Possible interethnic differences in quinidine-induced QT prolongation between healthy Caucasian and Korean subjects

Jae-Gook Shin,^{1,4} Won-ku Kang,¹ Ji-Hong Shon,¹ Million Arefayene,⁴ Young-Ran Yoon,¹ Kyung-Ah Kim,¹ Doo-Il Kim,² Dong-Soo Kim,² Kwang-Hyun Cho,³ Raymond L. Woosley⁴ & David A. Flockhart⁴

¹Department of Pharmacology and Pharmacogenomics Research Centre, Inje University College of Medicine, Department of Clinical Pharmacology, Departments of ²Internal Medicine and ³Thoracic and Cardiovascular Surgery, Inje University Busan Paik Hospital, Busan, Korea and ⁴Division of Clinical Pharmacology, Department of Medicine and Pharmacology, Georgetown University Medical Centre, Washington DC, USA

Correspondence

David A. Flockhart, MD, PhD,
Division of Clinical Pharmacology,
Indiana University School of
Medicine, Wishard Hospital, Room
7123, 1001 West 10th Street,
Indianapolis, IN 46203, USA.
Tel.: +1 317 630 8795
Fax: +1 317 630 8185
E-mail: dflockha@iupui.edu

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Aims

The aim of this study was to evaluate the pharmacokinetics and pharmacodynamics of quinidine-induced QT prolongation in healthy Caucasian and Korean subjects to investigate interethnic differences in susceptibility to drug-induced arrhythmia.

Methods

A randomized, double-blind crossover study was conducted in 24 (12 male and 12 female) Korean and 13 (seven male and six female) Caucasian subjects. After a 20 min infusion of quinidine (4 mg kg⁻¹) or saline, the serum concentration of quinidine and the QT interval corrected by Bazett's formula (QTc) were monitored. The dynamic data were analyzed by means of a population modelling approach using NONMEM.

Results

There were no statistical differences in the pharmacokinetic profiles of quinidine between ethnic groups. The QTc values in Caucasians were higher than those in Koreans at the same quinidine concentrations, especially at higher quinidine concentrations and in female subjects. According to an E_{max} model $\left(E_t = E_0 + \frac{\Delta E_{\max}[C_t]}{EC_{50} + [C_t]}\right)$, the population modelling approach revealed that E₀ (ms) was related to gender (408 + [34*(1 - Sex)]; 1 for male and 0 for female), ΔE_{max} (ms) was related to ethnicity ((136*f_{ETHN}) + C_{female}: f_{ETHN} = 1 for Koreans and 1.26 for Caucasians; C_{female} was 106 only for Caucasian females), and EC₅₀ was estimated to be 3.13 μM.

Conclusions

These results suggest that Korean subjects were less sensitive to quinidine-induced QT prolongation than Caucasian subjects, and that this trend was particularly true for females. Further population-based studies are merited to characterize more completely the ethnic differences in drug-induced QT prolongation between Asians and other ethnic groups.

Introduction

Drug-induced QT interval prolongation is known to be associated with the occurrence of the polymorphic ventricular tachycardia known as 'torsades de pointes' [1]. The prolonged QT interval occurs as an adverse reaction to some commonly used anti-arrhythmic agents as well as to various medications, including antibiotics, antihistamines, and antipsychotics [2–4]. Quinidine has been used for the treatment of ventricular and atrial arrhythmia for more than 70 years and has been clearly documented to prolong the QT interval [5]; it has been well documented that ventricular arrhythmia can develop within the first day of initiating therapy [6, 7]. Drug-induced arrhythmias are more likely to occur in patients with pre-existing QT prolongation, which may be congenital or caused by myocardial disease, starvation, alcoholism, ischaemia, left ventricular hypertrophy, or electrolyte abnormalities such as hypokalaemia or hypomagnesaemia [8, 9].

Pharmacological effects that differ between ethnic groups may be influenced by inherited genotypes in combination with a variety of environmental factors. These determinants might lead to differences in the basic pattern and/or drug-induced electrocardiographic (ECG) changes. Several investigators have addressed the differences in ECG patterns and drug-induced changes in the QT interval between Africans and Caucasians, whereas few studies have been reported in other ethnic groups, including Asian populations [10–12]. In the present study, we conducted a prospective clinical trial to investigate the differences in quinidine-induced QT prolongation between healthy Caucasian and Korean subjects. To the best of our knowledge, this is the first direct comparison of the pharmacokinetic and pharmacodynamic effects of a QT-prolonging drug between Caucasians and Asians.

Methods

Subjects

Twenty-four healthy Korean subjects (12 males and 12 females) and 13 healthy Caucasian subjects (seven males and six females) participated in this study. The subjects gave written informed consent, and the study protocol was approved by the institutional review boards at Georgetown University Medical Center in Washington DC, USA and at Busan Paik Hospital in Korea, respectively. All procedures were performed in accordance with the recommendations of the Declaration of Helsinki on biomedical research involving human subjects and with the International Conference on Harmonization of Technical Requirements for Reg-

istration of Pharmaceuticals for Human Use – Good Clinical Practice (ICH-GCP) guidelines.

There were no clinically significant abnormalities in any of the subjects' medical histories, physical or mental examinations, blood chemistries, haematological tests, or electrocardiograms. A negative result from a urine pregnancy test was required for each female subject. All female subjects had regular menstrual cycles, and none was taking oral contraceptives. Volunteers ate their usual diet but were asked to refrain from alcohol, grapefruit juice, and caffeine-containing beverages, beginning 3 weeks before and continuing through to the end of the study.

Study design

The study was designed as a randomized, double-blind crossover study with a month washout period between single-dose quinidine and placebo administration. All subjects were administered a single intravenous (i.v.) dose of quinidine gluconate (4 mg kg^{-1} of base, Eli Lilly, Indianapolis, IN, USA) or matching i.v. placebo (saline). The quinidine gluconate dose was based on the body weight of each subject, and was diluted to a total volume of 20 ml with normal saline and infused over 20 min with a Harvard infusion pump (Harvard Apparatus Inc, Holliston, MA, USA). Each subject received the infusion at 08.00 h after an overnight fast. An angiocatheter was inserted into each arm of each subject; one was used for the infusion of i.v. quinidine or placebo administration, and the other for drawing blood samples. Each subject remained in a supine position in bed for the first 4 h after receiving the dose, after which each subject ate a light standardized lunch and was allowed to walk around the study room.

Blood samples were drawn repeatedly from the arm opposite the infusion site at 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, and 55 min and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 h after the administration of quinidine or placebo. Plasma was separated and kept frozen at -20°C until analyzed. Before each blood sample was taken, a 12-lead ECG was recorded on paper and on a computer diskette with a MacVu ECG machine (Marquette Electronics, Milwaukee, WI, USA) at Georgetown University Medical Center and with a Hewlett-Packard PageWriter 200/2001 EKG recorder at Inje University Hospital using a paper speed of 50 mm s^{-1} . For the measurement of baseline QTc, ECGs were recorded three times within 10 min before the infusion of quinidine or placebo, and each subject was asked to remain supine in bed for 15 min before each ECG. All ECGs were recorded with uniformed range of heart rate, from 60 to $70 \text{ beats min}^{-1}$.

A second clinical trial using quinidine or placebo was performed with exactly the same protocol as described above, 1 month after the first study. All ECG leads were applied to the same chest and limb sites as in the first study.

For the female subjects, the study day was scheduled to be within 5 days after the cessation of menses in order to minimize any possible potential contribution of the menstrual cycle to gender differences and to ensure that subjects were not pregnant.

Quinidine assay

The plasma quinidine assay was conducted using a validated HPLC method with a modified solid-phase extraction [6]. Plasma or urine (0.5 ml) was added to a 10 ml glass tube containing an internal standard (5 ng quinine), 0.5 ml of 0.1 M NaOH, and 3 ml of methylene chloride. After vigorous stirring for 3 min on a vortex mixer, the aqueous phase was separated by centrifugation (1000 g for 10 min) and discarded. The remaining organic phase was subsequently evaporated to dryness in a vacuum centrifuge and then reconstituted with 100 ml of mobile phase. Subsequent chromatographic separation was performed on a reverse-phase column (LiChrospher RP-18, 250 × 3.9 mm, 5 µm; Merck Co. Darmstadt, Germany) with an isocratic mobile phase consisting of acetonitrile and water (9 : 1, including 0.3% triethylamine, pH 2.5). Extraction recoveries were in the range of 95.2–98.4% for quinidine. The lower limit of quantification was 50 ng ml⁻¹, and the coefficient of variation was 2.5% at the lowest quantifiable concentration.

QT interval measurement

The QT interval was estimated in Dr Flockhart's laboratory at Georgetown University Medical Center in Washington, DC, after transporting the ECG charts of all Korean subjects there. The QT interval data were obtained by a trained technician, blinded to the study protocol, using a previously described computer operator-interactive method, which was developed and has been used extensively by our study group [2, 13]. The QT interval was measured from the beginning of the Q wave to the end of the T wave. When a U wave was present, the end of the T wave was determined by drawing a tangent from the descending limb of the T wave to where it intersects the baseline. The QT interval at each time point was corrected for differences in heart rate by use of Bazett's formula [14]: QTc = QT/(RR)^{1/2}, where RR is the time in seconds between two R waves. The change in the QTc (ΔQTc) was calculated as the

difference between the QTc intervals of subjects after saline administration vs. that after quinidine.

Pharmacokinetic analysis

Pharmacokinetic parameters of individual subjects were calculated by noncompartmental analysis using the program WinNonlin® (Pharsight, Cary, NC, USA). The peak concentration (*C*_{max}) of quinidine was taken directly from the measured value. The area under the concentration-time curve (AUC(0,12 h)) was calculated using a numerical integration method and extrapolated to infinity for AUC(0, ∞). The clearance (CL) of quinidine was determined as Dose/AUC(0, ∞). The elimination rate constant (*λ*_z) was calculated from the terminal phase of the quinidine concentration-time profile. The steady state volume of distribution (*V*_{ss}) was estimated as CL/*λ*_z.

Population pharmacodynamic analysis

In the relationship between the plasma quinidine concentration and QTc, hysteresis was not generally seen in individual plots, indicating that there was no time delay between the i.v. administration of quinidine and the resultant dynamic effect. Therefore, the plasma quinidine concentration was directly associated with QTc measurements to characterize the time course of the QTc in the absence of an effect compartment. The model development was an iterative process both with regard to the underlying datasets and the selected model structures. According to the principle of parsimony, the simplest best model was selected that could fully describe the time profile of the QTc in relation to the change in plasma quinidine concentration. A linear model was not sufficient to explain the effect; instead the plasma concentration–effect (*E*_{*t*}) relationship was best explained by a hyperbolic *E*_{max} model [15], and an additional Hill factor did not improve the relationship:

$$E_t = E_0 + \frac{\Delta E_{\max} [C_t]}{EC_{50} + [C_t]}$$

where *EC*₅₀ is the plasma concentration of quinidine that corresponds to 50% of the maximum effect (Δ*E*_{max}; the maximum value of ΔQTc), *E*₀ is the QTc baseline value, and *C*_{*t*} is the measured plasma quinidine concentration at a given time *t*.

The population pharmacodynamic parameters of the mixed effect population model were also estimated using NONMEM. For estimation of the interindividual variability of all pharmacodynamic parameters, log-normal distributions of the parameter in the population were assumed.

$$E_{0j} = TV(E_0) \times \exp(\eta E_{0j})$$

$$\Delta E_{\max j} = TV(\Delta E_{\max}) \times \exp(\eta \Delta E_{\max j})$$

$$EC_{50j} = TV(EC_{50}) \times \exp(\eta EC_{50j})$$

where i and j mean the j th value in the i th individual, TV is the mean subpopulation value of parameter ('typical value'), and η is an interindividual error normally distributed around zero.

The model for the residual errors that describes the intraindividual variability was chosen after investigating various error models.

$$E_{ij} = \left(E_{0j} + \frac{\Delta E_{\max j} [C_{ij}]}{EC_{50j} + [C_{ij}]} \right) \times \exp(\epsilon_{ij})$$

where ϵ is a random variable normally distributed around zero.

Initially the data was analyzed with a simple regression model in the absence of covariates. Body weight (BWT), gender (SEX), and ethnicity (ETHN) were subsequently included in the analysis as covariates in order to investigate whether these variables could account for the substantial interindividual variation observed. For the j th element of the i th individual's parameter set (θ_{ij}), the assumed model was $\theta_{ij} = \theta_{\text{pop},j} (1 + \eta_{ij})$, where $\theta_{\text{pop},j}$ is the mean population parameter of the j th element, and η_{ij} represents the parameter shift of the i th individual from the population mean. Furthermore, η_{ij} was assumed to be independent, multivariate, and normally distributed, with a mean of 0 and a variance-covariance matrix (Ω) of diagonal elements ($\omega_{12}, \omega_{22}, \dots, \omega_{n2}$); ω_j is the coefficient of variation of the j th parameter with respect to the

typical value $\theta_{\text{pop},j}$. The intraindividual variability that describes the residual errors was expressed as the variance (σ_2) of a random effect, ϵ_{ij} , and was described by a constant coefficient of variation model. The following information was used to evaluate the goodness of fit and the quality of parameter estimates: coefficients of variation of parameter estimates (CVs), parameter correlation matrix, sums of squares of residuals, visual examination of the distribution of residuals, and the objective function value.

Statistics

Pharmacokinetic data were expressed as mean values $\pm$ SEM. Pharmacokinetic parameters and baseline of heart rate and QTc interval were analyzed using ANOVA with gender and ethnicity as sources. Statistical comparisons to test for gender and ethnic differences within the serial quinidine-induced QT prolongation effect were performed with a one-way ANOVA with repeated measurements. P values of less than 0.05 were considered statistically significant. All analyses were conducted using SAS Version 8.1 (SAS Institute, Cary, NC, USA). The likelihood ratio test was used to determine the significance of covariate changes in the nested results from the differences of covariates [16]. The effect of a single covariate was considered statistically significant when the change in the objective function was higher than 3.8 points ($P < 0.05$ on the chi-square distribution).

Results

Table 1 shows the demographic characteristics of the study population and the results of clinical laboratory

Table 1

Demographic characteristics and results of clinical laboratory in screening of subjects participated in the present study

	Korean		Caucasian	
	Male ($n = 12$)	Female ($n = 12$)	Male ($n = 7$)	Female ($n = 6$)
<i>Demography</i>				
Age (years)	22.1 $\pm$ 1.6	22.7 $\pm$ 2.4	26.2 $\pm$ 7.5	27.7 $\pm$ 3.6
Body weight (kg)	66.5 $\pm$ 7.3	53.4 $\pm$ 3.7	69.8 $\pm$ 8.8	60.7 $\pm$ 5.5
Quinidine dose (mg)	266.1 $\pm$ 29.4	213.7 $\pm$ 14.6	279.2 $\pm$ 35.2	242.7 $\pm$ 22.2
<i>Clinical laboratory</i>				
AST (U l ⁻¹)	25.6 $\pm$ 5.2	21.4 $\pm$ 3.7	31.3 $\pm$ 7.3	28.5 $\pm$ 8.9
ALT (U l ⁻¹)	31.2 $\pm$ 4.3	33.8 $\pm$ 6.5	35.2 $\pm$ 4.6	25.7 $\pm$ 5.5
Albumin (g dl ⁻¹)	3.2 $\pm$ 0.4	3.4 $\pm$ 0.7	3.5 $\pm$ 0.7	3.4 $\pm$ 0.9
Cr _{serum} (mg dl ⁻¹)	0.9 $\pm$ 0.2	0.8 $\pm$ 0.2	1.0 $\pm$ 0.3	0.9 $\pm$ 0.3
BUN (mg dl ⁻¹)	11.2 $\pm$ 1.5	10.9 $\pm$ 2.2	12.5 $\pm$ 1.7	13.9 $\pm$ 2.5
K ⁺ (mEq l ⁻¹)	4.1 $\pm$ 0.3	4.3 $\pm$ 0.4	4.5 $\pm$ 0.3	4.2 $\pm$ 0.2
Mg ⁺⁺ (mEq l ⁻¹)	2.1 $\pm$ 0.2	2.2 $\pm$ 0.2	2.3 $\pm$ 0.3	2.1 $\pm$ 0.2

Each value indicates mean $\pm$ SD.

Figure 1

Mean plasma quinidine concentration-time profiles and the time course of QTc interval after a 20 min infusion of quinidine (4 mg kg^{-1}) in 24 healthy Korean subjects (open symbol) and 13 healthy Caucasian subjects (closed symbol). (A) and (B) Mean plasma quinidine concentration-time curve in female and male subjects, respectively. (C) and (D) Mean QTc interval-time curve in female and male subjects, respectively. Each point indicates mean $\pm$ SD

screening. There were no significant differences in demographics between ethnic groups or genders, but women weighed less than men. All clinical laboratory results from all subjects were within the normal range.

Figures 1A and B show the average plasma concentration-time profiles obtained after the 20 min infusion of quinidine in female and male volunteers, respectively. After reaching a peak at the end of the infusion, the curve decayed rapidly within 15 min, followed by a slow decline. Although mean concentrations of quinidine in Caucasian male subjects tended to be higher than those in Koreans (Figure 1B), pharmacoki-

netic differences between the two ethnic groups were not statistically significant for both males and females, as shown in Table 2.

The time courses of the quinidine-induced QTc changes in female and male subjects are illustrated in Figures 1C and D, respectively. The changes in the QTc profiles were generally paralleled by plasma quinidine concentrations. There were no significant differences in heart rates or QTc at baseline between the ethnic groups ($P > 0.05$; Table 2). The QTc values at baseline tended to be higher in females than in males by about 10% and this difference between gender groups was significant in Korean subjects ($P < 0.05$) but not in Caucasians

Table 2

Pharmacokinetic parameters after an infusion of quinidine (4 mg kg⁻¹) for 20 min and baseline values of heart rate and QTc in healthy subjects

	Korean			Caucasian		
	Male (n = 12)	Female (n = 12)	Total (n = 24)	Male (n = 7)	Female (n = 6)	Total (n = 13)
C _{max} (mg l ⁻¹)	2.63 ± 0.19	2.35 ± 0.23	2.49 ± 0.15	3.69 ± 0.60 (-1.45, -0.67)	2.46 ± 0.33 (-0.39, 0.17)	3.12 ± 0.39 (-0.81, -0.45)
AUC(0,12h) (mg l ⁻¹ h)	10.28 ± 0.62	10.17 ± 1.03	10.22 ± 0.59	11.2 ± 1.03 (-1.71, -0.13)	9.92 ± 0.99 (-0.83, 1.33)	10.61 ± 0.71 (-0.83, 0.05)
AUC(0, ∞) (mg l ⁻¹ h)	14.97 ± 0.83	13.67 ± 1.46	14.33 ± 0.83	14.73 ± 1.26 (-0.77, 1.25)	13.21 ± 1.39 (-1.06, 1.98)	14.03 ± 0.92 (-0.30, 0.90)
CL _{tot} (l h ⁻¹ kg ⁻¹)	0.28 ± 0.02	0.34 ± 0.04	0.31 ± 0.02	0.27 ± 0.02 (-0.05, 0.05)	0.32 ± 0.04 (-0.11, 0.15)	0.29 ± 0.02 (-0.06, 0.02)
V _{ss} (l kg ⁻¹)	2.85 ± 0.24	2.70 ± 0.23	2.78 ± 0.17	2.18 ± 0.21 (-0.09, 1.43)	2.66 ± 0.26 (-0.77, 0.85)	2.4 ± 0.17 (-0.14, 0.90)
Baseline heart rate (beats min ⁻¹)	64 ± 5	66 ± 2	65 ± 1	62 ± 3	67 ± 2	64 ± 2
Baseline QTc interval (ms)	402 ± 9	443 ± 8*	423 ± 7	421 ± 13 (-29.62, 8.38)	445 ± 24 (-17.86, 13.86)	438 ± 15 (-22.31, -7.68)

Numbers in parentheses are 95% confidence intervals for difference in mean value between ethnic groups. Data are mean values ± SEM. **P* < 0.05, ANOVA test between male and female Korean subjects. C_{max}: maximum plasma concentration, AUC(0,12h) and AUC(0,∞); area under the concentration-time curve from 0 to 12 h and infinity, CL_{tot}: total clearance, V_{ss}: volume of distribution at steady state.

(Table 2). The quinidine-induced QTc changes were smaller in Koreans than in Caucasians during the period of higher quinidine concentrations, until 2 h after dosing (*P* < 0.05, ANOVA with repeated measurement). The QTc-time profiles of males were parallel to, but shifted downward from, those of females. The infusion of saline did not cause significant QTc prolongation.

The relationships between quinidine concentration and QT prolongation in Korean and Caucasian subjects are illustrated in Figure 2. The QTc values in Caucasians were higher than those in Koreans, especially at higher quinidine concentrations and in female subjects. The QTc values in female subjects tended to be higher than those in male subjects for both ethnicities.

The population pharmacodynamic analysis revealed that the time course of quinidine-induced QTc prolongation was directly associated with the estimated plasma quinidine concentration and did not have a significant lag time. The addition of two covariates, gender and ethnicity, greatly improved the fit of the data and substantially decreased the minimum value of the objective function (Table 3). Testing all possible combinations of covariates revealed that gender was a significant covariate for the QTc baseline value and that both ethnicity and gender were related as covariates to the maximum effect

of quinidine [$E_0(\text{ms}) = 408 + [34 \cdot (1 - \text{Sex})]$], where SEX = 0 for female and 1 for male; $\Delta E_{\text{max}}(\text{ms}) = (136 \cdot f_{\text{ETHN}}) + C_{\text{female}}$, where $f_{\text{ETHN}} = 1$ for Koreans and 1.26 for Caucasians; $C_{\text{female}} = 106$ only for Caucasian females and 0 for the other groups; and $EC_{50}(\mu\text{M}) = 3.13$].

Discussion

This study represents the first examination of interethnic differences in drug-induced QT prolongation between Caucasians and Koreans. Our data quantify the differences between these two groups using a population analysis methodology.

An examination of the relationship between serum quinidine concentration and ECG QTc prolongation in the two groups studied revealed that the QTc increase was smaller in Koreans than in Caucasians, especially in women, when normalized to the same baseline level. Caucasians were more susceptible to the electrophysiological effects of quinidine on QTc than Koreans, and the QTc values of Caucasians were higher than those of Koreans at the same quinidine concentration. Finally, the population pharmacodynamic modelling that we conducted demonstrated that gender and ethnicity are significant covariates for quinidine-induced QTc prolon-

Figure 2

Scatter plot of the relationship between plasma quinidine concentration and the QTc value observed after intravenous infusion of quinidine (4 mg kg^{-1}) over 20 min to 24 healthy Korean subjects (—) and 13 healthy Caucasian subjects (—). (A) Comparison between scatter plots of Korean (○) and Caucasian female subjects (●). (B) Comparison between scatter plots of Korean (○) and Caucasian male subjects (●). Each line indicates the simulation of the QTc interval predicted from the best final pharmacodynamic model obtained in this study. $E_t = E_0 + \frac{\Delta E_{\max}[C_t]}{EC_{50} + [C_t]}$; $E_0 \text{ (ms)} = 408 + [34 \times (1 - \text{Sex})]$, where $\text{SEX} = 0$ for female and 1 for male; $\Delta E_{\max} \text{ (ms)} = (136 \times f_{\text{ETHN}}) + C_{\text{female}}$, where $f_{\text{ETHN}} = 1$ for Koreans and 1.26 for Caucasians; $C_{\text{female}} = 106$ for Caucasian females only and 0 for all others; $EC_{50} \text{ (}\mu\text{M)} = 3.13$

Table 3

Population pharmacodynamic parameters after a single 20 min i.v. infusion of quinidine (4 mg kg^{-1})

	$E_0 \text{ (ms)}$	$\Delta E_{\max} \text{ (ms)}$	$EC_{50} \text{ (}\mu\text{M)}$	$\omega^2 E_0$	$\omega^2 E_{\max}$	$\omega^2 EC_{50}$	σ^2	OBF
Simple model	425 (6.7)	175 (19.1)	3.73 (0.73)	0.006 (0.002)	0.08 (0.06)	0.21 (0.19)	0.004 (0.004)	6687
Adjusted model	$408 + [34 \times (1 - \text{Sex})]$ (7.9)	$(136 \times f_{\text{ETHN}}) + C_{\text{female}}$ (18.7)	3.13 (0.71)	0.004 (0.002)	0.0002 (0.004)	0.48 (0.20)	0.004 (0.003)	6650

Numbers in parentheses are the standard errors of the estimated parameters. OBF, minimum value of the objective function; ETHN, ethnicity: Korean = 1, Caucasian = 0; SEX, male = 1, female = 0; f_{ETHN} : Korean = 1, Caucasian = 1.26; C_{female} : Caucasian female = 106, all others = 0.

gation. These results suggest that Koreans may be less vulnerable to quinidine-induced fatal arrhythmia than Caucasians.

There are relatively few data on interethnic differences in drug-induced QT prolongation. Olatunde & Price Evans examined the relationship between serum quinidine concentrations and cardiac effects in white British and Nigerian subjects [17]. They reported that quinidine concentrations in white British subjects tended to be lower than those in Nigerians, yet the

quinidine-induced QTc increase was greater in white British subjects than in Nigerians. The mechanism underlying this ethnic difference remains unclear.

Several reports have suggested that genetic predisposition, in addition to disease, may confer susceptibility to arrhythmia during drug challenge. Genetic factors related to the length of QT interval are well recognized. Mutations in genes encoding cardiac sodium and potassium channels are associated with specific subtypes of the long QT syndrome (LQTS).

Makita *et al.* reported that a group of patients with a subclinical mutation in the sodium channel α subunit gene (SCN5A) may be prone to drug-induced arrhythmia [18]. In a Chinese family, the KCNE1 mutation led to a fatal prolongation of the cardiac action potential as a result of reduced potassium current density [19]. Ackerman *et al.* reported that the spectra and frequencies of potassium channel variants differed among four different ethnic populations including black, white, Asian, and Hispanic [20]; black populations appeared to have a wider spectrum and higher frequency of potassium channel variants than any other ethnic population. Recently, this group reported the first determination of the prevalence and spectrum of cardiac sodium channel variants in a range of different ethnic groups [21]. Genetic polymorphisms of other cardiac potassium, sodium, and calcium channel coding genes have been associated with the occurrence of the LQTS or with drug-induced QT interval prolongation [22–27]. Ethnically specific genetic polymorphisms in these genes contribute to the length of the QT interval, both in the resting state and in the context of drug-induced changes, and these might account for ethnic differences in drug-induced QTc prolongation or arrhythmia. Ishak *et al.* investigated ECG patterns (PR, QRS, and QT) in healthy individuals from six different ethnic groups (Saudi, Indian, Jordanian, Filipino, Sri Lankan, and Caucasian) living in the Middle East [12]. No significant differences in ECG parameters were found among the male members of these groups, whereas the ECG patterns differed significantly among women; the P-wave axis in Caucasian women and the QRS duration in Jordanian women were significantly greater than those of the other populations, but there were no differences in QTc. Although these results were obtained in a relatively small sample of patients and therefore cannot be generalized to entire ethnic populations, an approach using subjects of similar socioeconomic and nutritional conditions is very suggestive of ethnic differences. A multiethnic cohort study of rural Hawaiians showed that significant differences in the prevalence of prolonged QTc persisted after controlling for known metabolic and biochemical covariates related to the QT interval length [28]. These data support the hypothesis that genetic background is an important factor that contributes to ethnic disparities in cardiac electrophysiology.

In the present study, we do not have a ready, mechanistic explanation for the differences in quinidine-induced QT interval changes between Caucasians and Koreans. It is possible that the differences we observed resulted from genetic characteristics, environmental

factors, or a combination of the two. In this study, we found no statistically significant difference between the two ethnic groups, although Caucasians tended to have a higher sensitivity to quinidine-induced QTc prolongation than Koreans. Using a *post hoc* power analysis based on the $\Delta E_{\max}$ data obtained in this study, at least 26 subjects per ethnic group would be necessary to achieve statistical significance in a *t*-test comparison of mean values between the two ethnic groups at the 0.05 significance level with 80% power. In addition, the clinical trial that we conducted was performed in Korea for Koreans and in the United States for Caucasians. It follows that we cannot rule out the possibility that various environmental factors, including diet and cultural habits, could have contributed to the interethnic difference observed in this study.

We observed that the baseline QTc was about 10% higher in women than in men. The quinidine-induced QTc prolongation appeared to be greater in female subjects of both ethnic groups. The longer baseline QT interval in women has been proposed as one factor that causes women to be at greater risk than men of a potentially fatal arrhythmia [29–31]. Quinidine has been demonstrated in other studies to cause greater QT prolongation in women than in men [32]. Sex hormones may affect either the autonomic nervous system or the expression or activity of cardiac ion channels that contribute to gender-related differences in cardiac repolarization and possibly to greater susceptibility to torsades de pointes in women [33, 34]. In this study, insignificant gender difference of the baseline QTc observed in Caucasian subjects seemed likely to result from the shortage of sample size.

In conclusion, Koreans seemed to be less sensitive to quinidine-induced QT interval prolongation than Caucasians, and this effect was more pronounced in females than in males. We are cautious in our interpretation of these data because of the small number of study subjects. Further large-scale clinical trials of drug-induced QT interval prolongation are necessary to demonstrate ethnic differences and to understand the underlying mechanisms of the susceptibility to drug-induced arrhythmia in Asian and Caucasian populations.

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School of Medicine, Indiana University, Bloomington, IN, USA. Present address of Dr Raymond L. Woosley is: The Critical Path Institute, Tucson, AZ, USA.

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