The pharmacokinetics of Casodex enantiomers in subjects with impaired liver function

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- 1 Casodex is a novel non-steroidal antiandrogen being developed for the treatment of prostatic cancer. The antiandrogenic activity is predominantly in the R(–) enantiomer with little, if any, activity in the S(+) enantiomer.
- 2 The pharmacokinetics of the enantiomers of Casodex have been investigated over 28 days following a single oral dose of Casodex (50 mg) to 10 male subjects with histologically verified liver cirrhosis or fatty liver with fibrosis. Ten age matched male subjects with normal hepatic function served as a control group.
- 3 For both groups plasma concentrations of (S)-Casodex were lower than those for (R)-Casodex; this difference was about 10-fold at early time points and increased to about 25-fold by 24 h after dosage.
- 4 The kinetics of (R)-Casodex were similar in subjects with and without liver disease ($C_{\max}$: 750 vs 848 ng ml⁻¹; $t_{\max}$: 24 – 30 h; $t_{1/2}$: 7.40 vs 7.22 days; AUC: 182 vs 225 µg ml⁻¹ h).
- 5 The kinetics of (S)-Casodex could not be described in the majority of subjects; in the remainder the mean terminal phase half-life for both groups was less than 1 day.

Keywords Casodex enantiomers pharmacokinetics hepatic impairment

Introduction

Casodex (trade mark the property of Zeneca Limited) ((R,S) - *N* - (4' - cyano - 3 - (4 - fluorophenylsulphonyl) - 2 - hydroxy-2-methyl-3' - (trifluoromethyl)propionanilide), ICI 176,334, see Figure 1) is a novel, non-steroidal antiandrogen being developed for the treatment of prostatic cancer. After oral administration at doses from 0.25 to 100 mg kg⁻¹ it inhibits testosterone propionate-stimulated seminal vesicle growth in immature castrated rats, but has no agonist activity when given alone at 25 mg kg⁻¹ [1]. (R)-Casodex was shown to be 2000 times more potent than (S)-Casodex when assessed after 7 daily doses using the above method (Furr BJA, personal communication). The 10-fold higher plasma concentrations of (R)-Casodex when compared with (S)-Casodex observed at steady state in the rat, are inadequate to account for this large difference in activity.

Daily dosing of Casodex (50 mg) to patients with prostatic cancer produced biochemical and clinical responses comparable with standard hormonal therapies used in advanced prostatic cancer [2]. The pharmacokinetics of Casodex have been investigated using an achiral assay following single oral doses (10–50 mg) and during daily oral administration over the same dose range to prostate cancer patients [3].

Figure 1 Structure of Casodex.

McKillop *et al.* [4] have reported that a 50 mg dose of [¹⁴C]-Casodex is extensively absorbed by healthy volunteers. The clearance of Casodex was observed to be primarily metabolic with about half of the radiochemical dose recovered in urine as glucuronide conjugates of the parent compound and hydroxy-Casodex and the remainder recovered in faeces as Casodex and hydroxy-Casodex. Hepatic impairment could, therefore, significantly affect the clearance of Casodex. The rate of hepatic metabolism has been shown to diminish with age [5], this being most likely the result of cirrhosis caused by alcoholism or diseases such as congestive heart failure. Prostatic cancer is primarily a disease of an elderly population, with the additional complication of the presence of liver metastases in some subjects.

This present study was undertaken to evaluate whether impaired liver function has any effect on the pharmacokinetics of either Casodex enantiomer and on the basis of the results to ascertain the need for dosage adjustment in prostatic cancer patients having impaired liver function.

Methods

Subjects

Ten male patients with histologically verified liver cirrhosis (liver group) were investigated. They had liver cirrhosis ($n = 6$; Child-Pugh Class C, $n = 5$; Class B, $n = 1$) or fatty liver plus fibrosis ($n = 4$; Class B, $n = 2$; Class A, $n = 2$). At the time of investigation they had an active liver disease, documented by liver function tests (see below). Their mean ($\pm$ s.d.) age was 56.5 ± 8.2 years and their mean ($\pm$ s.d.) bodyweight was 79.1 ± 13.4 kg. A control group consisted of 10 age matched (57.2 ± 8.8 years) and bodyweight matched (79.3 ± 9.9 kg) male subjects; they had normal liver function tests. Over the assessment period there was no change in liver function test data for any subject.

Prior to dosing with Casodex all subjects had normal creatinine clearance with values in the range 90 – 144 ml min⁻¹ and 78 – 138 ml min⁻¹ for the liver and control groups, respectively. No subject was receiving any concomitant therapy which could affect hepatic function. Six liver patients were treated with other drugs; frusemide ($n = 4$), digoxin and atenolol ($n = 2$), sotalol ($n = 1$) and prednisolone ($n = 1$). Four control subjects were receiving drug therapy; frusemide ($n = 3$), digoxin ($n = 1$). The groups differed significantly from each other in their clearance of antipyrine, which is an index of the drug metabolising ability of the liver [6]. Antipyrine plasma clearance, assessed within 1–2 weeks prior to dosing with Casodex, was 33.2 ± 7.3 (s.d.) ml min⁻¹ and 54.8 ± 10.6 ml min⁻¹ ($P < 0.01$, Student's *t*-test) in the liver and control groups, respectively. Serum albumin levels were similar in both groups with values of 37 ± 6 and 39 ± 4 g l⁻¹ in the impaired liver and control groups, respectively. Other serum markers of liver function were about two-fold higher and appreciably more variable in the impaired liver group compared with the controls with mean values as follows: aspartate transaminase 48 ± 28 and 20 ± 4 iu l⁻¹; alanine transaminase 56 ± 47 and 20 ± 5 iu l⁻¹; bilirubin 21 ± 15 and 9 ± 3 μ mol l⁻¹; alkaline phosphatase 290 ± 213 and 124 ± 34 iu l⁻¹, respectively.

Study design

This was an open study which received local ethics committee approval and was conducted in accordance with the Declaration of Helsinki (Venice amendment, 1983). The subjects gave their written, informed consent to participate in the study. They were admitted to hospital the day before dosing, for creatinine clearance estimation, and for 2 days after dosing. Subjects were fasted overnight and until after the 3 h blood sample had been taken; each received a single film-coated tablet

containing 50 mg of micronised Casodex. Venous blood samples for the assay of (R)- and (S)-Casodex were taken before and at 1, 2, 3, 5, 7, 9, 12, 15, 24, 36 and 48 h after dosing. Further samples were taken 3, 7, 14, 21 and 28 days after dosing; the exact post dose sampling times were recorded. In the first six impaired liver and four control subjects, additional samples were taken 42 and 56 days after dosing. Blood samples were collected into tubes containing lithium heparin and after thorough mixing plasma was separated by centrifugation and stored at -20° C until analysis.

Sample analysis

Plasma concentrations of the enantiomers of Casodex were determined by h.p.l.c. Plasma samples (0.5 ml) were buffered with 0.05 M phosphate buffer pH 7 (1 ml) and extracted with methyl *t*-butyl ether (5 ml). An aliquot (4 ml) of the organic phase was removed, evaporated to dryness and reconstituted in a mixture of 70% v/v aqueous methanol (2.5 ml) and hexane (2.5 ml). The upper layer was discarded and a 2 ml aliquot of the lower layer was mixed with chloroform (0.7 ml). A further 0.7 ml chloroform and 0.66 ml distilled water were added and the mixture was centrifuged. After discarding the upper layer, the lower layer was evaporated to dryness and redissolved in methanol (45 μ l) followed by the addition of 0.02 M phosphate buffer pH 7 (255 μ l). The enantiomers of Casodex were detected by their ultra-violet absorbance (270 nm) after elution from a 5 μ m Chiral-AGP column (J.T. Baker Inc) using 8% v/v ethanol in 0.02 M phosphate buffer pH 7 at a flow rate of 0.75 ml min⁻¹. Typical retention times obtained using pure synthetic samples of the enantiomers were 6.0 min and 9.5 min for (S)-Casodex and (R)-Casodex respectively; baseline resolution was observed. Measurement of (R)- and (S)-Casodex in test samples was achieved by comparison of the peak height of each enantiomer in the test samples to those in a calibration series, extracted in the same assay run.

The inter-batch coefficient of variation of the assay ($n = 11$) was 13.7% and 25.9% for (R)-Casodex at mean measured concentrations of 368 and 51 ng ml⁻¹ respectively; the corresponding values for (S)-Casodex were 13.4% and 21.8% at mean measured concentrations of 367 and 50 ng ml⁻¹ respectively. The sum of the enantiomer concentrations was compared with results from the achiral assay described by Cockshott *et al.* [2] but modified to use ethyl acetate in place of diethyl ether as the extraction solvent. The agreement between the assays was reasonable ($< 20\%$ difference) for all samples. The limit of determination of the assay was defined as the concentration estimated from the line of best fit, corresponding to the ordinate intercept of the upper 95% confidence interval for the calibration curve. The mean values for all low concentration range calibration curves used in this study were 16.3 ng ml⁻¹ and 17.6 ng ml⁻¹ for (R)-Casodex and (S)-Casodex, respectively.

Pharmacokinetic analysis

Values of $C_{\max}$ and $t_{\max}$ for each enantiomer in each subject were noted directly from the data. A bi-

exponential function incorporating a lag time, as described by Gibaldi & Perrier [7], was fitted to the (R)-Casodex plasma concentration data for each subject using the least squares curve fitting program MODFIT [8] with a weighting of $1/C^2$. The fitting was repeated for the (S)-Casodex data from each individual using the bi-exponential function and, where appropriate, a corresponding tri-exponential function. For (S)-Casodex the preferred model was chosen on the basis of a visual assessment of the residuals of the observed values from the line of best fit and by reference to the confidence with which the parameters were estimated.

AUC values of (R)-Casodex were calculated using the linear trapezoidal approximation up to the last concentration (C_z) above the assay limit of detection with extrapolation to infinity on the basis of the slope of the terminal phase. For (S)-Casodex it was not possible to define the parameters of the terminal phase in all subjects with confidence. Therefore, the AUC value up to C_z (AUC trap) has been reported for all subjects. The half-life ($t_{1/2,z}$) was calculated from the slope of the terminal phase.

Statistical analysis

For both enantiomers C_{max} , t_{max} , AUC and $t_{1/2,z}$ and for (R)-Casodex the absorption half-life ($t_{1/2,abs}$) were assessed for normality using Normal Probability Plots of the raw data and residuals; log transformation of the AUC data for both enantiomers, $t_{1/2,abs}$ for (R)-Casodex and C_{max} for (S)-Casodex was found necessary.

Differences between the impaired liver and control groups in AUC, C_{max} , $t_{1/2,z}$ and $t_{1/2,abs}$ were assessed using an analysis of variance. Differences between groups in t_{max} were assessed using the Wilcoxon Rank Sum Test. Median t_{max} values were calculated.

Results

Data from the first six liver and four control group subjects indicated that sampling up to 1 month was adequate to define the elimination kinetics of the (R)-enantiomer. Sampling was therefore terminated at 1 month for all subsequent subjects.

Comparisons between enantiomers

For both groups plasma concentrations of (S)-Casodex were much lower than those of (R)-Casodex. This difference was about 10-fold at early time points and increased to about 25-fold by 24 h (Figure 2). It was not possible to obtain data beyond 24 h for (S)-Casodex as concentrations were below the limit of determination in this period. The median t_{max} for (S)-Casodex was much shorter than that for (R)-Casodex, although it should be noted that (R)-Casodex concentrations in many subjects were relatively constant for 48 h (Figure 2).

The elimination of (R)-Casodex was monophasic and slow in all subjects, with a mean half-life of about 7 days (Figure 3, Tables 1 and 2). The plasma concentrations of (S)-Casodex were erratic in the majority of subjects, precluding the fitting of a model. However, in three

Figure 2 Mean ($\pm$ s.e. mean) plasma concentrations of Casodex enantiomers up to 24 h post-dose; --- $\blacktriangle$ --- (R)-Casodex control, — $\bullet$ — (R)-Casodex impaired liver, $\blacksquare$ (S)-Casodex control, -.- $\blacktriangledown$ -.- (S)-Casodex impaired liver.

Figure 3 Mean ($\pm$ s.e. mean) plasma concentrations of Casodex enantiomers up to 28 days post-dose; --- $\blacktriangle$ --- (R)-Casodex control, — $\bullet$ — (R)-Casodex impaired liver, $\blacksquare$ (S)-Casodex control, -.- $\blacktriangledown$ -.- (S)-Casodex impaired liver.

liver-disease and six control subjects a biexponential function ($n = 8$) or a triexponential function ($n = 1$) could be fitted to the data. The terminal elimination half-lives from the above nine subjects were in the ranges 6.2 to 28 h for the impaired liver subjects and 11 to 37 h for the control subjects (Table 1). No statistical analyses were performed on these limited data.

Comparisons between groups

For (R)-Casodex there was no significant difference between the groups in C_{max} , t_{max} , AUC, or $t_{1/2,z}$ values (Table 2). For (S)-Casodex there was no significant difference between the groups in C_{max} or AUC trap. However, the median t_{max} was significantly shorter in the subjects in the liver group (2.5 h) when compared with the controls (5.0 h, Table 2). Estimates of the apparent absorption rate constant were only possible for (R)-Casodex with individual half-life values in the range 0.8 to 12.8 h (mean 3.9 h) and 0.9 to 14.9 h (5.2 h) for the liver and control groups, respectively. There was no significant difference ($P = 0.351$) between these mean values.

Discussion

Our results confirm data obtained in healthy subjects [4] indicating that the two enantiomers of Casodex have

Table 1 Comparison of the pharmacokinetics of (R)- and (S)-Casodex following a single oral dose of racemate (50 mg)

Subject	C_{max} (ng ml ⁻¹)		t_{max} (h)		AUC (µg ml ⁻¹ h)			$t_{1/2,z}$ (days) (h)	
	R	S	R	S	R*	S**	R/S	R	S
<i>Impaired liver</i>									
1	831	89.5	15	2	284(14%)	0.981	290	10.00	
2	433	71.4	15	3	120(16%)	1.62	74	8.88	
3	769	145.0	36	3	247(9%)	1.11	223	8.21	
4	483	39.4	24	2	109(2%)	0.320	341	4.71	
5	585	68.7	36	1	213(22%)	1.35	158	10.25	
6	916	65.3	9	3	135(3%)	0.833	162	3.93	
7	628	51.5	36	1	137(3%)	1.27	108	5.63	28.0
8	1300	182.0	24	3	313(5%)	1.14	275	6.67	6.2
9	781	103.0	5	2	131(16%)	1.05	125	4.88	14.7
10	774	80.9	36	3	274(18%)	NC		10.80	
<i>Control</i>									
1	812	68.2	24	2	228(7%)	1.56	146	7.13	21.5
2	885	83.2	7	5	337(19%)	1.38	244	10.91	
3	958	74.5	36	5	274(12%)	1.95	141	8.08	25.8
4	701	73.1	15	2	152(6%)	1.35	113	5.08	36.9
5	647	57.2	36	3	180(7%)	0.709	254	7.33	17.0
6	783	79.4	36	5	179(6%)	0.617	290	5.17	
7	1190	182.0	15	5	303(5%)	3.12	97	6.96	23.0
8	778	123.0	36	2	249(13%)	1.03	242	9.17	11.0
9	855	59.0	48	9	192(11%)	1.57	122	5.67	
10	871	98.4	24	9	218(13%)	1.97	111	6.75	

* Extrapolated to infinity (% extrapolated); ** up to last measurable concentration; NC = not calculable as measurable concentration only at single time point.

Table 2 Comparison of pharmacokinetic parameters for both (R)- and (S)-Casodex between groups following a single dose of racemate (50 mg)

	Least squares mean			95% CL		
	Impaired liver	Control	Difference	Lower	Upper	P
<i>(R)-Casodex</i>						
$C_{\max}$ (ng ml ⁻¹)	750	848	-98	-291	95	0.299
$AUC^{\dagger}$ (µg ml ⁻¹ h)	182*	225*	0.81*	0.59	1.12	0.187
$t_{1/2,z}$ (days)	7.40	7.22	0.17	-1.91	2.25	0.864
$t_{\max}$ (h)	24§	30§				0.571
<i>(S)-Casodex</i>						
$C_{\max}$ (ng ml ⁻¹)	81.4*	84.4*	0.96*	0.66	1.42	0.847
$AUC^{\dagger}$ (µg ml ⁻¹ h)	0.996*	1.38*	0.72*	0.46	1.15	0.157
$t_{\max}$ (h)	2.5§	5.0§				0.025

* Geometric means; difference between means reported as a ratio. § Median values.

C_{max} = peak plasma concentration, AUC = area under the plasma concentration-time curve, $t_{1/2,z}$ = terminal elimination half-life, t_{max} = time of maximum concentration.

† AUC_{∞} reported for (R)-Casodex and AUC_{trap} (up to the last measurable concentration) reported for (S)-Casodex.

appreciably different pharmacokinetics (Figures 2 and 3). It is unlikely that this is a consequence of differences in the extent of absorption between the enantiomers as McKillop *et al.* [4] have reported that a single dose (50 mg) of [^{14}C]-Casodex is extensively absorbed. It is more probable that (S)-Casodex, in contrast to (R)-Casodex, is subject to extensive first-pass metabolic clearance.

The clearance of Casodex is primarily metabolic with contributions to its elimination from both conjugative and oxidative mechanisms [4]. The magnitude of the observed enantioselectivity in the metabolism of drugs in man has been generally less than about 2, although much larger differences have been reported for nicoumalone (14-fold) [9] and mephenytoin in extensive metabolisers (100- to 200-fold) [10].

The pharmacokinetics of Casodex following a single 50 mg dose to prostate cancer patients [3] are similar to those observed for (R)-Casodex in the present study. This is to be expected in view of the relatively low concentrations of (S)-Casodex in the circulation and its rapid elimination from plasma. Furthermore, on daily administration to prostate cancer patients Casodex was observed to accumulate about 10-fold in plasma [3]. The similarity of the pharmacokinetics of (R)-Casodex and Casodex suggests that at steady state during daily dosing, the ratio of (R)- to (S)-Casodex will be much larger than that observed after the single dose used in this study. The trough plasma concentration ratio is estimated to be about 100:1 at steady state. Differences of this magnitude in trough plasma concentrations of the enantiomers, have been observed after 8 to 12 weeks daily dosing of Casodex to prostate cancer patients (data on file).

The observed plateau in the (R)-Casodex plasma concentration profiles of several subjects may in part be a consequence of absorption of this enantiomer continuing over a prolonged period. Studies with rat isolated gut loops [11] have demonstrated that absorption can continue throughout both the small and large intestines. Additional contributions from enterohepatic recirculation cannot be excluded, as it has been reported that a significant proportion of a human dose is secreted into bile either as unchanged drug or its glucuronide conjugate [4].

The reduced hepatic function, as documented here histologically, biochemically and by antipyrine clearance, in the liver group, did not alter the pharmacokinetic parameters of (R)-Casodex and had only a slight effect on the t_{max} of the (S)-enantiomer. Both Casodex and antipyrine are metabolised by oxidation and glucuronidation, however, the enzymes involved may be different. It is known that hepatic cirrhosis affects liver enzymes to differing degrees [12]. It is possible that the enzymes responsible for the metabolic clearance of the Casodex enantiomers are minimally affected by this degree of hepatic impairment, whilst the activity of those metabolising antipyrine are significantly diminished. In addition, the dose of each enantiomer (25 mg) used in this study may have been inadequate to saturate its hepatic metabolic pathways.

As all the antiandrogenic activity in Casodex resides in the (R)-enantiomer, these data indicate that the clinical effect of Casodex will, assuming unchanged receptor sensitivity, remain unaltered in prostatic cancer patients with this degree of liver disease and therefore no dose adjustment will be necessary in such patients.

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