A question based approach to drug development

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CHAPTER 10

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Pharmacokinetic differences between Caucasian and Japanese subjects after single and multiple doses of a potential combined oral contraceptive (Org 30659 and EE)

Abstract

OBJECTIVES To compare the pharmacokinetic parameters and safety of the progestagen Org 30659 ((17α)-17-hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one) and ethinyl estradiol (EE) in Caucasian and Japanese women after single and multiple doses.

METHODS This was an open-label parallel design of a single dose followed by a multiple dose period in healthy young Japanese and Caucasian subjects.

RESULTS The AUC of Org 30659 after single dosing was increased by a factor 1.75 (90% CI: 1.48-2.08) in Japanese women compared to Caucasian women. At steady-state this difference increased to a factor 1.90 (90% confidence interval [CI]: 1.60-2.25). The AUC of EE after single dosing was similar in Caucasian and Japanese women but at steady-state it was increased by a factor 1.38 (90% CI: 1.15-1.64) in the Japanese. Weight normalisation reduced but did not remove all the observed differences. Sex Hormone Binding Globulin (SHBG) played no significant role in the differences between Caucasian and Japanese subjects. Both the single and multiple dose treatment with Org 30659/EE were generally well tolerated by all subjects. The Japanese population reported more and different treatment related adverse events than the Caucasian population.

CONCLUSIONS The peak concentration and extent of exposure of Org 30659 and to a lesser extent of EE in Japanese women are higher than in Caucasian women. Furthermore, the peak concentration and extent of exposure at steady-state of Org 30659 and to a lesser extent of EE are higher than would be predicted assuming linear pharmacokinetics over time. No major safety issues were observed.

Introduction

The main goal of combined oral contraceptives is prevention of pregnancy by inhibiting ovulation without jeopardising safety. Because the early combined oral contraceptives (COCS) had a relatively high steroid content, the preparations showed good contraceptive efficacy but also produced a great variety of adverse effects, including some serious ones. In the late 1960s, various reports raised concern about venous thromboembolic events occurring in

ref. 1 COC users, which were attributed to the estrogen administered with the pill. Therefore, the estrogen content of newly developed COCs has been reduced. Howeve, concern continued when in the late 1970s also the progestagenic
ref. 2 component became suspected in causing arterial thromboembolic accidents (particularly, myocardial infarction). Thus, development of new oral contraceptives has been directed towards designing regimens with aminimal effective dose of both the estrogen and the progestagen. However, this carries a number of drawbacks. Firstly, reducing the steroid dosage may jeopardise contraceptive efficacy in certain subgroups of women, for example, women with a low steroid bioavailability. Secondly, low steroid doses may lead to an increase in the incidence of irregular bleeding. Thirdly, as the dose is reduced in an effort to eliminate the negative effects, several of the positive properties associated with oral contraceptives (OCS), like reduced
ref. 3-10 risk of fibrocystic tumors of the breasts and endometrial and ovarian cancer, could also be eliminated.

In addition to the desired progestagenic activity, currently available progesta-
ref. 11 gens have a varying degree of intrinsic androgenicity. When these progestagens are used at a high a dose, typical androgen-associated side effects such as acne and hirsutism may become more frequent. Furthermore, androgenic progestagens are associated with more pronounced metabolic disturbances (*e.g.* in lipid metabolism and carbohydrate metabolism) than non-androgenic
ref. 12 progestagens. Research has been directed towards the development of progestagens showing a strong dissociation between progestagenic and androgenic activity like desogestrel and etonogestrel, in order to minimise metabolic side effects. The new progestagen Org 30659 ((17α)-17-hydroxy-
ref. 13 11-methylene-19-norpregna-4,15-dien-20-yn-3-one) is a novel selective progestagenic steroid with low intrinsic androgenic activity.

Modern low-dose OCS were launched in Japan in 1999, following the lifting of a ban on their licensing and sale. Ethnic differences could occur in the pharmacological or pharmacokinetic properties of investigational new drugs. Therefore, before a new drug is introduced in Japan sufficient data should be presented on the effects of the drug in a Japanese population. In some cases a comparison between the 'western' population and the Japanese population can be used to extrapolate the data from 'western' studies to the Japanese (especially when no differences are observed). In the current study, the pharmacokinetics and safety of Org 30659 and ethinyl estradiol (EE) in Caucasian and Japanese women were compared after single and multiple dose administration of tablets containing a combination of 200 µg Org 30659 and 20 µg EE.

Methods

Design

This was a two-centre, open-label, parallel design of a single dose (SD) followed by a multiple dose (MD) period in 18 Japanese and 18 Caucasian healthy females. Japanese subjects were studied in Tokyo, Japan and Caucasian subjects concurrently in Leiden, The Netherlands using the same study protocol. Subjects not using oral contraception were to start treatment (administration of SD) between 3 and 8 days after the first day of their last menstrual cycle. Subjects using oral contraception were to start treatment (administration of SD) between 28 and 30 days after they had stopped taking their last oral contraceptive pill. All subjects enrolled in this study were instructed to use adequate non-hormonal contraceptive measures throughout the study period.

Subjects

Japanese (both parents Japanese) and Caucasian (both parents Caucasian) female subjects were healthy as determined during screening. The study was approved by the Medical Ethics Review Board of Leiden University Medical Center and approved by the Institutional Review Board of Obara hospital, and performed according to the principles of ICH-GCP, the Helsinki Declaration and Dutch and Japanese law.

Treatments

All subjects received treatments from the same batch of study medication. A single oral administration of Org 30659/EE (1 tablet containing 200 μg Org 30659 and 20 μg EE) was followed by a 72 h pharmacokinetic (PK) sampling period (SD). The single dose was followed by a washout period of 5 to 7 days, before the start of the multiple dose period. This consisted of once daily oral intake of Org 30659/EE (1 tablet containing 200 μg Org 30659 and 20 μg EE) for 24 days, followed by a 72 h PK sampling period. Treatment administration was supervised on the first dose and at the multiple doses on days 2, 4, 6, 15 and 24. Additionally, compliance with the dosing regimen was checked on days 9, 12, 18 and 20. Furthermore, subjects were instructed to record the exact time of drug administration on a diary provided by the centre. At each visit to the trial centre, a pill count was performed by the site's staff.

Blood Sampling and Measurements

Testing for drugs of abuse (cocaine, morphine and tetrahydrocannabinoid) was performed during screening and before administration of the single dose. For all subjects a qualitative, colour immuno- urine pregnancy test was performed during screening, pre-dose SD period, pre-dose MD period and pre-dose on MD days 6, 15 and 24. Upon arrival on Day –1 a breath test to detect the use of alcohol was performed.

A 12-lead electrocardiogram was obtained regularly throughout the study period. At regular time intervals, systolic and diastolic blood pressure (BP, mm Hg) and pulse rate (PR, BPM) were measured using an automated blood pressure monitor. Vital signs were recorded before any other procedures, took place. The subject was sitting or semi-recumbent for at least 5 minutes prior to start of the measurement.

Blood samples for routine laboratory safety were drawn pre-dose and 24 hours after SD and pre-dose on days 6, 15 and 24 after the start of the MD period and at post study screening. From these samples, Sex Hormone Binding Globulin (SHBG) was also determined. Analysis of the laboratory safety blood samples was performed at the two centres except for SHBG, which was analysed at the Leiden University Medical Centre using immunometric assay and luminescentic detection (Immulite, DCP, Los Angeles, CA, USA).

Blood was collected and processed to Potassium-EthyleneDiamineTetra-Acetic acid (K-EDTA) plasma for the assessment of Org 30659 concentrations and to serum for the assessment of EE concentrations. Org 30659 concentrations were determined at the Department of Drug Metabolism and Kinetics, NV Organon, Oss, the Netherlands using a validated gas chromatographic assay with mass spectrometric detection. The range for the Org 30659 assay was 0.05 - 25 ng/mL plasma. EE concentrations were measured at PPD Pharmaco, Richmond, Virginia, USA using a validated radioimmunoassay after high performance liquid chromatography isolation of EE. The range for the EE assay was 2.25 – 48 pg/mL serum. Blood samples for Org 30659 and EE determination were drawn pre-dose and ¼, ½, ¾, 1, 1½, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after SD and after the last MD. Furthermore, pre-dose blood samples were taken at days 2, 4, 6 and 15.

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Pharmacokinetic analysis

Based on the Org 30659 concentrations in plasma and the EE concentrations in serum, the following (non-compartmental) pharmacokinetic parameters

were calculated, both after the first single dose and at steady-state after the final dose: the peak concentration (C_{max}) and its time of occurrence (t_{max}), the elimination half-life ($t_{½}$), the area under the concentration-versus-time curve ($AUC_{0-\infty}$ and $AUC_{0-\tau}$), the apparent clearance (CL_{app}) and the apparent volume of distribution ($V_{z,app}$). From the steady-state wash-out curve after the final dose (dosing interval, τ=24h), the following additional pharmacokinetic parameters were calculated: the peak concentration at steady-state corrected for pre-dose concentration ($C_{max,corr}$), the average concentration at steady-state (C_{av}) and the degree of fluctuation (DF). Also weight-normalised (wn) pharmacokinetic parameters were calculated. Two types of accumulation ratios were calculated from the single-dose and steady-state parameters: R_{A1} (=$C_{ss,max}/C_{sd,max}$) and R_{A2} (=$AUC_{ss,0-\tau}/AUC_{sd,0-\tau}$). Based on the pre-dose concentrations during the multiple-dose treatment, the mean pre-dose concentration at steady-state ($C_{ss,min,av}$) and the mean time of attainment of steady-state (t_{ss}) were obtained. All calculations were performed using SAS V6.12 (SAS Institute, Inc., Cary, NC).

Statistical analysis

Analysis of Variance (ANOVA) was performed on the PK parameters using a mixed model with fixed factors 'Ethnic group' (Japanese versus Caucasian) and 'Regimen' (steady-state versus single dosing), interaction 'Ethnic group'-by-'Regimen' and random factor 'Subject' nested within 'Ethnic group'. The primary PK parameters were (wn-)AUC and (wn-)C_{max}: for single dose $AUC_{0-\infty}$ and C_{max} were used and for steady-state AUC_{0-24} and $C_{max,corr}$, respectively. For the factor 'Ethnic group', point estimates and 90% confidence intervals for the ratio of Japanese over Caucasian means were calculated, both at steady-state and after single dosing. Similar pharmacokinetics between Japanese and Caucasian subjects was to be concluded when the 90% confidence intervals for the primary PK parameters were fully contained within the acceptance range of 0.70-1.43.
For the factor 'Regimen', point estimates and 95% confidence intervals for the ratio of steady-state over single-dose means were calculated, both for Japanese and Caucasian subjects. When the 95% confidence intervals for the primary PK parameters contained a ratio of one (indicating non-significance at the 5% level of significance), the absence of a regimen effect on the pharmacokinetics was to be concluded (i.e. time independent pharmacokinetics). To study the influence of SHBG on the primary pharmacokinetic parameters of Org 30659 and EE, additional ANOVAs were performed using the same model extended with pre-dose SHBG value as covariate (after logarithmic

transformation). For the single-dose PK parameters the pre-dose SHBG value from single-dose period day 1 was used and for the steady-state PK parameters the pre-dose SHBG value from multiple-dose period day 24 was used.
For all other (supportive) pharmacokinetic parameters, point estimates and 95% confidence intervals for the ratio of ethnic group means and for the ratio of regimen means were calculated using the same ANOVA model as for the primary PK parameters. Conclusions for these parameters were based on classical hypothesis testing (at the 5% level of significance).
Log-transformed values of the parameters were used in the ANOVAS except for t_{max} for which an ANOVA on ranks was performed.
All analyses were performed using SAS V6.12 (SAS Institute, Inc., Cary, NC).

Data management

Data from working copies of case report forms, obtained from ProMaSys (Protocol Management System v3.2, CHDR, The Netherlands), were directly entered into the ProMaSys. The Japanese site had access to this database system using an Internet connection.

Results

Demographics

In the Netherlands, a total of 19 subjects were included in this trial. One subject dropped-out due to difficulty in blood sampling immediately after the first dose and was subsequently replaced. In Japan, a total of 18 subjects were included in this trial. Mean (SD) age, weight, height and BMI of the Caucasian subjects were 25.4 (4.5) years, 69.4 (8.8) kg, 172 (6.4) cm and 23.4 (2.3) kg/m^2, respectively. Mean (SD) age, weight, height and BMI of the Japanese subjects were 27.8 (6.1) years, 53.6 (5.4) kg, 158 (5.7) cm and 21.5 (2.3) kg/m^2, respectively.

Comparison of single-dose and steady-state pharmacokinetics

The single-dose and steady-state pharmacokinetic parameters for both ethnic groups are summarised in Tables 1 and 2. The average time-effect profiles from 0-8 hours after dosing are displayed in Figure 1. The results of

the ANOVAs for the statistical comparison of single-dose and steady-state PK parameters are given in Table 3. For two subjects, both after single dosing and at steady-state, several plasma concentrations of Org 30659 around t_{max} were unreportable and therefore no PK parameters for Org 30659 were reported for these subjects.

TABLE 1 **Single-dose and steady-state pharmacokinetics of Org 30659 in Caucasian and Japanese subjects. Based on n=34 subjects for Org 30659. Presented are median (min-max) for t_{max}; geometric mean (geometric CV%) for other PK parameters**

	Org 30659			
	CAUCASIAN WOMEN		**JAPANESE WOMEN**	
Parameter (unit)	**Single Dose**	**Steady-state**	**Single Dose**	**Steady-state**
C_{max} (ng/mL)	1.78 (32.8)	3.99 (32.7)	2.85 (34.1)	7.87 (28.8)
t_{max} (h)	0.75 (0.50-1.02)	0.50 (0.45-1.50)	0.767 (0.75-1.50)	0.583 (0.50-1.00)
$t_{½}$ (h)	10.4 (47.8)	13.3 (26.5)	14.4 (31.9)	12.1 (25.6)
AUC* (ng(h/mL)	6.23 (27.4)	13.6 (29.5)	10.9 (31.3)	25.4 (30.1)
wn-CL_{app} (L/h/kg)	0.469 (28.2)	0.213 (30.3)	0.346 (27.1)	0.149 (29.3)
wn-$V_{z,app}$ (L/kg)	6.80 (43.8)	4.30 (44.7)	7.22 (47.5)	2.60 (43.4)
C_{av} (ng/mL)	-	0.567 (29.5)	-	1.06 (30.1)
DF (%)	-	674 (23.2)	-	713 (18.6)
$C_{min,av}$ (ng/mL)	-	0.157 (48.7)	-	0.319 (43.2)
R_{A1}	-	2.17 (23.1)	-	2.76 (34.2)
R_{A2}	-	2.52 (21.9)	-	2.93 (36.4)

*: $AUC_{0-\infty}$ for single dose and AUC_{0-24} for steady-state; -: not applicable.

Steady-state was reached for Org 30659 after 24 days of multiple dosing and for EE after 15 days of multiple dosing. The pharmacokinetics of Org 30659 and EE are time-dependent, both in Caucasian and in Japanese women, after administration of this combination drug. In general, C_{max} and AUC at steady-state are higher than would be predicted assuming linear pharmacokinetics over time.

Assuming linear pharmacokinetics over time for Org 30659 there would have been no significant differences in C_{max} and AUC between steady-state and single dosing. In Table 3 it can be read that the C_{max} at steady-state is 111% higher than after single dosing in Caucasian women (in Japanese women 165%). The daily AUC_{0-24} at steady-state is 115% higher than the total $AU_{0-\infty}$ after single dosing in Caucasian women (in Japanese women 132%).

For EE, the C_{max} at steady-state is 37% higher than after single dosing in Caucasian women (in Japanese women 53%). The AUC_{0-24} at steady-state is 11% lower than the total $AUC_{0-\infty}$ after single dosing in Caucasian women, whereas in Japanese women the AUC is 24% higher at steady-state than after single dosing.

TABLE 2 **Single-dose and steady-state pharmacokinetics of EE in Caucasian and Japanese subjects. Presented are median (min-max) for t_{max}; geometric mean (geometric CV%) for other PK parameters**

	EE			
	CAUCASIAN WOMEN		JAPANESE WOMEN	
Parameter (unit)	**Single Dose**	**Steady-state**	**Single Dose**	**Steady-state**
C_{max} (pg/mL)	49.2 (37.7)	80.6 (31.2)	74.5 (34.0)	128 (37.0)
t_{max} (h)	2.00 (0.75-4.02)	1.50 (0.50-2.02)	1.50 (1.00-2.00)	1.50 (0.50-2.02)
$t_{½}$ (h)	27.9 (48.9)	19.8 (24.2)	19.8 (46.8)	17.4 (25.3)
AUC* (pg·h/mL)	747 (42.8)	664 (26.2)	741 (33.5)	912 (25.7)
wn-CL_{app} (L/h/kg)	0.389 (40.2)	0.438 (26.2)	0.511 (33.2)	0.411 (25.8)
wn-$V_{z,app}$ (L/kg)	15.7 (38.8)	12.5 (29.4)	14.6 (40.6)	10.3 (25.7)
C_{av} (pg/mL)	-	27.6 (26.2)	-	38.0 (25.7)
DF (%)	-	241 (20.6)	-	296 (19.2)
$C_{min,av}$ (pg/mL)	-	13.2 (42.6)	-	15.1 (40.1)
R_{A1}	-	1.64 (23.5)	-	1.73 (28.4)
R_{A2}	-	1.70 (28.6)	-	1.96 (22.9)

*: $AUC_{0-\infty}$ for single dose and AUC_{0-24} for steady-state; -: not applicable.

TABLE 3 **Comparison of single-dose and steady-state pharmacokinetic parameters for both Caucasian and Japanese subjects. Point estimates are ratios of geometric least-squares (LS) means. Based on n=34 subjects for Org 30659 and n=36 subjects for EE. Time-independent pharmacokinetics if Regimen effect was not significant**

Compound	Ethnic group	Parameter	Point Estimate μ(ss)/μ(sd)	95% Confidence Interval	Significance
Org 30659	Caucasian	C_{max}	2.11	1.82-2.45	yes
		AUC	2.15	1.87-2.47	yes
		$t_{½}$	1.28	1.08-1.52	yes
	Japanese	C_{max}	2.65	2.30-3.05	yes
		AUC	2.32	2.03-2.65	yes
		$t_{½}$	0.84	0.71-1.00	yes
EE	Caucasian	C_{max}	1.37	1.21-1.54	yes
		AUC	0.89	0.76-1.04	no
		$t_{½}$	0.71	0.56-0.90	yes
	Japanese	C_{max}	1.53	1.34-1.74	yes
		AUC	1.24	1.05-1.45	yes
		$t_{½}$	0.88	0.68-1.13	no

FIGURE 1 **Average (+ SD) concentration-time profiles (from 0-8 hours after dosing) of Org 30659 and EE after single dose (○) and at steady state (●) for both Caucasian and Japanese subjects**

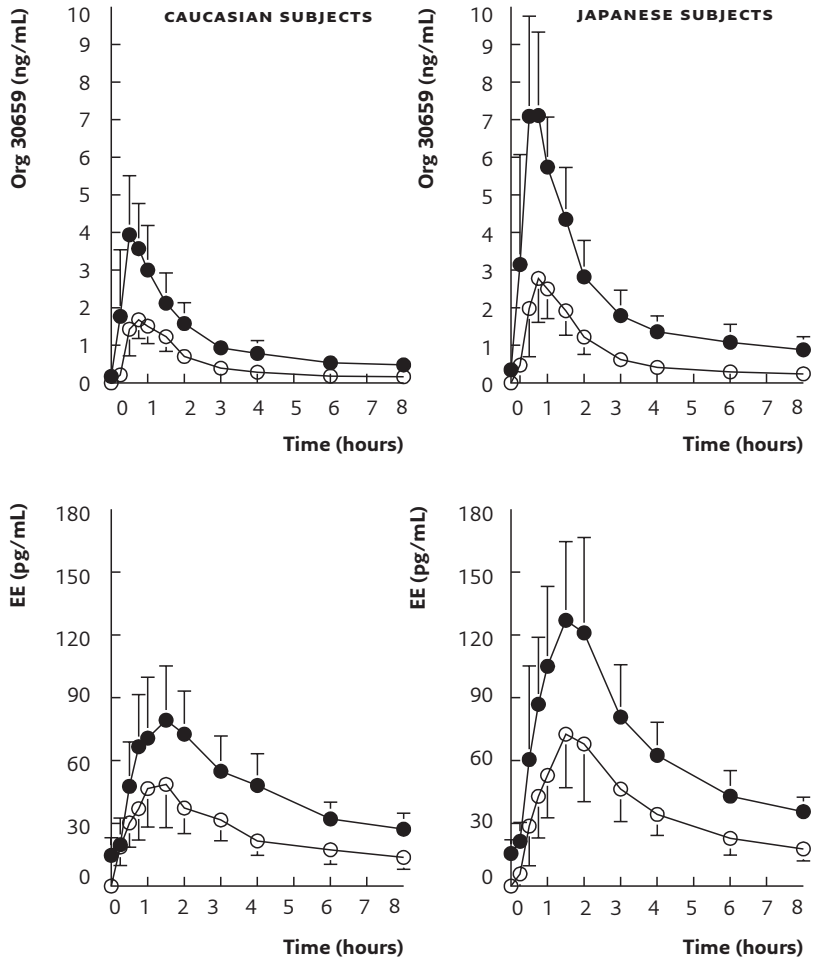


Table 3 shows that the elimination half-life of Org 30659 in Caucasian subjects is significantly longer at steady-state than after single dosing, whereas in Japanese subjects the half-life is significantly shorter at steady-state. For EE, the half-life at steady-state in Caucasians is significantly shorter than after single dosing.

For Org 30659, the median t_{max} at steady-state (0.5 h) was found to be significantly shorter than the median t_{max} after single dosing (0.75 h). Also for EE, the median t_{max} at steady-state was somewhat shorter than after single dosing.

Comparison of pharmacokinetics in Caucasian and Japanese women

The results of the ANOVAs for the statistical comparison of primary PK parameters between Caucasian and Japanese women are given in Table 4.

TABLE 4 **Comparison of Caucasian and Japanese pharmacokinetic parameters after single dose and at steady state. Point estimates are ratios of geometric least-squares (LS) means. Based on n=34 subjects for Org 30659 and n=36 subjects for EE. Similar pharmacokinetics if 90% Confidence Interval contained within acceptance range 0.70-1.43**

Compound	Regimen	Parameter	Point Estimate μ(Jap)/μ(Cauc)	90% Confidence Interval	Conclusion kinetics
Org 30659	Single dose	C_{max}	1.60	1.33-1.93	not similar
		wn-C_{max}	1.24	1.04-1.48	not similar
		AUC	1.75	1.48-2.08	not similar
		wn-AUC	1.36	1.15-1.60	not similar
	Steady state	C_{max}	2.01	1.67-2.43	not similar
		wn-C_{max}	1.55	1.29-1.86	not similar
		AUC	1.90	1.60-2.25	not similar
		wn-AUC	1.46	1.23-1.72	not similar
EE	Single dose	C_{max}	1.51	1.24-1.84	not similar
		wn-C_{max}	1.17	0.97-1.40	similar
		AUC	0.99	0.82-1.19	similar
		wn-AUC	0.76	0.64-0.91	not similar
	Steady state	C_{max}	1.69	1.39-2.05	not similar
		wn-C_{max}	1.31	1.09-1.57	not similar
		AUC	1.38	1.15-1.64	not similar
		wn-AUC	1.07	0.89-1.27	similar

Pharmacokinetics of Org 30659 in Japanese and Caucasian women are not similar after administration of this combination drug. The C_{max} of Org 30659 after single dosing is 60% higher in Japanese women than in Caucasian women. At steady-state this difference mounts up to 101%. Corrected for

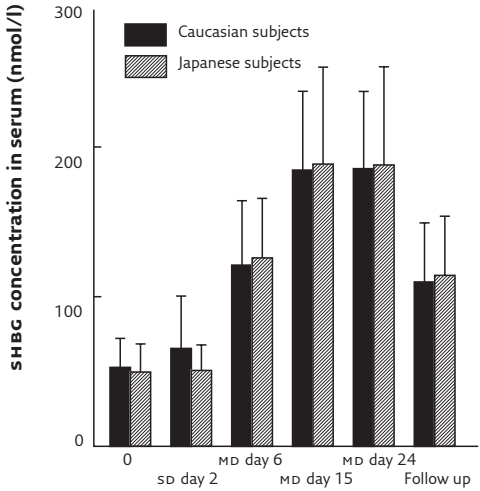
differences in body weight between Caucasian and Japanese women, the weight normalised-C_{max} of Org 30659 after single dosing is 24% and at steady-state 55% higher in Japanese women than in Caucasian women. The AUC of Org 30659 after single dosing is 75% higher in Japanese women than in Caucasian women. At steady-state this difference mounts up to 90%. Corrected for differences in body weight between Caucasian and Japanese women, the wn-AUC of Org 30659 after single dosing is 36% and at steady-state 46% higher in Japanese women than in Caucasian women. No overall significant differences in elimination half-life or t_{max} were observed between the two ethnic groups.

The C_{max} of EE follows the same pattern as the C_{max} of Org 30659. The C_{max} of EE after single dosing is 51 % higher in Japanese women than in Caucasian women. At steady-state this difference mounts up to 69%. After weight-normalisation the difference disappears for the single dose (17% higher, but not significantly different). At steady-state the wn-C_{max} is still 31% (statistically significant) higher in Japanese women. The AUC of EE after single dosing is similar in Caucasian and Japanese women. After weight normalisation, the wn-AUC is 24% lower in Japanese women. The AUC of EE at steady-state is 38% higher in Japanese women than in Caucasian women. Corrected for differences in body weight, this difference is reduced to 7%. The mean $t_{1/2}$ after single dosing for Caucasians was significantly longer than the $t_{1/2}$ after single dosing for Japanese women (see Table 2). There were no significant differences in t_{max} between Caucasian and Japanese women.

Sex hormone binding globulin

Averaged sex hormone binding globulin (SHBG) values are represented in Figure 2. SHBG increased during the trial for all subjects. At follow up all SHBG values had decreased but were still above the baseline values. After inclusion of SHBG into the PK model of Org 30659, the ratio of geometric AUC means for steady-state over single dose decreased from 2.15 to 1.12 for Caucasian subjects and from 2.32 to 1.20 for Japanese subjects. The statistical analysis showed that SHBG played no significant role in the comparison of the pharmacokinetics between Caucasian and Japanese subjects. However, the increase in SHBG after multiple dosing provided an explanation for the observed differences in pharmacokinetics of Org 30659 between single dose and steady-state.

FIGURE 2 **Average (+ SD) Sex Hormone Binding Globulin concentrations for both Caucasian and Japanese subjects. (Follow-up was performed 7-15 days after last intake of study medication)**



Safety parameters

There were neither serious adverse events reported nor any deaths. None of the reported adverse events led to the drop-out of any subject from the trial. One reported severe adverse event was in fact an exacerbation of pre-existing shoulder pain. All the other adverse events were of mild or moderate intensity. The most frequently reported drug related adverse events included bleeding irregularities. Adverse events in this trial were somewhat differently reported between the two ethnic groups, particularly regarding the reproductive disorder class. Adverse events in the reproductive disorder class were reported by Caucasian subjects as abdominal pain associated with bleeding irregularities (n=6 and n=15 respectively) while the Japanese subjects reported this as dysmenorrhoea with bleeding irregularities (n=3 and n=18 respectively). Breast enlargement (n=5), peripheral oedema (n=9), treatment related hot flushes, somnolence and malaise (n=4) were reported only by Japanese. In general more treatment related adverse events were reported by the Japanese population compared to the Caucasian population (82 and 45 respectively). No clinically relevant abnormalities were found in vital signs, nor were there any consistent changes observed in ECG parameters and other safety measures. No other clear difference in any of the safety measurements was noted between the two ethnic groups.

Discussion

The primary objectives of this trial were to compare the pharmacokinetic parameters and safety of Org 30659 and EE in Caucasian and Japanese women after single and multiple dose administration and to compare the single dose and steady-state pharmacokinetics of Org 30659 and EE.

The pharmacokinetics of Org 30659 and to a lesser extent EE were significantly different between the two ethnic groups following the single dose administration of the tablet containing both 200 µg Org 30659 and 20 µg EE. This difference in the kinetics was further increased after steady-state was reached, following multiple administration of these tablets. Weight normalisation reduced but did not diminish the observed differences. SHBG concentrations could not explain these findings either. Therefore, other factors like phenotypic differences (including dietary or environmental factors) and genetic differences in absorption and/or metabolism could account for the observed kinetic differences between the two ethnic groups.

Ethnic differences in the pharmacokinetics of EE have been reported previously. EE is extensively metabolised by UDP-gluceronosyltransferase (UGT) 1A1, which also catalyses the glucuronidation of bilirubin and xenobiotic phenols and some steroids. Mutations of UGT1A1 cause the unconjugated hyperbilirubinemias known as Crigler-Najjar syndrome and Gilbert's syndrome. The frequencies of individual UGT1A1 polymorphisms show extensive variability across ethnic groups. The incidence of nonphysiologic neonatal hyperbilirubinemia is twice as high in East Asians as in whites. Furthermore, consistent inter-individual and ethnic differences have been reported in the degree of oxidative metabolism of EE that could attribute to the differences observed in the current study.

ref. 15-17
ref. 18-22
ref. 23
ref. 24
ref. 25-26

Phase II metabolism, and in particular conjugation with glucuronic acid is also suggested to be the major metabolic route for Org 30659 *in vivo*. UGT2B7 is suggested to play an important role in this conjugation. Large differences in polymorphism between Asians and Caucasians have been suggested. It is reported that only 9.4% of the investigated Asian population are UGT2B7(Y^{268}) homozygous compared with 29.2% of Caucasians. Asians had a higher prevalence of the homozygous UGT2B7(H^{268}) compared to the Caucasian population: 56.2% vs 21.8%. The corresponding phenotypical differences of these polymorphisms have not been determined. The data from this study suggests that the homozygous UGT2B7(Y^{268}) genotype might be associated with higher metabolic activity compared to the homozygous UGT2B7(H^{268}) genotype.

ref. 27
ref. 22

The apparent accumulation of Org 30659 after multiple dosing is probably related to the strong increase in SHBG levels induced by EE. The reduced clearance at steady-state could be a reflection of the binding of Org 30659 to proteins or change in metabolism at steady-state. However, the accumulation of EE cannot be explained by increased SHBG levels because EE binds for 98% to albumin and has no affinity for SHBG. The accumulation of EE is notably less than of Org 30659.

ref. 28

Adverse events in this study were somewhat differently reported between the two ethnic groups. More treatment related adverse events were reported by the Japanese population compared to the Caucasian population. The clear difference in pharmacokinetics between the two groups (higher Org 30659 concentrations and (peak) EE concentrations in the Japanese population) could contribute to these apparent differences. However, another factor that may explain these differences could be the number of OC-users before the start of the trial. None of the Japanese subjects were OC-users, while all but five of the Caucasian subjects were OC-users. This difference in experience with the use of COC may have contributed to the difference in AE reporting. No consistent changes were found in vital signs, ECG and clinical laboratory data and no clear differences for these safety measures were noted between the two ethnic groups, supporting that the combination of Org 30659 and EE was safe.

This study showed that it is possible to adequately perform a bridging study between Japanese subjects studied in Japan and Caucasian volunteers studied in the Netherlands using a single protocol and data management system. This type of study can be performed at an early stage in the drug development and can provide essential information for the future development of western drugs in Japan. There appear to be differences in the pharmacokinetic handling of both EE and a new synthetic progestagen between Japanese and Caucasian women. The clinical consequences of these differences require further investigation.

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REFERENCES

1 Inman WH, Vessey MP, Westerholm B, Engelund A. Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. *Br Med J* 1970; 2(703):203-209

2 Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 30-microgram oestrogen preparations. *Br Med J* 1980; 280(6224):1157-1161

3 Hulka BS, Chambless LE, Kaufman DG, Fowler WC, Jr., Greenberg BG. Protection against endometrial carcinoma by combination-product oral contraceptives. *JAMA* 1982; 247(4):475-477

4 Brinton LA, Vessey MP, Flavel R, Yeates D. Risk factors for benign breast disease. *Am J Epidemiol* 1981; 113(3):203-214

5 (RCGP) Royal College of General Practitioners' Oral Contraception Study. Effect on hypertension and benign breast disease of progestagen component in combined oral contraceptives. *Lancet* 1977; 1(8012):624

6 Rosenblatt KA, Thomas DB. Hormonal content of combined oral contraceptives in relation to the reduced risk of endometrial carcinoma. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer* 1991; 49(6):870-874

7 Weiss NS, Sayvetz TA. Incidence of endometrial cancer in relation to the use of oral contraceptives. *N Engl J Med* 1980; 302(10):551-554

8 Kaunitz AM. Oral contraceptive health benefits: perception versus reality. *Contraception* 1999; 59 (1 Suppl):29S-33S

9 Rohan TE, Miller AB. A cohort study of oral contraceptive use and risk of benign breast disease. *Int J Cancer* 1999; 82(2):191-196

10 Sanderson M, Williams MA, Weiss NS, Hendrix NW, Chauhan SP. Oral contraceptives and epithelial ovarian cancer. Does dose matter? *J Reprod Med* 2000; 45(9):720-726

11 Kloosterboer HJ, Vonk-Noordegraaf CA, Turpijn EW. Selectivity in progesterone and androgen receptor binding of progestagens used in oral contraceptives. *Contraception* 1988;38:325-32

12 Thorneycroft IH. Evolution of progestins. Focus on the novel progestin drospirenone. *J Reprod Med* 2002;47:975-80.

13 Obruca A, Korver T, Huber J, Killick SR, Landgren B, Struijs MJ. Ovarian function during and after treatment with the new progestagen Org 30659. *Fertil Steril* 2001; 76(1):108-115

14 Timmer CJ, Mulders TM. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. *ClinPharmacokinet* 2000;39:233-42.

15 Fotherby K, Akpoviroro J, Abdel-Rahman HA, Toppozada HK, de Souza JC, Coutinho EM et al. Pharmacokinetics of ethynyloestradiol in women for different populations. *Contraception* 1981;23:487-96.

16 Fotherby K. Variability of pharmacokinetic parameters for contraceptive steroids. *J Steroid Biochem* 1983;19:817-20.

17 Goldzieher JW, Dozier TS, de la PA. Plasma levels and pharmacokinetics of ethynyl estrogens in various populations. I. Ethynylestradiol. *Contraception* 1980;21:1-16.

18 Burchell B, Soars M, Monaghan G, Cassidy A, Smith D, Ethell B. Drug-mediated toxicity caused by genetic deficiency of UDP-glucuronosyltransferases. *Toxicol Lett* 2000; 112-113:333-340

19 Ebner T, Remmel RP, Burchell B. Human bilirubin UDP-glucuronosyltransferase catalyzes the glucuronidation of ethinylestradiol. *Mol Pharmacol* 1993; 43(4):649-654

20 Green MD, King CD, Mojarrabi B, Mackenzie PI, Tephly TR. Glucuronidation of amines and other xenobiotics catalyzed by expressed human UDP-glucuronosyltransferase 1A3. *Drug Metab Dispos* 1998; 26(6):507-512

21 de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans. Pharmacogenetic and developmental aspects. *Clin Pharmacokinet* 1999; 36(6):439-452

22 Lampe JW, Bigler J, Bush AC, Potter JD. Prevalence of polymorphisms in the human UDP-glucuronosyltransferase 2B family: UGT2B4(D458E), UGT2B7(H268Y), and UGT2B15(D85Y). *Cancer Epidemiol Biomarkers Prev* 2000; 9(3):329-333

23 Mackenzie PI, Miners JO, McKinnon RA. Polymorphisms in UDP glucuronosyltransferase

genes: functional consequences and clinical relevance. *Clin Chem Lab Med* 2000; 38(9):889-892

24 Maruo Y, Nishizawa K, Sato H, Doida Y, Shimada M. Association of neonatal hyperbilirubinemia with bilirubin UDP- glucuronosyltransferase polymorphism. *Pediatrics* 1999; 103(6 Pt 1):1224-1227

25 Goldzieher JW, Brody SA. Pharmacokinetics of ethinyl estradiol and mestranol. *Am J Obstet Gynecol* 1990;163:2114-9.

26 Williams MC, Goldzieher JW. Chromatographic patterns of urinary ethynyl estrogen metabolites in various populations. *Steroids* 1980;36:255-82.

27 Verhoeven CH, Gloudemans RH, Groothuis GM, Rietjens IM, Vos RM. Excretion balance and metabolism of the progestagen Org 30659 in healthy postmenopausal women. *J Steroid Biochem Mol Biol* 2000; 73(1-2):39-48

28 Serin IS, Ozcelik B, Basbug M, Aygen E, Kula M, Erez R. Long-term effects of continuous oral and transdermal estrogen replacement therapy on sex hormone binding globulin and free testosterone levels. *Eur J Obstet Gynecol Reprod Biol* 2001; 99(2):222-225