Raloxifene pharmacokinetics in males with normal and impaired renal function

David Czock,¹ Frieder Keller,¹ Mette Heringa² & Franz Maximilian Rasche¹

¹University Hospital Ulm, Division of Nephrology, Ulm, Germany, ²University of Utrecht, Department of Pharmaceutics, Utrecht, Netherlands

Correspondence

Frieder Keller, M.D., University Hospital Ulm, Division of Nephrology, Robert-Koch-Strasse 8, 89070 Ulm, Germany.
Tel: +(49) 731 50024341
Fax: +(49) 731 50024483
E-mail: frieder.keller@medizin.uni-ulm.de

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Aims

To compare raloxifene pharmacokinetics between renally impaired and healthy subjects.

Methods

Raloxifene 120 mg was administered to 10 males with renal impairment (creatinine 2–4 mg dl⁻¹) and to 10 healthy males. Data were analysed by two noncompartmental and one compartmental nonlinear regression methods.

Results

The medians (95% confidence interval) of the area under the curves (AUC) were 35.1 (25.8, 74) and 20.5 (16.8, 28.0) h ng ml⁻¹ per mg kg⁻¹, $P < 0.01$, and of the clearances (CL/F) were 28.5 (13.5, 38.8) and 48.8 (35.8, 59.4) l h⁻¹ kg⁻¹, $P < 0.01$, in renally impaired and healthy subjects, respectively. 95% Confidence intervals on the differences for AUC and CL/F were 6.5–44.1 and –35.1 to –7.9, respectively.

Conclusion

Exposure to raloxifene was twice as high in males with renal impairment compared with healthy subjects.

Introduction

Raloxifene, a selective oestrogen receptor modulator, is used to treat osteoporosis in postmenopausal women, but it may also be effective in men with this disease, and also in patients with renal bone disease [1].

Raloxifene is metabolized by UDP-glucuronosyl-transferases in the liver, and the resulting glucuronides are excreted via the bile into the intestine [2]. Raloxifene is assumed to undergo enterohepatic recycling, because of the appearance of multiple peaks in its plasma concentration time profile [2, 3]. Renal impairment is

expected not to affect the pharmacokinetics of raloxifene because the renally excreted fraction is only 6% in healthy subjects [2, 4].

In the present study we compared the pharmacokinetics of raloxifene in males with renal impairment to those with normal renal function.

Materials and methods

Subjects and ethics

Twenty Caucasian males were studied. Ten subjects had normal renal function with a median (range) serum cre-

atinine of 1.1 mg dl^{-1} (0.9–1.2) and a creatinine clearance of 117 ml min^{-1} (90–128) as estimated by the Cockcroft and Gault formula. Their median (range) age was 37 years (30–51), height 182 cm (175–194), and weight 82 kg (74–102). Ten subjects were from our outpatient nephrology clinic and had stable renal impairment with a serum creatinine of 2.8 mg dl^{-1} (2.3–3.9) and a creatinine clearance 33 ml min^{-1} (24–51). Their median (range) age was 49 years (34–69), height 172 cm (164–189), and weight 72 kg (63–105). No patient was in need of dialysis, and none were taking drugs known to interact with raloxifene. All subjects were informed of the investigational nature of the study and provided written consent. The study protocol and consent document were approved by an ethics committee (General Medical Council, Baden-Württemberg, Germany).

Study protocol

All subjects received a single oral dose of two tablets (60 mg each) raloxifene hydrochloride (Evista®, Eli Lilly Company), i.e. a total of 111.42 mg of the free raloxifene base. Blood samples were taken before and at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144, and 192 h after administration. Raloxifene was administered after overnight fasting and standardized meals were provided at 4, 10–12, and 24 h after drug administration. Adverse events were recorded during the hospitalization phase (14 h before to 26 h after drug administration), and on each follow-up visit up to 8 days after dosing.

Determination of raloxifene

Plasma concentrations of unconjugated raloxifene were determined by HPLC (at PPD Development, Richmond, Virginia). In brief, extraction buffer (1 ml 0.5 M K_2HPO_4 solution) was added to each 1.0 ml aliquot of human plasma containing sodium heparin. Extraction solvent (5.0 ml heptane/ethyl acetate (50/50, v/v)) was added, and centrifuged for 10 min at 3200 rpm (3023 g) at a temperature of 15°C . The samples were placed in an isopropanol bath at -35 to -40°C for 10 min, and the upper heptane/ethyl acetate layer was decanted into a glass centrifuge tube. The extraction solvent was evaporated under nitrogen at 45°C and 20–25 psi for 10–15 min, and the tubes were covered in foil and stored at -20°C for at least 30 min. After warming to room temperature freshly prepared reconstitution solution (300 μl water/methanol/TFA, 80/20/0.05 (v/v/v)) was added to each tube. Analysis was performed by liquid chromatography/tandem mass spectrometry (LC/MS/MS) using a liquid chromatograph coupled to a PE Sciex API 3000TM with an Atmospheric

Pressure Chemical Ionization Interface and with multiple reaction monitoring ion detection (MDS Sciex, Concord, ON, Canada). Precision was $<4\%$ and accuracy was 15.1% at the lower limit of quantification (0.05 ng ml^{-1}) and $<8\%$ at concentrations up to 5 ng ml^{-1} .

Pharmacokinetic analysis

A first noncompartmental analysis (Method I) used standard equations whereas a second noncompartmental analysis (Method II) used equations that do not depend on the terminal rate constant λ_z , as it was suspected that the estimate of this parameter might not be accurate in some subjects due to multiple raloxifene concentration peaks. As raloxifene absorption is much faster than its elimination [2, 3], it can be assumed (for Method II) that mean residence time can be equated to mean disposition residence time ($\text{MRT} \approx \text{MDRT}$). As concentrations were measured until the limit of quantification was reached, it can also be assumed that $\text{MRT} \approx \text{AUMC}_{0-\text{last}}/\text{AUC}_{0-\text{last}}$. The AUC was estimated as $\text{AUC}_{0-\infty} = \text{AUC}_{0-\text{last}} + C_{\text{last}} \cdot \text{MRT}$, the clearance after oral administration as $\text{CL}/F = D/\text{AUC}_{0-\infty}$, the apparent volume of distribution as $V_d/F = \text{CL}/F \cdot \text{MRT}$, and the elimination half-life as $t_{1/2} = 0.693 \cdot \text{MRT}$.

In order to predict accumulation kinetics, parameters were estimated for each individual using compartmental nonlinear regression analysis (Method III). An explicit function was used that allows mechanistic modelling of enterohepatic recycling and of two peak concentrations. Plasma concentrations (C) measured at times (t) were computer-fitted with the sum of two biexponential Bateman functions with concentration parameters A_1 and A_2 , absorption rate constants k_{a1} and k_{a2} , and elimination rate constants k_{e1} and k_{e2} for a fast and a slow component, respectively.

$$C(t) = A_1 \cdot (e^{-k_{e1} \cdot t} - e^{-k_{a1} \cdot t}) + A_2 \cdot (e^{-k_{e2} \cdot t} - e^{-k_{a2} \cdot t}) \quad (1)$$

Fits with variants of equation 1 (e.g. $k_{a1} = k_{a2}$ and inclusion of a lag-time) were inferior as measured by the sum of the squared residuals. For Method III the $\text{AUC}_{0-\infty}$ was derived from an integrated form of equation 1 and clearance was estimated as $\text{CL}/F = D/\text{AUC}_{0-\infty}$. The apparent volume of distribution was estimated using the lower of the two elimination-rate constants as $V_d/F = (\text{CL}/F)/k_{e2}$.

Pharmacokinetic analyses (Methods I and III) were performed using WinNonlin professional 4.0.1 software (Pharsight Corporation, Mountain View, California). The parameters for Method II and descriptive statistics were calculated using Excel 2000 (Microsoft Corporation, Washington).

Statistical analysis

Pharmacokinetic parameters and differences between groups are reported as median with the 95% confidence interval [5]. Differences between groups were tested for statistical significance by the two-sided Wilcoxon rank-sum (Mann–Whitney) test. Linear regression analysis was performed using creatinine clearance and age as independent variables and the various pharmacokinetic parameters as dependent variables.

Statistical tests and linear regression analysis were performed using S-PLUS 6.0 (Insightful Corp., Seattle, Washington). We considered differences as statistically significant at $P < 0.05$.

Results

The subjects with renal impairment had a significantly larger area $AUC_{0-\infty}$, a significantly lower clearance CL/F , and a significantly longer half-life $t_{1/2}$ compared with

the healthy subjects (Table 1). Differences between C_{max} , T_{max} , and V_d/F were not significant (Table 1).

Significant correlations with creatinine clearance were found for all pharmacokinetic parameters, for which significant differences between groups had been found (e.g. $CL/F_{\text{raloxifene}}$ ($l\ h^{-1}\ kg^{-1}$) = $20 + 0.28 \cdot Cl_{\text{crea}}$ ($ml\ min^{-1}$); $r = 0.60$, $P < 0.01$). In contrast, there was no significant correlation between age and any pharmacokinetic parameter (data not shown).

Overall, 19 plasma concentration-time curves showed a secondary peak and could be modelled by equation 1 (Figure 1). Predictions of raloxifene accumulation kinetics using a modified equation 1 where each term is multiplied by the respective accumulation factor $1/(1 - e^{-k\tau})$ suggest that steady-state concentrations in renal impairment would be on average 2.3 times higher compared with those in normal renal function.

No severe adverse events were observed. One renally

Table 1

Raloxifene pharmacokinetics in subjects with normal renal function (healthy group, $n = 10$) and patients with renal impairment (renal group, $n = 10$) as estimated by Methods I, II, and III

	Method*	Healthy group	Renal group	P-value†	Difference
C_{max} (ng ml ⁻¹)‡		0.7 (0.3, 1.1)	1.0 (0.5, 1.3)	0.26	0.3 (-0.2, 0.7)
T_{max} (h)‡		6 (4, 12)	8 (6, 24)	0.20	2 (-2, 6)
$AUC_{0-\infty}$ (h ng ml ⁻¹)	I	20.5 (16.8, 28.0)	35.1 (25.8, 74)	<0.01	16.4 (6.5, 44.1)
per mg kg ⁻¹)	II	18.8 (16.3, 27.7)	36.0 (25.6, 74.3)	<0.01	17.3 (7.1, 45.7)
	III	21.1 (17.8, 26.7)	38.9 (25.7, 63.5)	<0.01	18.1 (7.8, 36.0)
CL/F (l h ⁻¹ kg ⁻¹)	I	48.8 (35.8, 59.4)	28.5 (13.5, 38.8)	<0.01	-22.8 (-35.1, -7.9)
	II	53.3 (36.1, 61.5)	27.8 (13.5, 39.0)	<0.01	-25.9 (-39.7, -8.4)
	III	47.5 (37.5, 56.1)	25.8 (15.7, 38.9)	<0.01	-22.2 (-31.5, -9.1)
V_d/F (l kg ⁻¹)	I	1388 (820, 2943)	922 (691, 1408)	0.10	-435 (-1535, 110)
	II	1362 (900, 2581)	1064 (690, 1648)	0.11	-344 (-965, 141)
	III	1314 (825, 3562)	998 (519, 1257)	0.12	-376 (-1098, 75)
$t_{1/2}$ (h)	I	19.5 (15.6, 32.3)	29.9 (21.2, 32.5)	0.05	7.4 (-0.2, 13.7)
	II	20.7 (16.7, 25.7)	31.2 (23.7, 42.4)	<0.01	9.6 (3.9, 16.1)
MRT (h)	I	37.1 (28.2, 62.8)	50.5 (46.5, 72.9)	0.04	15.1 (0.5, 25.3)
	II	29.9 (24.1, 37.1)	45.0 (34.2, 61.2)	<0.01	13.9 (5.7, 23.2)
A_1 (ng ml ⁻¹)	III	5.5 (1.3, 13.2)	6.8 (0.7, 11.9)	0.91	0.1 (-5.7, 5.4)
k_{a1} (h ⁻¹)	III	0.56 (0.18, 4.95)	0.30 (0.13, 1.58)	0.22	-0.18 (-1.36, 0.13)
k_{e1} (h ⁻¹)	III	0.32 (0.15, 1.36)	0.17 (0.11, 0.45)	0.07	-0.16 (-0.92, 0.01)
A_2 (ng ml ⁻¹)	III	3.8 (0.4, 5.9)	4.6 (1.5, 11.6)	0.39	1.8 (-1.5, 6.9)
k_{a2} (h ⁻¹)	III	0.06 (0.04, 0.20)	0.05 (0.03, 0.08)	0.20	-0.02 (-0.06, 0.01)
k_{e2} (h ⁻¹)	III	0.04 (0.01, 0.05)	0.03 (0.02, 0.03)	0.31	-0.01 (-0.02, 0.01)

Data are median values (95% confidence interval)

*I standard noncompartmental analysis; II noncompartmental analysis without using the terminal slope; III nonlinear regression analysis using equation 1 that allows modelling of two peak concentrations;

†Wilcoxon rank-sum test;

‡The maximum concentrations C_{max} at times T_{max} are observed values.

Figure 1

Median plasma raloxifene concentrations after oral administration of 120 mg raloxifene hydrochloride to healthy subjects (open circles) or patients with renal impairment (closed circles). Two curves from the compartmental model (Method III) using mean values are shown (for healthy group: $A_1 = 3.8 \text{ ng ml}^{-1}$, $k_{a1} = 0.36 \text{ h}^{-1}$, $k_{e1} = 0.29 \text{ h}^{-1}$, $A_2 = 1.97 \text{ ng ml}^{-1}$, $k_{a2} = 0.059 \text{ h}^{-1}$, $k_{e2} = 0.036 \text{ h}^{-1}$; and for the renal group: $A_1 = 1.84 \text{ ng ml}^{-1}$, $k_{a1} = 0.37 \text{ h}^{-1}$, $k_{e1} = 0.21 \text{ h}^{-1}$, $A_2 = 3.1 \text{ ng ml}^{-1}$, $k_{a2} = 0.05 \text{ h}^{-1}$, $k_{e2} = 0.027 \text{ h}^{-1}$). LLQ = lower limit of quantification

impaired patient had three possibly related adverse events (asthenia, dizziness and somnolence). Laboratory parameters, vital signs, or ECG findings were not affected by raloxifene.

Discussion

In contrast to our expectations, raloxifene pharmacokinetics were significantly altered in subjects with renal impairment. The impaired clearance in the renal group indicates decreased elimination of raloxifene. This would not have been predicted from the pharmacokinetic profile of raloxifene, little of which is excreted unchanged into the urine.

The observation might be explained by a decreased metabolic clearance in the renal tubules, or by impairment of biliary excretion of raloxifene glucuronides by uremic toxins. The back-conversion of raloxifene glucuronide to raloxifene has been seen in ovariectomized rats [6] and can be assumed for humans since plasma concentrations of both were observed to decline in parallel [3].

Published pharmacokinetic data for raloxifene in postmenopausal woman are $\text{CL/F} = 44 \text{ l h}^{-1} \text{ per kg}$, $\text{AUC } 27 \text{ (h ng ml}^{-1}) \text{ per (mg kg}^{-1})$, $t_{1/2} 27.7 \text{ h}$, and apparent volume of distribution 2348 l kg^{-1} [4]. Our estimate (in healthy males) for raloxifene oral clearance was higher, whereas that for the apparent volume of distribution was lower. This is in contrast to a previous study

that reported a higher apparent volume of distribution in males [3].

Enterohepatic recycling might be the explanation for the double plasma concentration peaks seen with raloxifene, as indicated by animal data [7] and an observed interaction with cholestyramine [2]. Compared with our model, much more complex models have been used to describe two concentration peaks [8, 9]. Our model explains the decreased elimination of raloxifene in renal impairment with lower values of the rate-constants k_{a2} and k_{e2} indicating that altered enterohepatic recycling might play a role. Our model predictions based on the modified equation 1 suggests limited accumulation of raloxifene, but mean steady-state concentrations are predicted to be 2.3 times higher in renal impairment compared with those in normal renal function.

In conclusion, the elimination of raloxifene is decreased in patients with renal impairment. Thus, dosage adjustment may be required in this patient group.

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