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ORIGINAL ARTICLE

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The effects of degree of hepatic or renal impairment on the pharmacokinetics of exemestane in postmenopausal women

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Abstract *Purpose*: Two studies were conducted to compare the pharmacokinetics and tolerability of exemestane in postmenopausal subjects with various degrees of impairment of hepatic or renal function with those in healthy postmenopausal subjects. *Methods*: All subjects were postmenopausal females. In study 1, nine subjects had normal hepatic function (Child-Pugh grade A), and nine had moderately (grade B) and eight severely (grade C) impaired hepatic function. In study 2, six subjects had normal renal function, and six moderately (creatinine clearance, CrCL, 30–60 ml/min per 1.73 m^2) and seven severely (CrCL <29 ml/min per 1.73 m^2) impaired renal function. Each subject took a single oral dose of 25 mg exemestane. Samples of plasma (to 168 h after dosing) and urine (to 72 h in study 1, or 96 h in study 2) were taken for pharmacokinetic analysis. Safety and tolerability were assessed by monitoring vital signs, laboratory safety tests, ECG and adverse events. *Results*: Exposure to exemestane was increased two- to threefold in patients with hepatic impairment. Thus, the geometric mean $AUC_{0-\infty}$ values were 41.71 (90% CI 32.2 to 54.0), 99.02 (76.5 to 128.2) and 118.59 ng·h/ml (90.2 to 156.0) in healthy subjects, and in patients with moderate and severe hepatic impairment, respectively ($P<0.01$). C_{max} also increased twofold. Compared with healthy subjects, patients with hepatic impairment had lower apparent oral clearance and apparent volume of distribution of exemestane. Renal impairment was also associated with two- to threefold increases in $AUC_{0-\infty}$: 34.64 (90% CI 23.9 to 50.2), 94.10 (64.9 to 136.4) and 65.52 ng·h/ml (46.5 to 92.4) in healthy subjects, and in patients with moderate and severe hepatic impairment, respectively ($P<0.05$). C_{max} did not change significantly. Apparent oral clearance was directly correlated with CrCL ($r^2=0.43$). Exemestane was tolerated well, with no safety concerns. *Conclusions*: Oral clearance of exemestane was reduced in the presence of significant hepatic or renal disease. However, in view of the relatively large safety margin and the mild nature of the side effects of exemestane, the therapeutic implications of these changes in pharmacokinetics are considered minor and of no clinical significance.

Keywords Exemestane · Aromatase inhibitor · Renal impairment · Hepatic impairment · Pharmacokinetics

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Introduction

Approximately one-third of human breast cancers are hormone-dependent and regress following oestrogen deprivation [5]. The principal source of oestrogens in postmenopausal women is the peripheral (i.e. extra-ovarian) conversion of androstenedione to oestrone and testosterone to oestradiol by the enzyme aromatase. Inhibition of aromatase is therefore a rational approach to the treatment of breast cancer in postmenopausal patients [3, 6].

Exemestane (Aromasin, 6-methylenandrosta-1, 4-diene-3,17-dione) is an orally active and well-tolerated steroidal selective aromatase inactivator, structurally related to the natural substrate androstenedione [1, 3, 6]. It is indicated for the management of advanced breast cancer in postmenopausal women in whom antioestrogen therapy has failed. Two studies were conducted to compare the pharmacokinetics and tolerability of exemestane in postmenopausal patients with varying degrees of impairment of hepatic function (study 1) or renal function (study 2) with those in healthy postmenopausal subjects.

Material and methods

The studies were approved by the local research ethics committee before starting at any site and were conducted in accordance with the relevant version of the Declaration of Helsinki. Written informed consent was obtained from all subjects before entry into the study.

Subjects

Exemestane is indicated for use in postmenopausal females, and therefore all study subjects were postmenopausal females (no menstrual loss for at least 1 year and appropriate concentrations of follicle-stimulating hormone, luteinizing hormone and oestradiol, or at least 6 months since bilateral oophorectomy). Other selection criteria were: age 45 to 70 years, non-smokers or moderate smokers (up to ten cigarettes per day), weight within 20% of ideal, and no more than moderate consumers of xanthine-containing beverages. All subjects underwent clinical examination, recording of electrocardiogram (ECG), screening for drugs of abuse, serological testing for hepatitis B and C and human immunodeficiency virus, and safety laboratory tests within 3 weeks of study entry. Subjects were permitted to take concomitant medication as indicated for the management of their renal or hepatic disease and simple analgesia, minerals and vitamins. Subjects taking any other medication or with evidence of any condition other than the disease under study that might affect the pharmacokinetics of exemestane were excluded.

Three groups of subjects were enrolled in study 1: healthy volunteers (control, grade A, normal hepatic function, score 5, according to Child and Pugh's classification [11]), and patients with stable moderate (grade B, score 7 to 9) or severe (grade C, score 10 to 15) hepatic impairment. Patients with significant encephalopathy or advanced ascites were excluded.

Three groups of subjects were enrolled in study 2: healthy volunteers (measured creatinine clearance, CrCL, in normal range for age) and patients with stable moderate (CrCL 30 to 60 ml/min per 1.73 m^2) or severe (CrCL below 29 ml/min per 1.73 m^2) renal impairment.

Assuming that the variability in pharmacokinetic parameters in subjects with renal or hepatic impairment is the same as in healthy volunteers, a sample size of six per group was considered sufficient to recognize a difference of 50% in area under concentration versus time profile (AUC, power 80%, α 0.05 [7]).

Study design

Study 1 was conducted in four centres in France and two in Germany. Study 2 was conducted in two centres in France and one in Germany. Both studies employed an open-label parallel-group design. Each subject received a single oral dose of exemestane as a 25-mg sugar-coated tablet (Aromasin, Pharmacia) after a standard breakfast, i.e. the usual daily dose of exemestane taken in accordance with the manufacturer's recommendations. Blood (5 ml heparinized sample) was collected for assay of plasma concentration of exemestane before and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 120 and 168 h after dosing. Samples were cooled immediately on ice and centrifuged within 20 min to avoid possible degradation of exemestane and/or back conversion from metabolites. Plasma was stored frozen at −20°C until assay. A blank urine sample was collected before dosing, and all urine collected during the periods 0 to 24 h, 24 to 48 h and 48 to 72 h after dosing; for study 2 only, an additional collection was made from 72 to 96 h. Urine was kept chilled during the collection period. At the end of each period, it was mixed well, measured, and an aliquot collected and stored frozen at −20°C until assay.

A validated high-performance liquid chromatography method coupled with radioimmunoassay was used to determine exemestane concentrations in plasma and urine [9]. The intra- and interassay coefficients of variation were 13.4% and 17.7% for the plasma assays and 8.7% and 14.5% for the urine assays, respectively. The lower limits of quantification (LLOQ) were 13.5 pg/ml in plasma and 27 pg/ml in urine. The upper limits of quantification were 500 pg/ml in plasma and 1000 pg/ml in urine. Standard pharmacokinetic parameters were determined for each subject using a noncompartmental approach and actual sample collection times.

Safety was assessed by measuring vital signs and laboratory safety tests before, and 24 and 168 h after dosing, ECG recording before and 168 h after dosing, and monitoring adverse events during the study period.

Statistical methods

Pharmacokinetic data were analysed using WINNONLIN (version 2.1; Pharsight Corporation, Mountain View, Calif.). Safety data were analysed using Statistical Analysis Systems (SAS) for Windows, version 6.12. Descriptive statistics were calculated for all parameters. The primary pharmacokinetic parameters used for statistical analysis were the log-transformed maximum plasma concentration (C_{max}) and AUC extrapolated to infinity ($AUC_{0-\infty}$), and untransformed terminal elimination half-life ($t_{1/2}$), time of C_{max} (t_{max}) and amount excreted in urine up to 72 h/96 h after dosing (Ae_{0-72}/Ae_{0-96}). Differences between groups were explored using analysis of variance (ANOVA; C_{max}, $AUC_{0-\infty}$, $t_{1/2}$, Ae_{0-72}/Ae_{0-96}) and the Kruskal-Wallis test (t_{max}). Confidence intervals (CI, 90%) were calculated using Scheffé's approach. Additionally, the correlation between apparent oral clearance (CL_{po}) and CrCL was explored (study 2).

Results

Due to slow accrual rate, study 1 was terminated after enrolment of eight of a planned nine subjects to the group with severe hepatic impairment. One subject with severe renal impairment was substantially heavier than permitted; an additional subject was enrolled to replace this subject. In total, 47 Caucasian postmenopausal female subjects entered these studies. One patient with severe hepatic impairment withdrew consent after the 120-h sample. All available data from all subjects are included in the analysis. Demographic and baseline characteristics of subjects in study 1 (hepatic impairment) are summarized in Table 1 and of subjects in study 2 (renal impairment) in Table 2, and concomitant medication use by subjects in studies 1 and 2 are summarized in Tables 3 and 4, respectively.

The expected impairments of hepatic and renal function were confirmed in each subgroup. Compared with subjects in other groups, subjects with severe hepatic or renal impairment were heavier. Those with severe hepatic impairment also had a higher calculated mean CrCL than those in other groups. Concomitant medication use was consistent with the underlying condition and was generally unchanged during the study. A high proportion of both groups of patients used diuretics and vitamin, herb or mineral supplements. Several patients with hepatic impairment additionally used β-adrenoceptor antagonists, lactulose and treatment or prophylaxis for peptic ulcer disease. A number of patients with renal impairment reported the use of other antihypertensive agents. It is considered unlikely

Table 1 Demographic and baseline characteristics of subjects in study 1 (hepatic impairment) (*CP* Child-Pugh)

	Hepatic function		
	Normal CP grade A	Moderate impairment CP grade B	Severe impairment CP grade C
No. of subjects	9	9	8
Age (years)			
Mean ± SD	57 ± 5.4	57 ± 4.2	54 ± 9.9
Range	50–68	51–64	36–65
Weight (kg)			
Mean ± SD	62 ± 5.8	66 ± 9.2	74 ± 9.7
Range	56–74	57–86	57–86
Height (cm)			
Mean ± SD	164 ± 6.6	161 ± 6.7	169 ± 5.6
Range	154–172	149–174	157–174
Creatinine clearance (ml/min)[a]			
Mean ± SD	77 ± 13	84 ± 12	100 ± 34
Range	62–99	68–104	43–137
Child-Pugh score			
Mean ± SD	5	7.6 ± 0.5	10.1 ± 0.4
Range		7–8	10–11

[a] Estimated as described by Cockcroft and Gault [2]

Table 2 Demographic and baseline characteristics of subjects in study 2 (renal impairment)

	Renal function		
	Normal CrCL > 60 ml/min/ 1.73 m^2	Moderate impairment CrCL 30–60 ml/min/ 1.73 m^2	Severe impairment CrCL 10–29 ml/min/ 1.73 m^2
No. of subjects	6	6	7
Age (years)			
Mean ± SD	53 ± 3.6	61 ± 6.8	56 ± 5.7
Range	47–57	51–69	49–63
Weight (kg)			
Mean ± SD	62 ± 9.7	62 ± 15	73 ± 12
Range	51–73	45–84	57–96
Height (cm)			
Mean ± SD	159 ± 6.2	158 ± 5.6	160 ± 4.4
Range	149–168	148–165	153–165
Creatinine clearance (ml/min/1.73 m^2)[a]			
Mean ± SD	103 ± 13	39 ± 8.7	17 ± 8.9
Range	86–123	30–51	5.7–29

[a]Determined using the formula of Du Bois and Du Bois for the calculation of body surface area [4]

Table 3 Concomitant medication use by subjects in study 1 (hepatic impairment)

	Hepatic function		
	Normal	Moderate impairment	Severe impairment
No. of subjects	9	9	8
No. with any concomitant medication	3 (33%)	9 (100%)	8 (100%)
Medication by category			
Loop or thiazide-related diuretics	0	5	8
Spironolactone	0	5	4
β-adrenoceptor antagonist	0	5	5
Vitamins/herbs/minerals	1	4	6
Lactulose	0	1	4
Analgesia	3	1	0
Other antihypertensive/antianginal medication	0	3	1
Treatment/prophylaxis for peptic ulcer disease	0	3	2
Other (≤ 1/category/group)	0	4	7

Table 4 Concomitant medication use by subjects in study 2 (renal impairment)

	Renal function		
	Normal	Moderate impairment	Severe impairment
No. of subjects	6	6	7
No. with any concomitant medication	0 (0%)	6 (100%)	7 (100%)
Medication by category			
ACE inhibitor/angiotensin receptor antagonist	0	5	4
Loop diuretic	0	2	5
Dihydropyridine calcium antagonist	0	1	4
Vitamins/herbs/minerals	0	2	5
Other (≤ 1/category/group)	0	3	6

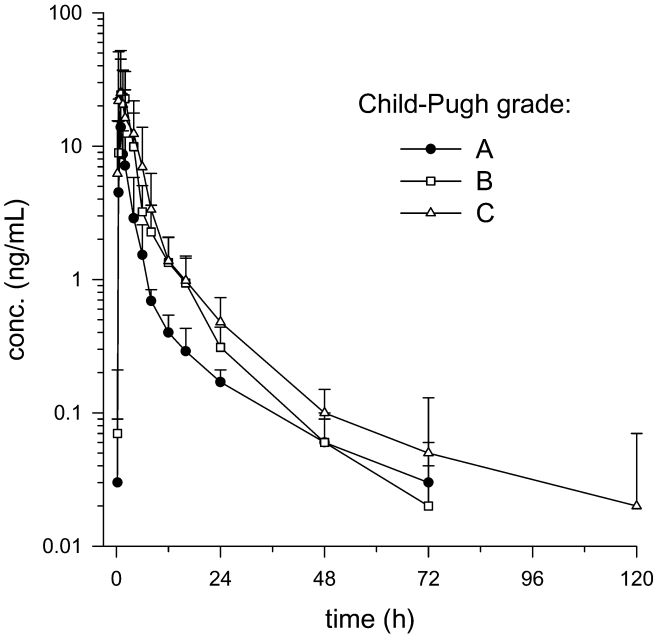

Fig. 1 Mean exemestane plasma concentration versus time profile in subjects with various degrees of hepatic impairment according to Child-Pugh grade (*A* healthy, *B* moderate, *C* severe). Values below the LLOQ are set to zero

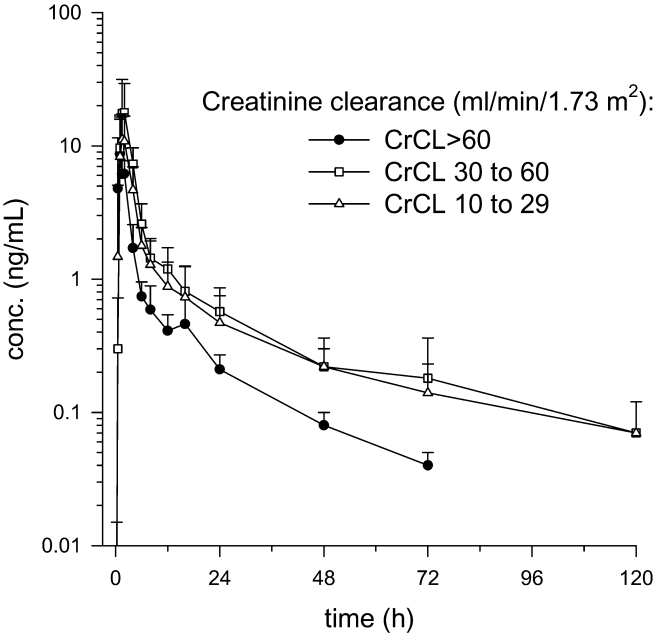

Fig. 2 Mean exemestane plasma concentration versus time profile in subjects with various degrees of renal impairment according to creatinine clearance: >60 ml/min/m^2 (healthy), 30 to 60 ml/min/m^2 (moderate), 10 to 29 ml/min/m^2 (severe). Values below the LLOQ are set to zero

that the reported use affected the pharmacokinetics of exemestane. Plasma concentration versus time profiles are illustrated in Fig. 1 (study 1) and Fig. 2 (study 2).

In both studies, exemestane was rapidly absorbed (median t_{max} within 2 h after dosing) and, following the peak, plasma concentrations declined polyexponentially. Pharmacokinetic parameters are summarized by subject group in Table 5.

Some subjects in study 1 had a short apparent terminal elimination half-life (about 10 h); this was considered to be due to the later concentrations of exemestane being below the LLOQ. However, the contribution of the extrapolated part of the AUC in these subjects was small (below 3%); hence, this is unlikely to have given rise to significant bias in the evaluation of $AUC_{0-\infty}$. Compared with healthy subjects, patients with hepatic impairment had lower values for apparent oral clearance (see Fig. 3) and apparent volume of distribution of exemestane. The mean ± SD apparent oral clearance values were 604 ± 83, 275 ± 134 and 228 ± 110 l/h in healthy subjects and patients with moderate or severe impairment, respectively. The mean ± SD apparent volume of distribution values were $20{,}706 \pm 13{,}573$, 5725 ± 5875 l and 5683 ± 2999 l, respectively.

There was a corresponding two- to threefold increase in $AUC_{0-\infty}$ and twofold increase in C_{max} in patients with hepatic impairment. The simultaneous 90% CIs of $AUC_{0-\infty}$ obtained in patients with moderate or severe hepatic impairment did not overlap with those in healthy subjects, but there was substantial overlap between the CIs in patients with moderate and severe hepatic impairment, indicating no major pharmacokinetic differences between these groups. Hepatic impairment was not associated with any change in the t_{max} or $t_{1/2}$ of exemestane.

Compared with healthy subjects, patients with moderate or severe renal impairment had lower apparent oral clearance of exemestane: 737 ± 165, 279 ± 98 and 433 ± 251 l/h, respectively. Creatinine clearance was positively correlated with the apparent oral clearance of exemestane ($r^2 = 0.43$, see Fig. 4).

A similar correlation was found based on oral clearance values corrected for the weight of the subjects. This was associated with a two- to threefold increase in

Table 5 Pharmacokinetic parameters obtained following oral administration of exemestane to healthy postmenopausal female subjects and to those with moderate or severe impairment of hepatic or renal function according to Child-Pugh grade and creatinine clearance, respectively

		Hepatic function				Renal function			
		Normal	Moderate impairment	Severe impairment	*P* value	Normal	Moderate impairment	Severe impairment	*P* value
		Grade A	Grade B	Grade C		CrCL > 60 ml/min/1.73 m^2	CrCL 30–60 ml/min/1.73 m^2	CrCL 10–29 ml/min/1.73 m^2	
t_{max} (h)	Median	1.00	1.50	1.50	NS	1.50	2.00	1.50	NS
	90% CI	0.5 to 4	1 to 4	0.5 to 6		1 to 2	1 to 4	1 to 2	
C_{max} (ng/ml)	Geometric mean	17.22	30.69	33.38	< 0.05	9.59	17.19	10.92	NS
	90% CI	11.7 to 25.4	20.8 to 45.3	22.1 to 50.4		5.27 to 17.5	9.45 to 31.3	6.27 to 19.0	
$AUC_{0-\infty}$ (ng·h/ml)	Geometric mean	41.71	99.02	118.59	< 0.01	34.64	94.10	65.52	< 0.05
	90% CI	32.2 to 54.0	76.5 to 128.2	90.2 to 156.0		23.9 to 50.2	64.9 to 136.4	46.5 to 92.4	
$t_{1/2}$ (h)	Arithmetic mean	23.00	13.81	19.44	NS	25.71	59.68	44.87	NS
	90% CI	14.7 to 31.3	5.54 to 22.1	10.7 to 28.2		−2.24 to 53.7	31.7 to 87.6	19.0 to 70.7	
Urinary excretion (% of dose)[a]	Arithmetic mean	0.14	0.30	0.32	NS	0.10	0.04	0.05	NS
	90% CI	−0.04 to 0.31	0.12 to 0.47	0.14 to 0.51		0.05 to 0.15	−0.01 to 0.09	0.00 to 0.09	

[a]Urine collection intervals: 0–72 h in hepatic impairment study; 0–96 h in renal impairment study

systemic exposure ($AUC_{0-\infty}$) to exemestane in patients with renal impairment (Table 5). Patients with moderate renal impairment appeared to have a greater reduction in exemestane clearance than those with severe renal impairment. Thus, the simultaneous 90% CIs of $AUC_{0-\infty}$ obtained in patients with moderate renal impairment did not overlap with those in healthy subjects, whilst substantial overlap was observed between the CIs in patients with severe renal impairment and healthy subjects. This seems to relate to intersubject variability, with one subject in the severe renal impairment group having higher apparent oral clearance (913 l/h). If this subject were excluded, the CIs would not overlap. Renal impairment was not associated with any significant change in apparent volume of distribution, t_{max}, C_{max} or $t_{1/2}$.

Urinary excretion of unchanged exemestane was negligible (mean contribution below 0.35% of dose in all patient groups; Table 5). However, patients with renal impairment showed a lower urinary excretion of unchanged drug than those with hepatic impairment.

Exemestane was well tolerated during these studies. No serious adverse events, withdrawals due to adverse events or adverse events ongoing at the end of the study were reported. In total, 17 adverse events emerging during treatment were reported: five of five healthy volunteers (33%), six of five patients (56%) with moderate hepatic impairment, three of three patients (38%) with severe hepatic impairment, three of two patients (33%) with moderate renal impairment, and none in any patient (0%) with severe renal impairment. All adverse events were grade 1 or 2 of the National Cancer Institute Common Toxicity Criteria. Only two were considered to have a possible or probably relation with exemestane: grade 1 headache in a patient with moderate renal impairment and grade 1 nausea in a patient with moderate hepatic impairment. Observed abnormalities in laboratory safety tests, vital signs and ECGs were considered consistent with underlying disease and unrelated to study treatment.

Discussion

These studies were performed to evaluate the effects of hepatic or renal impairment on the pharmacokinetics of exemestane. Although not conducted in patients with breast cancer, the subjects in these studies were all of postmenopausal status and had demographic characteristics similar to the target population. Exemestane is reported to have linear pharmacokinetics in the dose range 25 to 200 mg [12]. The pharmacokinetic parameters of exemestane calculated for healthy volunteers in this study were similar to those reported previously [10, 12], suggesting that there was no relevant bias for methodological reasons.

In the present study, compared with healthy subjects, patients with hepatic impairment had significantly greater systemic exposure to exemestane. Reduction in

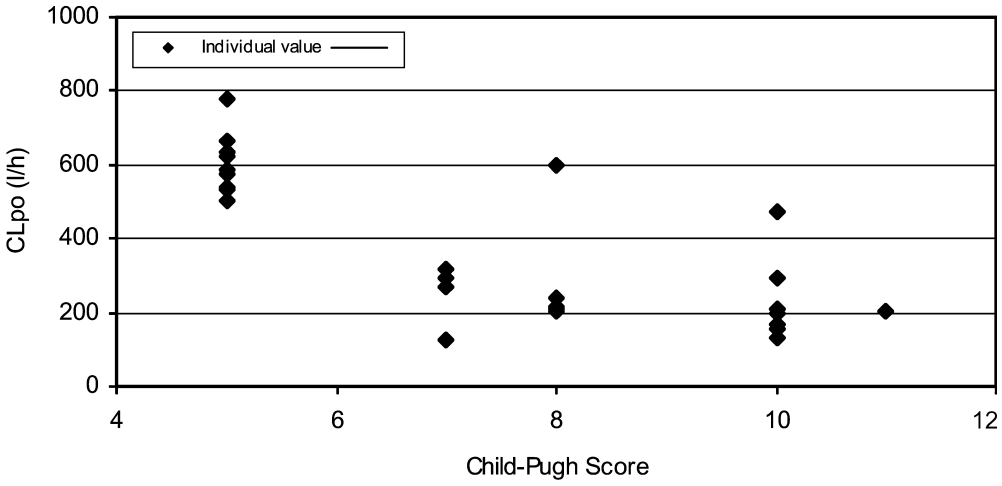

Fig. 3 Relationship between apparent oral clearance of exemestane (CLpo) and Child-Pugh score

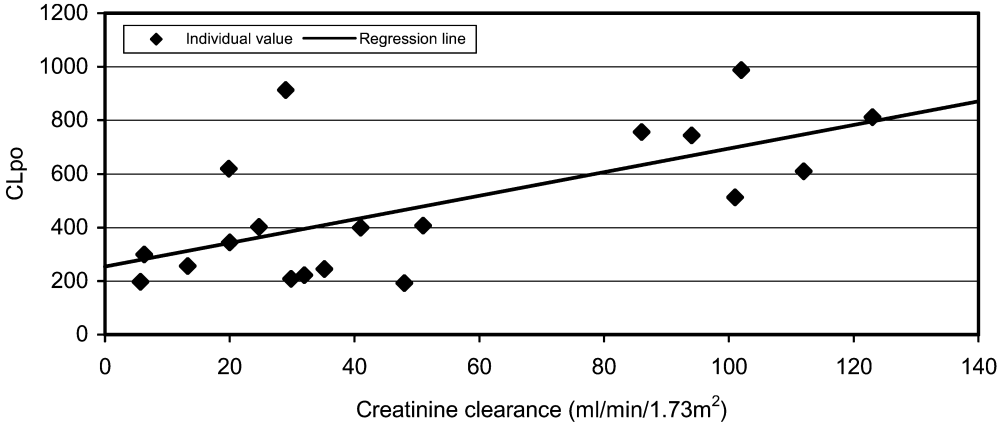

Fig. 4 Relationship between apparent oral clearance of exemestane (CLpo) and creatinine clearance (CLpo = 254 + 4.41*creatinine clearance, $r^2 = 0.43$)

hepatocellular activity could have a major effect on bioavailability via a reduction in first-pass effect. The observation that C_{max} also increased in patients with hepatic impairment is consistent with this interpretation, although possible contributions from other factors such as decreased hepatic blood flow and/or extrahepatic clearance cannot be excluded.

Patients with renal impairment also had an increase in exposure to exemestane. Despite some variability, there was a significant correlation between renal function (CrCL) and exemestane clearance. Maximal concentrations were not affected, suggesting that oral bioavailability was unchanged. Analysis of urine confirmed that renal elimination of unchanged exemestane was minimal, so it is unlikely that the observed differences in systemic exposure could be explained by differences in renal excretion of the parent compound. Other factors could be involved, such as decreased intrinsic clearance due to the accumulation of endogenous inhibitors of metabolism in patients with renal failure [14].

Exemestane has an excellent safety profile. During clinical trials, a daily dose of 200 mg, eightfold higher than the therapeutic dose level used in the present studies, was associated with some androgenic effects in a small proportion of patients [1, 13]. The maximum tolerated dose has not been identified because of lack of treatment-related toxicity even at daily doses up to 600 mg [8]. Therefore, the therapeutic implications of a threefold increase in exposure at the recommended dose of 25 mg as demonstrated in the present studies are considered minor and of no clinical significance. The results confirm the good tolerability of exemestane administered as a single dose to healthy volunteers and patients with moderate or severe hepatic or renal impairment.

It is concluded that hepatic and renal impairment have a significant effect on exposure to exemestane. However, no alteration in dose regimen is considered necessary.

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