PHARMACOKINETICS AND DISPOSITION

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Influence of gender on the pharmacokinetics, safety, and tolerability of cerivastatin in healthy adults

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Abstract The pharmacokinetics, safety, and tolerability of cerivastatin, a synthetic HMG-CoA reductase inhibitor were studied in 49 healthy volunteers. In this double-blind, parallel group, multiple-dose study, volunteers were randomized as age-matched, male-female pairs and stratified into younger (18–65 years, premenopausal females) or older (65–85 years, postmenopausal females) groups. Thirty-two (16 female, 16 male) subjects received 0.2 mg cerivastatin daily for 7 days; 17 received placebo. Between all males and females, no differences in cerivastatin pharmacokinetics were observed. The AUC\textsubscript{norm} in older females was 21% higher than in older males, while the AUC\textsubscript{norm} in younger females was 26% lower than in younger males. The C\textsubscript{max} in older females was 30% higher than in age-matched males or younger males and females. All other pharmacokinetic parameters, including half-life, t\textsubscript{max}, accumulation ratios, and steady state plasma levels were similar in all treatment groups. The most common adverse events, including headache (4), dyspepsia (4), and rash (4), were equally distributed between groups. Treatment-emergent elevations (<2×ULN) in creatine kinase occurred in one subject. Transaminase elevations occurred in nine subjects, most were less than 3×ULN, and were equally distributed between groups. In conclusion, cerivastatin was well tolerated. The minor differences in the pharmacokinetics of cerivastatin 0.2 mg between genders does not require modification of dosage.

Key words HMG-CoA reductase inhibitor · Cerivastatin · Statins

Introduction

The role of gender as a risk factor for the development of cardiovascular disease is now well established. Premenopausal women have relatively low cardiovascular risk compared to age-matched males. However, after the age of 50, the rate of coronary mortality is dramatically increased in both genders [1, 2].

Because of their efficacy and excellent tolerability, HMG-CoA reductase inhibitors (statins) are now the first choice for the pharmacologic treatment of hyperlipidemia when diet alone is insufficient to bring lipid parameters to levels recommended by the National Cholesterol Education Program [3, 4]. Several primary and secondary prevention studies (4S, CARE, LIPID, AFCAPS/ TexCAPS) [5, 6, 7, 8, 9] have demonstrated that some statins can reduce the risk of cardiovascular events in both male and female patients. The efficacy of these statins in reducing mortality appears, in some cases, to be gender-dependent favoring women, although this has not been consistently observed. For example, pravastatin reduced the risk of a cardiovascular event by 46% in females and 20% in males [7] while simvastatin reduced coronary vascular risk by 35% in both males and females [5, 6]. However, the differential degrees of reduction in mortality may not be due specifically to gender-dependent reductions in LDL-C. Other reports demonstrate that pravastatin reduced LDL-C by similar degrees in males and females [10], while simvastatin reduced LDL-C to a greater extent in women (35%) relative to men (27%) [11]. These findings suggest that women and men with cardiovascular disease, especially those above 50 years of age, benefit from lipid-lowering therapy.

Cerivastatin is a synthetic statin which reduces mean LDL-C from 28%–44%. [12, 13]. The pharmacokinetics of cerivastatin at doses ranging from 0.3 to 0.8 mg are linear, i.e., C\textsubscript{max} and AUC increase in proportion to
dose [13]. Cervistatin is well tolerated, with adverse events rates being nearly indistinguishable from placebo [14]. In a recently completed clinical trial, it was observed that the lipid-lowering effects of cervistatin were more pronounced in women [15].

The objectives of this extended phase I clinical study were twofold; first, to evaluate the pharmacokinetics, safety, and tolerability of multiple doses of cervistatin 0.2 mg administered to females versus age-matched males, and, secondly, to investigate the multiple-dose pharmacokinetics of cervistatin in older females relative to younger females.

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**Materials and methods**

**Study design and treatment regimens**

This was a two-center, double-blind, parallel group, multiple-dose study designed to assess the safety, tolerability and pharmacokinetics of cervistatin in male versus female subjects stratified for age. Twenty-four males were matched within 3 years of age to 24 females. The age-matched groups were stratified so that 12 pairs were older than 65 years of age and 12 pairs would be younger than or 65. The 24 pairs were then randomized so that 16 pairs received cervistatin and 8 pairs received placebo. Thirty-two individuals (16 males, 16 females) received cervistatin and 16 individuals (8 males, 8 females) received placebo.

Subjects were screened up to three weeks prior to onset of the study. Screening and other pretreatment procedures consisted of complete medical history, physical examination, chest X-ray, and an ophthalmological examination (fundoscopy and slit lamp examination). Laboratory tests included blood chemistries, thyroid hormone levels, complete blood count (CBC), urinalysis and urinary renal markers. A screen for drugs of abuse was also performed. At day 1, eligible subjects were requalified by a second laboratory screening and a physical examination. On day 1, qualified subjects were randomized, and began 7 days of double-blind study drug (cervistatin or placebo). Cervistatin was given as two 0.1-mg tablets, taken with the evening meal.

Concomitant medications, including nonsteroidal anti-inflammatory drugs and antacids, and drugs known to interfere with the metabolism of cervistatin were not permitted. Subjects taking aspirin on a continuous prescribed regimen were eligible for enrollment. Acetaminophen was the only medication permitted on an as-needed basis.

**Patient population**

Healthy normocholesterolemic male and female (postmenopausal or surgically sterile) volunteers between the ages of 18 and 75 years were selected for this study. Each group of younger (18–65) and older (65–85) subjects were comprised of 12 men and 12 women. Subjects provided informed consent prior to participation in this study. Subjects were excluded if they tested positive for HIV or hepatitis B antigen, had a history of gastrointestinal disorders, malignancy or psychiatric disorder, prior exposure to cervistatin, known hypersensitivity to HMG-CoA reductase inhibitors, abused alcohol or drugs, or had donated blood within 30 days of randomization. Other exclusion criteria included abnormal laboratory blood indices: hematocrit lower than 35%, CK greater than or equal to 2×ULN, serum creatinine higher than 1.6 mg/dl, or a fasting blood sugar equaling or exceeding 140 mg/dl.

**Pharmacokinetic evaluation**

Cervistatin was measured in plasma samples collected immediately prior to the first dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h postdose on days 1 and 7. On days 5 and 6, blood samples were collected immediately prior to dose, and 2 h postdose for drug concentration assay. Samples were collected into tubes containing EDTA and centrifuged; the plasma was then stored at −20°C until assayed by HPLC using fluorescence spectroscopy [16]. Pharmacokinetic variables evaluated in this study included the area under the curve for 24 h (AUC₀–24), peak concentration (Cmax), time of peak concentration (tmax), and half-life (t½). The AUC was corrected for dose (mg) and body weight (kg) to yield AUCₐₙₙₜ. To determine if cervistatin accumulated over the 7-day treatment period, two values were calculated: the 7-day accumulation ratio (defined as the ratio of day 7/day 1 AUC₀–24) and the linear accumulation ratio index (defined as the AUC₀–24, day 7/ AUC₀–ₙᵢₜ, day 1).

**Safety assessments**

All observations pertinent to the safety of cervistatin were recorded on all subjects, including results of laboratory analysis, physical examination, adverse events, concurrent illness, and vital sign data.

Brief physical examinations, including body temperature and respiratory rate were performed at day −1, prior to dosing on day 1, and on each day of the study. Each subject over 65 years of age received a 12-lead ECG recorded on days −1, 2, and 7. All subjects received a 12-lead ECG recorded on day 3. On day 8, a repeat ophthalmological evaluation was performed. Supine and standing blood pressure and pulse rates were measured within 15 min before dosing, and within 5 min of blood sample draws at the indicated times postdose on days 1 and 7, and within 15 min before the dose and within 5 min of blood sample draws at 1, 2, 4, 6, 8, 12, 16, and 24 h postdose on day 8. On days 2 through 6, supine and standing blood pressures and pulse rates were recorded within 15 min of each evening dose and at 2 h postdose. On day 10, the final day of the study, all subjects were given a complete physical examination.

Laboratory tests included blood chemistries, thyroid hormone levels, CBC, urinalysis, and a screen for drugs of abuse. On days −1, 2, 4, and 6, a full laboratory screen was performed, which included CBC, with differential and platelet count, PT, PTT, serum glucose, uric acid, calcium, phosphate, sodium, potassium, chloride, CO₂, creatinine, BUN, total protein, albumin, CK, SGOT, SGPT, LDH, albumin, alkaline phosphatase, γ-aminolevulinic acid, total and direct bilirubin. An abbreviated chemistry profile was performed on days 3, 5, and 7, which included total and direct bilirubin, alkaline phosphatase, SGPT, SGOT, LDH, CK, glucose, creatinine, BUN, γ-aminolevulinic acid, and total cholesterol. Thyroid hormone levels were measured on the screening visit and on day 10. Endocrine status was determined by measurements of cortisol, free and total testosterone, FSH, LH, and 17α-epiandrosterone, obtained on days −1, 1, 7, and 10.

**Statistical methodology**

Summary statistics of baseline and demographic variables were prepared for each gender stratified by age. For each gender, age, and treatment group combination, frequencies of adverse events are presented, as well as summary values for changes from baseline in demographic and pharmacokinetic variables.

For AUC, sample size was determined on the assumption of a greater than or equal to 50% increase in the AUC in older relative to younger subjects. Thus, with a sample size of 18 older and 8 younger control subjects, the point of the test of equality of the groups at a 10% two-sided significance level is 95%. This is based on a between-subject standard deviation of 0.28 for log AUC. For each pharmacokinetic parameter, logarithmically transformed estimates for each subject were analyzed by one-way analysis of variance (ANOVA). Log-scale differences in means between groups were exponentiated to obtain ratio estimates. Lower and upper confidence limits based on one-sided P < 0.05 level tests are demonstrated. Within-subject ratios for AUC and Cmax (day 7/day 1)