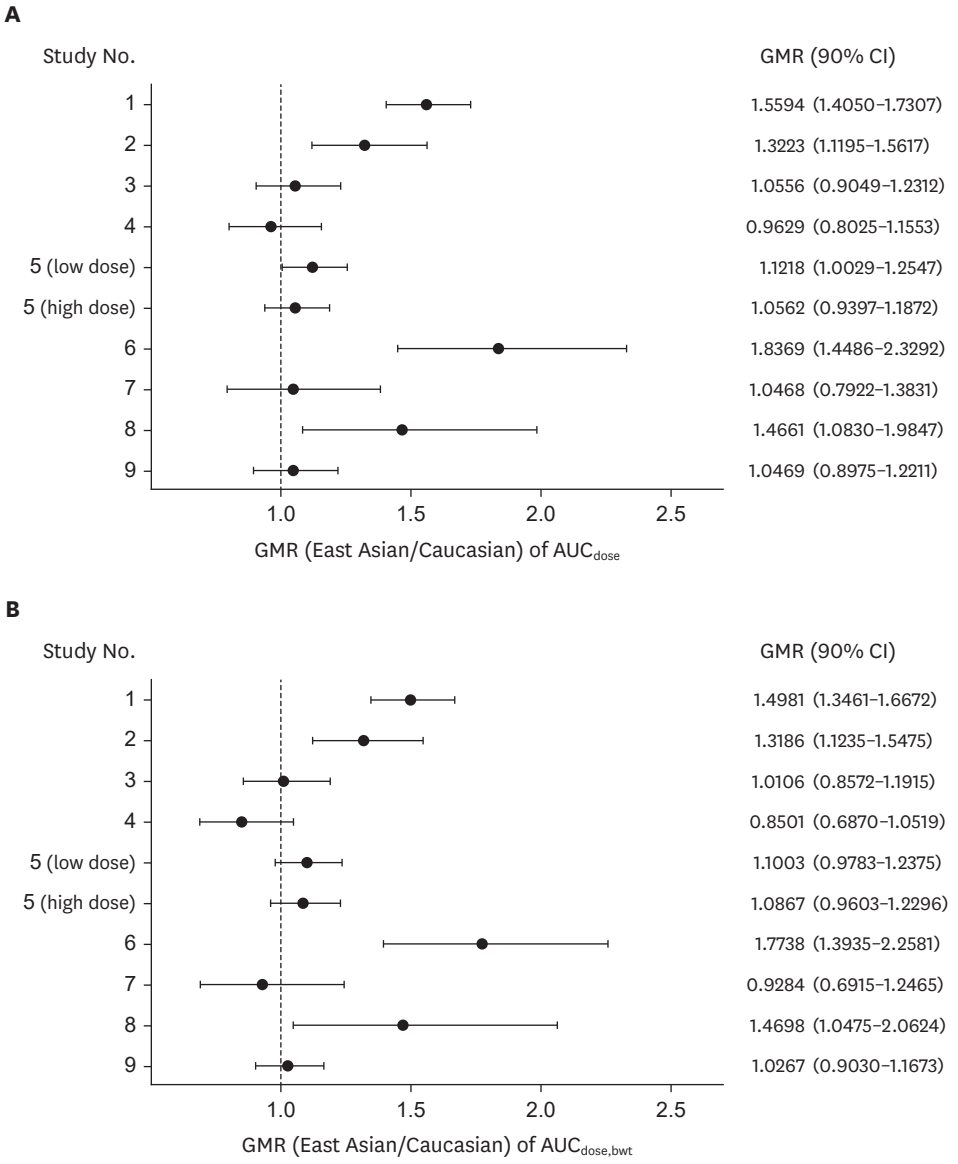

Figure 2. GMR of (A) AUC_{dose} and (B) $AUC_{dose,bwt}$ following a single administration. Circle (●) and error bars denote point estimates of GMR (reference: Caucasian) and 90% CIs, respectively.
GMR, geometric mean ratio; CI, confidence interval; AUC_{dose}, dose-normalized area under the time-concentration curve; $AUC_{dose,bwt}$, dose- and weight-normalized area under the time-concentration curve.

DISCUSSION

Interethnic variability in drug pharmacokinetics can significantly affect its efficacy and safety. However, identifying ethnic differences can be challenging, as they are highly responsive to non-genetic factors, such as environmental, socio-economic, and demographic factors [1,3,4]. A retrospective analysis of pharmacokinetic data from healthy subjects in clinical studies conducted at a single center can provide valuable insight into the existence of ethnic differences in drug exposure since these data are less affected by confounding factors.

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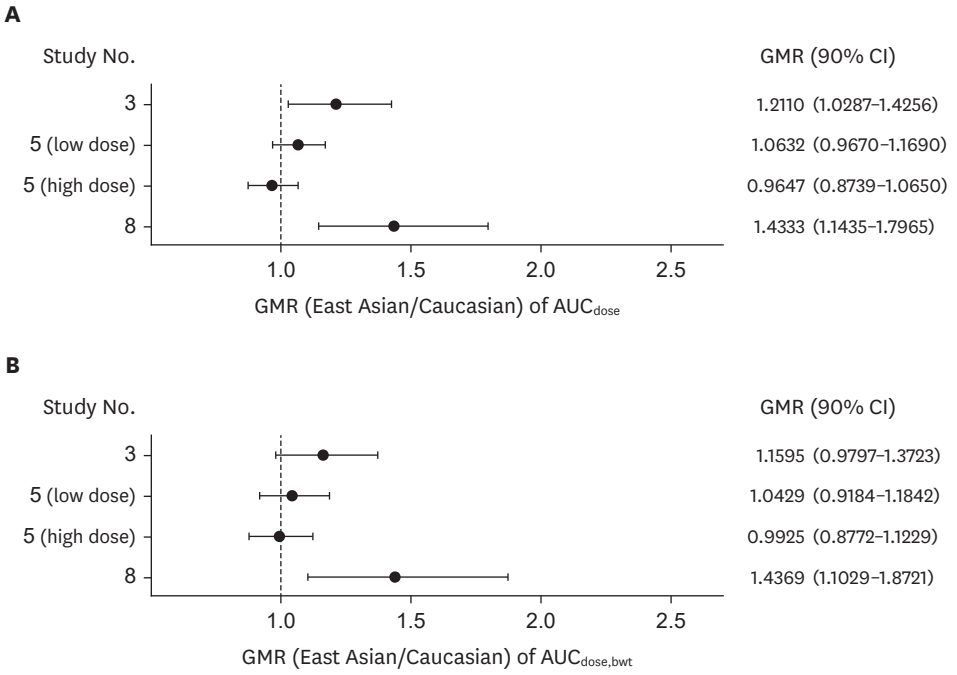

Figure 3. GMR of (A) AUC_{dose} and (B) $AUC_{dose,bwt}$ following multiple administrations. Circle (●) and error bars denote point estimates of GMR (reference: Caucasian) and 90% CIs, respectively.
GMR, geometric mean ratio; CI, confidence interval; AUC_{dose}, dose-normalized area under the time-concentration curve; $AUC_{dose,bwt}$, dose- and weight-normalized area under the time-concentration curve.

This analysis examined variability in drug exposure among East Asians (Korean, Japanese, or Chinese) and Caucasians in 9 clinical studies. AUC was selected as the primary parameter as it reflects overall drug exposure. The GMR and its 90% CI for AUC adjusted for dose (AUC_{dose}) was compared between the 2 ethnicities, and AUC adjusted for both dose and body weight ($AUC_{dose,bwt}$) was also compared to compensate for the differences in body size. Among the 9 studies, 4 showed ethnic differences in drug exposure, all showing higher drug exposure in East Asians compared to Caucasians. Notably, these study drugs were primarily eliminated through hepatic metabolism, with less than 5% excreted unchanged in the urine. In contrast, the study drugs that were predominantly eliminated through urine excretion (Study No. 5) or showed high interindividual variability in urine excretion (Study No. 4) showed no difference in drug exposure between the 2 ethnicities.

The most significant factor contributing to ethnic variabilities in drug exposure is a difference in drug metabolism, and genetic polymorphisms in drug-metabolizing enzymes contribute to 15–30% of this variability [1]. Given that other potential confounding factors were controlled in these studies, genetic polymorphisms of drug-metabolizing enzymes may have contributed to the observed ethnic differences.

In Study No. 1, the study drug was a potassium-competitive acid blocker (P-CAB) and showed 1.6 times higher drug exposure in East Asians compared to Caucasians. Interestingly, vonoprazan, another P-CAB, did not show ethnic differences in drug exposure between Japanese and Caucasians [5,6]. While the study drug is primarily metabolized by CYP3A4, vonoprazan is metabolized by multiple CYP enzymes, including CYP3A4, CYP2D6, CYP2C9, and CYP2C19, as well as sulfotransferase 2A1 [7]. This multi-enzyme metabolism may be the reason why vonoprazan is less susceptible to ethnic differences.

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The drug of Study No. 2 was sodium-glucose cotransporter (SGLT)-2 inhibitor and mainly metabolized by CYP3A4, sharing similar metabolic trait with Study No. 1. It also showed 1.3 times higher drug exposure in East Asians compared to Caucasians. The effect of ethnicity on the clearance of other SGLT-2 inhibitors, such as dapagliflozin, ertugliflozin, and canagliflozin, was observed [8-10], although the observed differences were not clinically significant. These drugs are predominantly eliminated through uridine diphosphate-glucuronosyltransferases (UGT)1A9 metabolism with the fraction excreted unchanged in the urine less than 5%, and individuals carrying UGT1A9*3 variant showed higher drug exposure in ertugliflozin and canagliflozin compared to those with the normal variant [10,11].

The impact of ethnicity on the pharmacokinetics of epidermal growth factor receptor tyrosine kinase inhibitors has produced inconsistent results in Study No. 6 and Study No. 7. In Study No. 6, East Asians exhibited a 1.8-fold higher drug exposure compared to Caucasians. In contrast, in Study No. 7, East Asians and Caucasians had comparable drug exposure. This inconsistency could have been affected by the GST genotype, the main metabolic enzyme of the study drugs (**Table 1**). GST polymorphism is known to be one of the reasons for high inter-individual variability in pharmacokinetics, clinical efficacy, and toxicity of drugs primarily eliminated through GST metabolism, such as busulfan [12,13]. Additionally, some research showed that the distribution of GST genotypes varies among different ethnic groups [14]. The GSTM1-null genotype (GSTM1 *0/*0) has similar frequencies in East Asians (0.521) and Europeans (0.51–0.53). For the GSTT1-null genotype (GSTT1 *0/*0), the gene frequency in East Asians is 0.476 and 0.17–0.19 in Europeans, suggesting a higher probability of loss of GST function in East Asians [15]. Considering these genomic influences, further investigation on pharmacogenomics seems necessary for Study No. 6 and Study No.7.

In Study No. 8, East Asians exhibited approximately 1.4 times higher drug exposure compared to Caucasians. The specific metabolic pathway of the study drug remains unidentified, although oxidation and hydroxylation are its main metabolic processes, potentially involving CYP enzymes. Further efforts are needed to identify metabolic processes and other possible factors that make ethnic differences.

CYP3A4 is quantitatively the most important CYP enzyme, contributing to the pre-systemic and systemic metabolism of up to 30% of all drugs [16]. While it has long been believed to be highly conserved due to its importance in processing both exogenous and endogenous substances [17], recent research has unveiled genetic diversity within the CYP3A4 gene. Most genetic variability seen in CYP3A4 arises from single nucleotide polymorphisms (SNPs) [18]. Only a limited number of SNPs are known to influence CYP3A4 enzyme expression or function, unlike other polymorphic CYP enzymes such as CYP2D6, CYP2C9, or CYP2C19 [19]. About 100 alleles of CYP3A4 have been discovered, but fewer than 40 of them are exonic SNPs that modify protein sequences [20]. So far, the most relevant CYP3A4 variant in explaining its activity appears to be the CYP3A4*22 (rs35599367 C > T) variant [19]. This variant is associated with a reduction of up to 50% in messenger ribonucleic acid expression and subsequent enzyme activity. It occurs with a minor allele frequency of 5–8% in Caucasians, but it is notably rare among East Asians, nearby absent at approximately 0% [19,21,22]. Interestingly, however, our study observed a tendency for higher drug exposure among East Asians compared to Caucasians, indicating lower clearance rates in East Asians. This finding contradicts the distribution of the CYP3A4*22 variants among ethnicities, necessitating further analysis to understand the factors contributing to this discrepancy.

This study has several limitations. Since the study drugs were administered orally, active transporters, including efflux by P-gp, which are highly likely to show ethnic differences in bioavailability, might have acted as confounding factors [23]. Second, the metabolic pathways and the proportion of each metabolic pathway were not fully identified for some study drugs. Finally, genotyping for previously known polymorphisms was not done.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Summary of demographics

Supplementary Table 2
Pharmacokinetic parameters following a single administration of study drugs

Supplementary Table 3
Pharmacokinetic parameters following multiple administrations of study drugs

Supplementary Table 4
Geometric mean for dose-normalized and dose- and weight-normalized pharmacokinetic parameters following a single administration of study drugs

Supplementary Table 5
Geometric mean for dose-normalized and dose- and weight-normalized pharmacokinetic parameters following multiple administrations of study drugs

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