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Comparable Pharmacokinetics and Pharmacodynamics of Melagatran in Japanese and Caucasian Volunteers after Oral Administration of the Direct Thrombin Inhibitor Ximelagatran

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Abstract

Objectives: Two studies were conducted to elucidate the pharmacokinetics and pharmacodynamics of melagatran after administration of the oral direct thrombin inhibitor ximelagatran to Caucasian and Japanese volunteers.

Methods: In study 1, with a single-blind, parallel-group design, young Japanese and Caucasian male volunteers were randomised to receive four single escalating oral doses of ximelagatran (12, 24, 36 and 60mg on separate days; n = 27 per ethnic group) or placebo (n = 6 per ethnic group). In study 2, with an open-label design, elderly Japanese male volunteers (n = 12) received three single escalating oral doses of ximelagatran (12, 24 and 36mg on separate days).

Results: Regardless of the ethnicity or age of the volunteers, ximelagatran given in single oral doses was rapidly absorbed and bioconverted to melagatran, and the melagatran area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) increased in proportion with the ximelagatran dose, with only small deviations from absolute linearity. Higher melagatran AUC and C_{max} were observed in young Japanese volunteers compared with young Caucasian volunteers, and in elderly Japanese volunteers compared with young Japanese volunteers. These results appear to be attributed to weight- and age-related decreases in renal elimination of melagatran rather than to absorption of ximelagatran and formation of melagatran. The pattern of metabolites in plasma and urine was comparable between young Japanese and Caucasian volunteers, and between young and elderly Japanese volunteers. The melagatran plasma concentration-activated partial thromboplastin time (aPTT, an *ex vivo* coagulation time measurement used to demonstrate inhibition of thrombin) relationship did not differ significantly between young Japanese and Caucasian volunteers or between young and elderly Japanese volunteers.

Conclusions: Ethnicity does not affect the absorption of ximelagatran or the formation of melagatran or the melagatran plasma concentration-aPTT relationship. The elimination of melagatran is correlated with renal function.

Background and Objectives

Ximelagatran is an oral direct thrombin inhibitor being developed for the prevention and treatment of thromboembolic disease, including prevention of stroke in patients with atrial fibrillation (who are at high risk of stroke) and prevention of thromboembolic complications following myocardial infarction.

After oral administration, ximelagatran is rapidly absorbed and bioconverted via two minor intermediates (ethyl-melagatran and hydroxy-melagatran) to its active form melagatran, which is primarily renally eliminated and is not subject to hepatic metabolism.[1] Ximelagatran differs from the currently available oral anticoagulation therapy, vitamin K antagonists (the most widely prescribed of which is warfarin), in its stable, predictable pharmacokinetics, lack of interaction with food, low potential for drug interactions, and lack of requirement for dose titration or coagulation monitoring.[2-5] In clinical studies, ximelagatran has been shown to be more effective than warfarin and the low-molecular weight heparins dalteparin and enoxaparin in reducing the frequency of venous thromboembolism in patients undergoing total hip or knee replacement.[6-8] It has also been shown to be more effective than placebo in preventing the recurrence of thromboembolic events in patients with previous venous thromboembolism,[9] and at least as effective as warfarin in preventing thromboembolic events in patients with nonvalvular atrial fibrillation.[10,11]

The increasing prevalence of thromboembolism among the Japanese, and its anticipated continued rise with the progressive westernisation of lifestyles, has heightened the need in Japan for effective and safe oral anticoagulation therapy. Ximelagatran is being investigated for possible introduction in Japan as an alternative to warfarin, which (in Japanese as in Caucasians) exhibits wide interpatient and intrapatient variability in pharmacokinetics and requires routine coagulation monitoring and dosage adjustment.[12-15]

While the pharmacokinetic, pharmacodynamic and clinical profiles of ximelagatran are well documented in Caucasian healthy volunteers and patients, the drug has been less extensively studied as yet in other ethnic groups, including Japanese volunteers. Major differences between Caucasians and Japanese in the pharmacokinetic profile of ximelagatran are not expected based on the observation that ximelagatran lacks the characteristics that render ethnic differences in pharmacokinetics likely, such as being subject to hepatic metabolism by enzymatic pathways with known genetic polymorphism.[16] In fact, ethnic differences in the pharmacokinetics and pharmacodynamics of melagatran after oral administration of ximelagatran were not observed in a study of 36 healthy young Black, Asian and Caucasian males residing in France.[17] While these data are consistent with the likelihood that the pharmacokinetics of ximelagatran in Japanese volunteers are similar to those in Caucasians, this possibility has not been carefully assessed. This paper describes two studies conducted to elucidate the pharmacokinetics and pharmacodynamics of melagatran after oral administration of ximelagatran to young Caucasian and young and elderly Japanese volunteers. It was expected that Japanese volunteers would show the same influence of age on melagatran pharmacokinetics as do Caucasian volunteers, i.e. higher exposure of melagatran in elderly volunteers because of age-related decreases in renal elimination.[3]

Methods

Two dose-escalation studies, one in young healthy male volunteers (study 1) and the second in elderly healthy male volunteers (study 2), were conducted in a manner consistent with Good Clinical Practice guidelines and the Declaration of Helsinki.

An institutional review board approved the protocols for the study site.

Study Design and Procedures

In study 1, with a single-blind, parallel-group design, young Japanese and Caucasian male volunteers were randomised to receive four single escalating oral doses of ximelagatran (12, 24, 36 and 60mg) or placebo. In study 2, with an open-label design, elderly Japanese male volunteers were assigned to receive three single escalating oral doses of ximelagatran (12, 24 and 36mg). In both studies, the study drug was administered in the morning to fasting volunteers on study days separated by washout periods of 2–7 days. No prescribed medicines were allowed from 2 weeks before the first study day through to a follow-up visit that occurred 2–7 days after the last study day. No medication (including over-the-counter drugs) except paracetamol (acetaminophen) for moderate to severe pain was permitted from 1 week before the first study day through to the follow-up visit.

Volunteers

Healthy male volunteers with a body mass index of 19–27 kg/m^2 were eligible for the studies. Study 1 enrolled Japanese and Caucasian volunteers aged 20–40 years and study 2 enrolled Japanese volunteers aged 65–74 years. The lower age limit for study 2 was defined with reference to regulatory guidelines. The upper limit of age for study 2 was defined with consideration of the expected age range of the target patient population and of the phase I requirement that the study enroll only healthy volunteers. The exclusion criteria for both studies included (i) any significant clinical illness within 3 weeks before the first dose of the study drug; (ii) history of bleeding or thrombotic disorder or of diseases that could affect the rate and extent of absorption of the study drug; (iii) donation of >400mL of blood within 12 weeks before the first dose of the study drug; (iv) use of prescription medicines within 2 weeks before the first dose of the study drug; (v) use of any medicine, including over-the-counter drugs, with the exception of occasional paracetamol within 1 week before the first dose of the study drug; and (vi) the requirement for concomitant medication throughout the duration of the study. All volunteers provided written informed consent.

Pharmacokinetic and Pharmacodynamic Sampling and Analysis

Venous blood samples for the determination of ximelagatran, ethyl-melagatran, hydroxy-melagatran and melagatran plasma concentrations were collected pre-dose, every 30 minutes through to 2 hours post-dose, and 3, 5, 7, 9, 12 and 24 hours post-dose. The activated partial thromboplastin time (aPTT), a pharmacodynamic marker of melagatran, was determined in plasma from the samples collected pre-dose and 2, 5 and 9 hours post-dose in study 1, and pre-dose and 2, 3, 5, 9 and 24 hours post-dose in study 2. The blood samples were drawn into glass tubes (Venoject® [1]; Terumo Europe, Leuven, Belgium) containing 0.13 mol/L trisodium citrate (with a ratio of anticoagulant to blood of 1 : 9 [vol/vol]) and centrifuged within 1 hour at 2000 × *g* and 4°C for 15 minutes. The plasma was separated and samples were stored at −20°C until shipping for aPTT and plasma concentration analyses. The laboratory for aPTT analyses was located in the Department of Clinical Chemistry, Sahlgrenska University Hospital, Göteborg, Sweden. The laboratory for analyses of pharmacokinetic samples was located at Bioanalytical Chemistry, AstraZeneca R&D, Mölndal, Sweden.

The plasma concentrations of ximelagatran, ethyl-melagatran, hydroxy-melagatran and melagatran were determined using liquid chromatography-mass spectrometry (LC-MS) with a lower limit of quantification (LLQ) of 0.010 μmol/L.[18] For determination of the aPTT, all plasma samples in the two studies were analysed at the same laboratory using local clinical laboratory procedures (reagent/manufacturer: STA-PTT Automate 5, Diagnostica Stago, Asnieres, France; coagulometers: STA-R Diagnosti-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ca Stago, Asnieres, France; and Thrombolyzer, Behnk Elektronik, Norderstedt, Germany).

In both studies, urine was collected before dosing and during the intervals of 0–4, 4–12 and 12–24 hours post-dose on each study day. After thorough mixing, 10mL aliquots of the urine samples were taken and stored at −20°C until analysis. The urine concentrations of ximelagatran, ethyl-melagatran, hydroxy-melagatran and melagatran were determined using LC-MS with an LLQ of 0.10 μmol/L.[18]

Pharmacokinetic Assessments

The area under the plasma concentration-time curve (AUC), peak plasma concentration (C_{max}), time to reach C_{max} (t_{max}) and elimination half-life ($t_{1/2}$) of melagatran were estimated by noncompartmental methods using WinNonlin-Professional software (version 1.5, Pharsight Corporation, Mountain View, CA, USA). The AUC was calculated using the log-linear trapezoidal rule to the last measurable plasma concentration and then extrapolated to infinity by adding $C_{last(pred)}/k_e$, where $C_{last(pred)}$ is the predicted plasma concentration at t_{last}, the time of the last sampling point with a measurable plasma concentration, and k_e is the elimination rate constant. $C_{last(pred)}$ and k_e were estimated by linear least-squares regression of the logarithm of the plasma concentrations versus time in the terminal phase of the decline. The $t_{1/2}$ was calculated as $0.693/k_e$.

The cumulative amounts of ximelagatran, ethyl-melagatran, hydroxy-melagatran and melagatran excreted in urine were calculated as percentages of the given dose of ximelagatran for the intervals 0–4, 0–12 and 0–24 hours in both studies. For study 1, the renal clearance (CL_R) of melagatran was calculated as Ae_{24}/AUC, where Ae_{24} was the mean (per dose level and ethnic group) amount of melagatran excreted in urine during the 0–24 hour collection period post-dosing and AUC was the mean (per dose level and ethnic group) AUC of melagatran.

Safety and Tolerability Assessments

Adverse events, defined as any untoward medical occurrence developing or worsening after administration of the study drug regardless of the suspected cause, were recorded from the time of first administration of the study drug through to the follow-up visit in both studies. Clinical laboratory investigations (standard haematology, clinical chemistry, urinalysis and faecal haemoglobin) were carried out at screening, pre-dose and 24 hours post-dose on each study day, and at the follow-up visit. The pulse and blood pressure were measured pre-dose and 2, 9 and 24 hours post-dose on each study day. An ECG was carried out at the expected C_{max} of melagatran on the highest dose levels in both studies to evaluate the effect on the QT interval.

Statistical Analysis

Because of the lower bodyweights of Japanese volunteers compared with Caucasian volunteers, their capacity for renal elimination was expected to be lower. Therefore, in study 1, the AUC and C_{max} were assessed in separate, prospective analyses designed to take into account expected ethnic differences in bodyweight and renal capacity. In one analysis, the AUC and C_{max} were normalised to a bodyweight of 70kg by adjusting these values according to the following formula: AUC (μmol • h/L) or C_{max} (μmol/L) • (bodyweight [kg]/70). In a second analysis, the AUC and C_{max} were normalised to a creatinine clearance (CL_{CR}) of 120 mL/min according to the following formula: AUC (μmol • h/L) or C_{max} (μmol/L) • (CL_{CR} [mL/min]/120).

To determine whether ethnicity affects the pharmacokinetics of melagatran, logarithmically transformed values of each of four variables (unadjusted AUC and C_{max}, weight-adjusted AUC, CL_{CR}-adjusted AUC of melagatran) were analysed in a one-way ANOVA in study 1. The ANOVA used mean values of the estimated pharmacokinetic parameters from the four study days normalised to the 24mg dose in the following model (equation 1):

$$y_{ij} = \mu + \alpha_i + \varepsilon_{ij} \quad \text{(Eq. 1)}$$

where y is the pharmacokinetic parameter, μ is the overall mean, α is the ethnic origin, ε is the error term, i = 1,2 and j = 1,…,27. In this equation, i = 1,2 denotes ethnic origin (1 = Caucasian, 2 = Japanese) and j = 1,2,…27 denotes the experimental units (subjects/healthy volunteers). Least-squares estimates with 90% confidence intervals (CIs) for the ratios between groups (Japanese/Caucasian) were calculated. No effect of ethnicity on melagatran pharmacokinetics was to be concluded if the 90% CI for the geometric mean treatment ratios fell within the interval of 0.8–1.25 for the AUC and C_{max}.

To determine whether the AUC and C_{max} of melagatran increased linearly with a linear increase in the dose of ximelagatran, log-transformed, dose-normalised (to 24mg) estimates for the melagatran AUC and C_{max} were tested in an ANOVA model, with the pharmacokinetic parameter as the dependent variable, and the subject and dose as the main effects. This analysis was conducted separately for Japanese and Caucasian volunteers, and for study 1 and study 2. Dose nonlinearity was to be concluded if the 95% CI for the estimated regression parameter did not include zero.

The aPTT ratio (prolongation of aPTT relative to the pre-dose value) was related to the square root of the melagatran plasma concentration. The relationship between aPTT prolongation (ratio post-dose vs pre-dose) and the plasma concentration of melagatran is not linear but becomes linear when plasma concentrations are transformed using the square root.[17] Therefore, the linear least-squares regression was done for the aPTT versus the square root of the plasma melagatran concentrations. To determine whether ethnicity affects the pharmacodynamics of melagatran, linear regression models were used to relate the aPTT ratio as the dependent variable with the independent variables of ethnic origin, the square root of the melagatran plasma concentration, and interaction between the two.

Results

Demographics and Disposition

The number of volunteers randomised to treatment in study 1 was 66 (33 young Japanese volunteers and 33 young Caucasians), 63 of whom completed the study (table I). The three volunteers who discontinued the study prematurely were excluded from pharmacokinetic and pharmacodynamic analyses but included in the safety and tolerability analyses. Two of these volunteers discontinued because of an adverse event and one was withdrawn because of difficulties with blood sampling. The number of volunteers included in study 2 was 12, all of whom completed the study.

For young volunteers, ethnic groups did not differ with respect to demographics and baseline clinical characteristics, with the exception of bodyweight and CL_{CR}, which were lower in Japanese compared with Caucasian volunteers (table I).

Pharmacokinetics

Figure 1 shows the mean plasma concentration-time profiles of ximelagatran and its metabolites following administration of an oral dose of ximelagatran 60mg to young Caucasian or Japanese volun-

Table I. Baseline demographics and clinical characteristics of young Japanese males (study 1), young Caucasian males (study 1) and elderly Japanese males (study 2)[a]

Parameter	Young				Elderly
	Caucasian volunteers		Japanese volunteers		Japanese volunteers
	ximelagatran (n = 27)	placebo (n = 6)	ximelagatran (n = 27)	placebo (n = 6)	ximelagatran (n = 12)
Age [y]	25 (3)	24 (6)	25 (5)	24 (3)	69 (2)
Bodyweight [kg]	76 (6)	74 (3)	65 (7)	65 (5)	63 (7)
BMI [kg/m^2]	24 (2)	22 (1)	22 (2)	22 (2)	24 (2)
CL_{CR} [mL/min]	106 (11)	107 (9)	96 (10)	94 (13)	59 (12)

a Values are expressed as mean (SD).

BMI = body mass index; **CL_{CR}** = creatinine clearance.

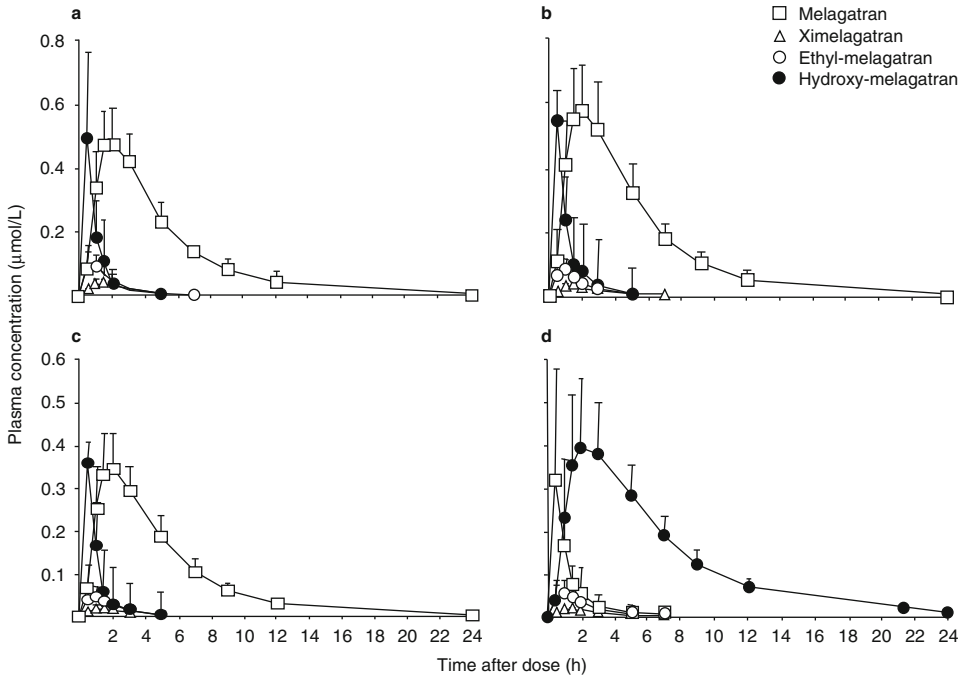

Fig. 1. Mean plasma concentration-time profiles of ximelagatran, melagatran and the intermediates ethyl-melagatran and hydroxy-melagatran after administration of a single oral dose of ximelagatran 60mg to (**a**) young Caucasian or (**b**) young Japanese volunteers (study 1), and after administration of a single ximelagatran 36mg dose to (**c**) young or (**d**) elderly Japanese volunteers (studies 1 and 2). Profiles at other dose levels in study 1 and study 2 were similar.

teers (study 1) and a single ximelagatran 36mg dose to young or elderly Japanese volunteers (studies 1 and 2). Similar profiles were observed at other ximelagatran doses. Among young volunteers, the unadjusted geometric mean AUC and C_{max} of melagatran were 22–37% higher (depending on the ximelagatran dose) in Japanese volunteers than in Caucasian volunteers (table II). After adjustment of these pharmacokinetic parameters for the lower weight and lower CL_{CR} of Japanese volunteers, the geometric mean AUC and C_{max} of melagatran were 4–17% and 13–26% higher, respectively, in Japanese volunteers than in Caucasian volunteers (table II). Only small deviations from absolute dose-linearity were observed for young Caucasian volunteers, young Japanese volunteers and elderly Japanese volunteers (table III).

The relationship between CL_{CR} and melagatran AUC was assessed *post hoc* in order to explore the possibility that the differences in AUC between young Caucasian and Japanese volunteers, as well as between young and elderly Japanese volunteers, are attributed to differences in capacity to excrete melagatran rather than to ethnic differences in absorption and bioconversion of ximelagatran. The mean dose-adjusted AUC (to 24mg) was plotted versus the mean calculated CL_{CR} with data from young Caucasian and Japanese volunteers in study 1, elderly Japanese volunteers in study 2 and 12 elderly Caucasian volunteers from a previously published study of ximelagatran.[3] The resulting scatterplot shows an inverse relationship between CL_{CR} and AUC (figure 2).

Urinary Excretion

At all doses, the metabolite profile of ximelagatran in urine was comparable between young Japanese volunteers and young Caucasian volunteers, as well as between young and elderly Japanese volunteers (figure 3). The mean CL_R of melagatran was

Table II. Least-squares estimates (90% CIs) of the inter-ethnic ratios (Japanese/Caucasian) of the non-adjusted, weight-adjusted and creatine clearance (CL_{CR})-adjusted geometric mean area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of melagatran as a function of the ximelagatran dose in young volunteers (study 1)

Dose group (mg)	Non-adjusted	Weight-adjusted	CL_{CR}-adjusted
AUC			
12	1.35 (1.21, 1.51)	1.16 (1.03, 1.30)	1.25 (1.11, 1.41)
24	1.37 (1.23, 1.52)	1.17 (1.06, 1.30)	1.26 (1.13, 1.41)
36	1.34 (1.19, 1.52)	1.15 (1.02, 1.29)	1.24 (1.10, 1.40)
60	1.26 (1.13, 1.40)	1.08 (0.97, 1.20)	1.16 (1.04, 1.30)
C_{max}			
12	1.37 (1.20, 1.56)	1.17 (1.03, 1.33)	1.26 (1.10, 1.45)
24	1.36 (1.20, 1.54)	1.16 (1.03, 1.32)	1.26 (1.10, 1.44)
36	1.34 (1.16, 1.55)	1.14 (0.99, 1.32)	1.24 (1.06, 1.43)
60	1.22 (1.10, 1.35)	1.04 (0.93, 1.17)	1.13 (1.00, 1.27)

115, 112, 107 and 97 mL/min in young Japanese volunteers compared with 122, 121, 110 and 114 mL/min in young Caucasian volunteers at doses of 12, 24, 36 and 60mg, respectively.

Pharmacodynamics

Melagatran prolonged the aPTT in a concentration-dependent and nonlinear manner. The increase in the aPTT ratio with increasing melagatran plasma concentration did not differ between young Japanese and Caucasian volunteers (figure 4). No statistically significant difference between young Japanese and Caucasian volunteers was observed in the intercept or slope of the estimated regression lines for each ximelagatran dose analysed separately.

Safety and Tolerability

No volunteer discontinued either study because of a drug-related adverse event, and no adverse events considered to be serious were reported. In study 1, two volunteers discontinued because of nonserious, nondrug-related adverse events (nausea

Table III. Estimated between-dose ratios of the dose-adjusted area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of melagatran (95% CIs) for young Caucasian volunteers (study 1), young Japanese volunteers (study 1) and elderly Japanese volunteers (study 2)

Dose (mg) ratio	Young		Elderly
	Caucasian volunteers (n = 26)	Japanese volunteers (n = 26)	Japanese volunteers (n = 12)
AUC			
24/12	1.05 (0.95, 1.16)	1.06 (0.99, 1.13)	1.03 (0.93, 1.13)
36/12	1.14 (1.04, 1.26)	1.13 (1.06, 1.21)	1.11 (1.00, 1.22)
36/24	1.09 (0.99, 1.20)	1.07 (1.00, 1.14)	1.08 (0.98, 1.19)
60/12	1.34 (1.21, 1.47)	1.24 (1.17, 1.33)	NA
60/24	1.27 (1.15, 1.40)	1.17 (1.10, 1.25)	NA
60/36	1.17 (1.06, 1.29)	1.10 (1.03, 1.17)	NA
C_{max}			
24/12	1.03 (0.91, 1.17)	1.03 (0.94, 1.12)	0.99 (0.84, 1.16)
36/12	1.10 (0.97, 1.25)	1.08 (0.98, 1.18)	1.10 (0.94, 1.29)
36/24	1.07 (0.94, 1.21)	1.05 (0.96, 1.15)	1.12 (0.96, 1.31)
60/12	1.23 (1.08, 1.39)	1.09 (1.00, 1.20)	NA
60/24	1.19 (1.05, 1.35)	1.07 (0.97, 1.17)	NA
60/36	1.12 (0.98, 1.27)	1.02 (0.93, 1.11)	NA

NA = not applicable.

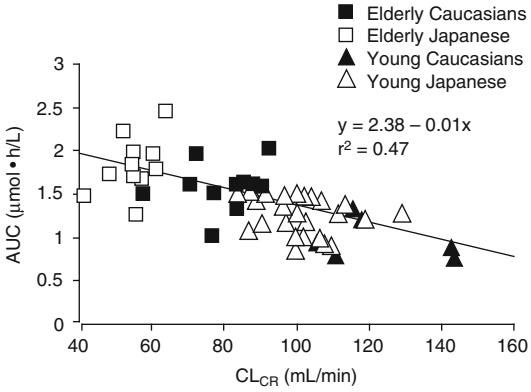

Fig. 2. Relationship between the melagatran area under the plasma concentration-time curve (AUC) and calculated creatinine clearance (CL_{CR}) among young Japanese and Caucasian volunteers (study 1), elderly Japanese volunteers (study 2) and elderly Caucasian volunteers[3] (n = 12).

and vomiting in a volunteer in the placebo group and upper respiratory infection in a volunteer in the ximelagatran group). The incident of nausea and vomiting was the only adverse event reported by a Japanese volunteer on a study day. Among Caucasian volunteers, the most common adverse event was headache, reported by volunteers in the ximelagatran group on study days on which they received 24mg (n = 2) and 36mg (n = 6) as well as by two volunteers in the placebo group. No other adverse event was reported by more than two volunteers in the ximelagatran group or the placebo group in study 1. No adverse events were reported in study 2.

No clinically significant patterns of abnormalities in clinical laboratory tests, vital signs or body temperature were observed. There were no findings indicating QT interval prolongation.

Discussion and Conclusion

These studies indicate that ethnicity does not affect the absorption of ximelagatran, the formation of melagatran, or the melagatran plasma concentration-aPTT relationship, and that the elimination of melagatran is correlated with renal function. In study 1, ximelagatran given in single oral doses of 12, 24, 36 or 60mg was rapidly absorbed and bioconverted to melagatran. The melagatran AUC and C_{max} increased in proportion with the ximelagatran dose, with only small deviations from absolute linearity. These findings support the results of a study showing that the absorption of ximelagatran and formation of melagatran were independent of ethnic origin in 36 healthy Black, Asian or Caucasian males residing in France.[17] In Asian volunteers in that study, as in Japanese volunteers in the current study, increases in AUC and C_{max} were observed compared with Caucasian volunteers. These differences are likely to be caused by the lower bodyweight of the Asian and Japanese volunteers, which is expected to be associated with reduced

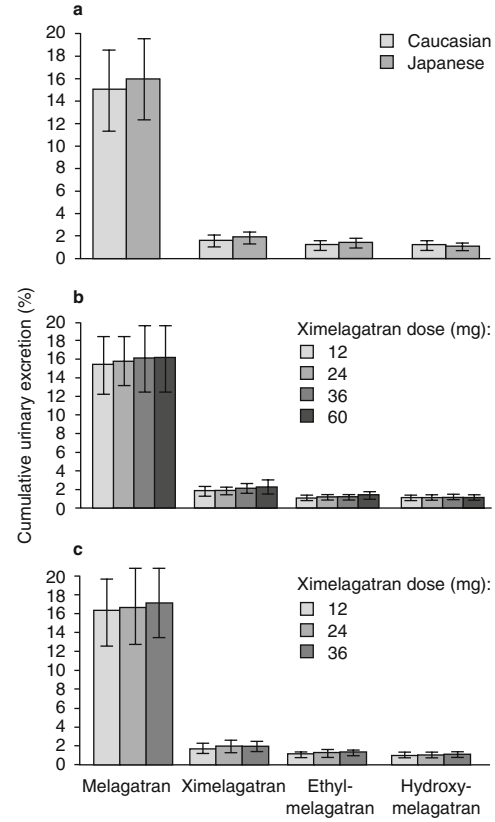

Fig. 3. Mean ± SD cumulative urinary excretion of ximelagatran and its metabolites from 0 to 24h after administration of (**a**) a single oral dose of ximelagatran 60mg (same observation for other doses not shown) to healthy young Japanese and Caucasians volunteers (study 1) and (**b**) a single ximelagatran 12, 24, 36 or 60mg dose to young Japanese volunteers, or (**c**) a single ximelagatran 12, 24 or 36mg dose to elderly Japanese volunteers (studies 1 and 2). Data are expressed as percentages of the administered dose of ximelagatran.

capacity for renal excretion (the primary route of elimination of melagatran) rather than to differences in absorption of ximelagatran or formation of melagatran. In support of this hypothesis, calculated CL_{CR} as well as CL_R was lower in Japanese volunteers compared with Caucasian volunteers in the current investigation. Furthermore, adjustment of AUC values for bodyweight and CL_{CR}, respectively, rendered the AUC values of Asian and/or Japanese volunteers similar to those of Caucasians. Finally, the pattern of metabolites in plasma and urine was comparable in Japanese and Caucasian volunteers.

Ximelagatran is bioconverted to melagatran by hydrolysis of an ethyl ester and reduction of a hydroxyamidine. There is no evidence that cytochrome P450 isoenzymes are involved in the bioconversion of ximelagatran.[4] Renal excretion through passive filtration is the major route of elimination for melagatran, the active form of ximelagatran.[1] Ethnic differences in passive pharmacokinetic processes such as renal elimination are not typically found.[16]

In elderly Japanese volunteers, as in young Japanese volunteers in the current studies, the melagatran AUC and C_{max} increased in proportion with the ximelagatran dose, with only small deviations from absolute linearity. In elderly Japanese volunteers compared with young Japanese volunteers, the melagatran AUC and C_{max} were approximately 50% and 20% higher, respectively, after administration of single oral doses of ximelagatran. Normal age-dependent decreases in renal function probably account for the latter result, which was also observed in previous research with young and elderly Caucasian volunteers.[3] Consistent with this possibility, the calculated CL_{CR} was lower in elderly Japanese volunteers (59 mL/min at baseline) than in young Japanese volunteers (96 mL/min at baseline) in the current studies. Moreover, the pattern of metabolites in plasma and urine was comparable in elderly and young Japanese volunteers, a finding that suggests that the observed difference in exposure of melagatran is not attributable to differences in the absorption of ximelagatran or the formation of melagatran.

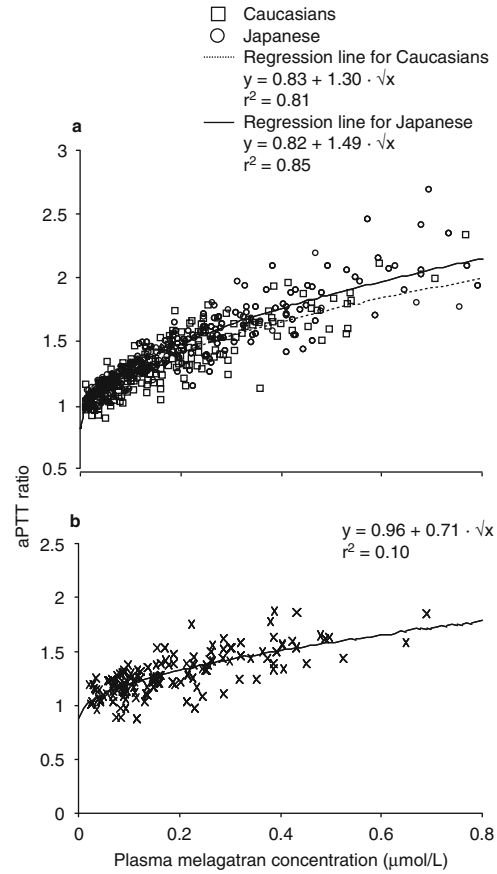

Fig. 4. Observed and predicted activated partial thromboplastin time (aPTT) ratio vs plasma concentration of melagatran after an oral dose of (**a**) ximelagatran 12, 24, 36 and 60mg in young Caucasian and Japanese volunteers (study 1) or (**b**) an oral dose of ximelagatran 12, 24 and 36mg in elderly Japanese volunteers (study 2). The relationship between aPTT prolongation (ratio post-dose vs pre-dose) and the plasma concentration of melagatran is not linear but becomes linear when plasma concentrations are transformed using the square root. Therefore, the linear least-squares regression was done for the aPTT vs the square root of plasma melagatran concentrations.

The melagatran plasma concentration-aPTT relationship did not differ between young Japanese and Caucasian volunteers or between young and elderly Japanese volunteers. Similarly, no effect of ethnicity on the aPTT was observed in the study of Black, Asian and Caucasian males residing in France,[17] and no effect of age was observed in the study of young and elderly Caucasians.[3] Regardless of age or ethnicity in these studies, the aPTT was pro-

longed by melagatran in a nonlinear manner, as has been previously reported.[3,17]

Ximelagatran was well tolerated in both Japanese and Caucasian volunteers. No serious adverse events or drug-related adverse events leading to discontinuation were reported in either ethnic group. Very few adverse events were reported among young and elderly Japanese volunteers, whereas the incidence of adverse events in Caucasian volunteers was slightly higher. This pattern of results could be attributed to better tolerability of ximelagatran in Japanese volunteers compared with Caucasian volunteers or, more likely, to cultural differences in the tendency to report adverse events.[19,20]

The results of the present study show that ethnicity does not affect the absorption of the oral direct thrombin inhibitor ximelagatran or the formation of melagatran. The elimination of melagatran is correlated with renal function.

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