

Sex and age differences in the pharmacokinetics of alosetron

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Aims To determine the effects of sex and age on the pharmacokinetics of alosetron.

Methods Single oral and intravenous 2 mg doses of alosetron were administered on separate occasions to 48 healthy, young and elderly, males and females. Serum was sampled for 12 h post-dose to measure alosetron concentrations.

Results Serum concentrations of alosetron were higher in females than in males, resulting from a sex difference in clearance by metabolism. Mean clearance values were 504 vs 677 ml min⁻¹ in young females vs males (mean ratio 0.75), and 461 vs 670 ml min⁻¹ in elderly females vs males (mean ratio 0.69). The sex difference in alosetron pharmacokinetics achieved statistical significance in the elderly, but not in the young. Irrespective of sex, alosetron clearance was increased by smoking. Serum concentrations tended to be higher in the elderly, although the effect of age was generally not significant. Volume of distribution was smaller in females (approximately 63 l) compared with males (approximately 84 l), regardless of age or the sex difference in body weight.

Conclusions A significant difference in clearance by metabolism of alosetron between the sexes, and possibly between the young and elderly was observed.

Keywords: age, alosetron, pharmacokinetics, sex

Introduction

Alosetron is a potent and selective 5-HT₃-receptor antagonist developed to treat irritable bowel syndrome (IBS) pain and discomfort in females whose predominant bowel habit is diarrhoea [1]. Although IBS occurs in both sexes, it is twice as prevalent in females [2]. As with many drugs during early clinical development, the pharmacokinetics of alosetron were initially examined in only healthy young males. Alosetron undergoes rapid oral absorption (t_{\max} at 1 h) with a bioavailability of 50–60%. It is rapidly eliminated with a 1.5 h half-life and a clearance of 600 ml min⁻¹, predominantly (94%) by hepatic cytochrome P450-mediated metabolism to a variety of products. Only a small portion of the dose (6%) is excreted unchanged renally.

Initial studies indicated that alosetron exhibited preferential efficacy in women [3]. Thus, it was important to characterize the disposition of alosetron in females in

attempting to explain the sex difference in efficacy. Therefore, this study was performed to characterize the effects of sex as well as age on the pharmacokinetics of alosetron.

Methods

Subjects and procedures

This open-label, single dose, parallel group, randomized two-period crossover study (Glaxo Wellcome protocol C92-058) was carried out at LAB GmbH & Co., Neu Ulm, Germany and the protocol was approved by the Freiburg Ethics Committee. All subjects provided written informed consent prior to participation.

Forty-eight subjects completed the study. Twelve subjects enrolled into each of four groups, composed of young (aged 18–40 years) males, young females, elderly (aged over 65 years) males, and elderly females. All subjects were healthy, had normal vital signs, ECG, and clinical laboratory tests, and had taken no regular medication within 2 weeks or any medication within 2 days of the first dose. Females of childbearing potential were

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requested to use adequate means of contraception and were tested for pregnancy at screening and before each dose. Subjects who smoked more than 15 cigarettes per day were not enrolled in the study, and smoking was not permitted while on the unit from the evening before to 12 h after dosing.

On two occasions separated by at least 7 days, each subject received a 2 mg dose of alosetron, consisting of either a single oral tablet or an intravenous injection in 15 ml saline given over 15 min, administered in random order. Subjects entered the unit the evening prior to each dosing and remained until the last blood sample was taken. Alcohol and caffeine were prohibited from 24 h prior to dosing and throughout the time spent in the unit. Subjects fasted overnight and for 4 h after each dose, and remained recumbent for 2 h after dosing.

Sample collection and bioanalysis

Blood samples (10 ml) were taken prior to dosing and at 15, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h after initiating dosing, and additionally at 20 and 25 min after initiating intravenous dosing. Blood was allowed to coagulate and serum was separated for bioanalysis.

Serum alosetron concentration was determined by reverse-phase h.p.l.c. with fluorescence detection using a previously described method [4]. The lower limit of quantification was 0.1 ng ml⁻¹. Concentrations were linear ($r \geq 0.996$) over the 0.1–20 ng ml⁻¹ standard range. Analytical precision was within 9%, and accuracy ranged from 95% to 103% of nominal.

Data analyses

Serum concentration data were analysed to determine peak concentration (C_{\max}) and the time at which it occurred (t_{\max}). Area under the concentration *vs* time curve (AUC) was determined using linear (ascending) and logarithmic (descending) trapezoidal interpolation and extrapolation to infinity. Elimination half-life ($t_{1/2}$) was calculated by

log-linear least-squares regression of the terminal phase. Data from the intravenous dose (D) were used to calculate clearance (CL) as $D \div \text{AUC}$, and steady-state volume of distribution (V_{ss}) as $[D \times \text{AUMC} \div \text{AUC}^2] - [D \div (2 \times \text{AUC})]$, where AUMC is the area under the first moment of the concentration–time curve. Absolute bioavailability (F) was calculated as the ratio of oral AUC to intravenous AUC.

Pharmacokinetic parameters (except t_{\max}) were log-transformed and assessed using an analysis of variance (AOV) model accounting for the effects of group, sequence, body weight, and smoking status (expressed as cigarettes smoked per day). Additionally, the effects of period, treatment, and subject within group and sequence were accounted for in the AOV for F using log-transformed values of oral and intravenous AUC. Parameters (except t_{\max}) were compared between groups, based on the AOV of log-transformed data, by calculating the estimated difference using contrasts, and exponentiating to obtain the least-squares mean ratio and associated 90% confidence interval (CI). Values of t_{\max} were compared between groups using the Wilcoxon Rank Sum test, and each median difference and associated 90% CI was estimated using the method of Hodges-Lehmann.

Results

Subject demographic characteristics are summarized in Table 1. Median alosetron serum concentration *vs* time plots for all groups are displayed in Figure 1 (intravenous dose) and Figure 2 (oral dose). Pharmacokinetic parameters are summarized for all groups and both doses in Table 2. Statistical comparisons of these parameters between groups are summarized in Table 3.

Although the characteristic sex difference in body weight was apparent in both young and elderly subjects, body weight (or body mass index) was not a significant factor in the analysis of any pharmacokinetic parameter ($P > 0.4$). Smoking was accounted for, independent of other subject characteristics, as a significant factor

Table 1 Summary of subject demographic characteristics.

	Young males	Young females	Elderly males	Elderly females
Age (years)*	28 (19–39)	30 (19–39)	69 (66–78)	70 (66–75)
Weight (kg)*	74 (61–87)	61 (53–70)	77 (61–91)	65 (58–77)
Smoking status (cigarettes/day)	0 ($n=8$)	0 ($n=6$)	0 ($n=9$)	0 ($n=10$)
	4 ($n=1$)	4 ($n=1$)	4 ($n=1$)	7 ($n=1$)
	5 ($n=1$)	10 ($n=3$)	5 ($n=1$)	10 ($n=1$)
	15 ($n=2$)	15 ($n=2$)	10 ($n=1$)	
Hormone use	–	No ($n=12$)	–	No ($n=10$)
				Yes ($n=2$)

*median (range); all groups $n=12$.

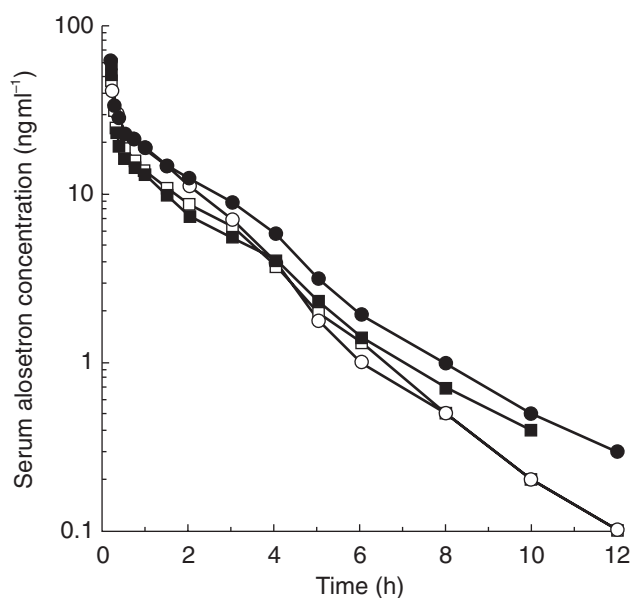


Figure 1 Median ($n=12$) alossetron serum concentration *vs* time following a 2 mg intravenous dose in young males (\square), young females (\circ), elderly males (\blacksquare), and elderly females (\bullet).

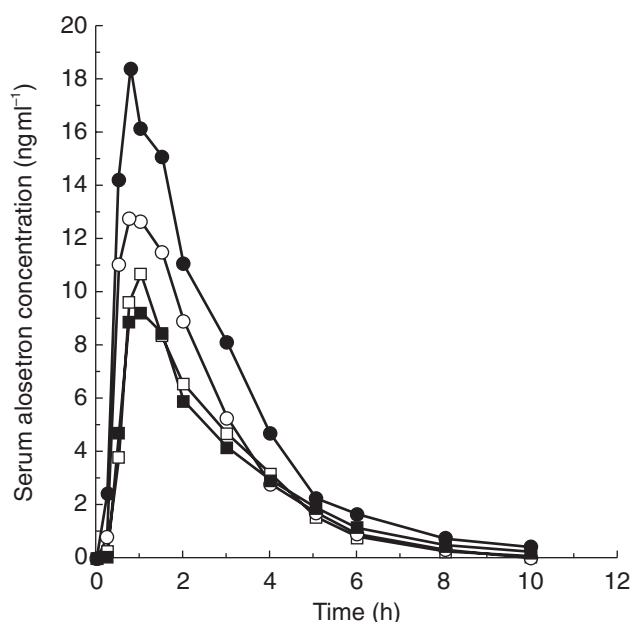


Figure 2 Median ($n=12$) alossetron serum concentration *vs* time following a 2 mg oral dose in young males (\square), young females (\circ), elderly males (\blacksquare), and elderly females (\bullet).

($P < 0.03$), increasing CL, and decreasing F , intravenous and oral AUC, and oral C_{\max} . Although none of the females used oral contraceptives during the study, two elderly females were receiving hormone replacement therapy. It was determined that including these two subjects made no important difference in the statistical analysis. *Post-hoc* analysis indicated that there was 80% power

to detect the observed between-group differences in each pharmacokinetic parameter.

During conduct of the study, no serious adverse events were reported, and no clinically relevant changes in laboratory tests attributable to alossetron were observed.

Sex comparison

In females who were elderly, compared with males of similar age, statistically significantly higher values were observed for intravenous AUC (45%), and oral AUC (87%) and C_{\max} (86%). These higher serum concentrations reflected the statistically significantly lower clearance (31%) observed in elderly females. Consistent with these sex differences, absolute bioavailability tended to be higher in elderly females, although this did not achieve statistical significance. The approximately two-fold larger sex difference in serum concentrations after oral dosing compared with intravenous dosing reflected the first-pass component of metabolic clearance. In young females compared with young males, a similar pattern of contrasts was observed, although these did not achieve statistical significance.

Volume of distribution was statistically significantly lower (approximately 25%) in females, irrespective of age or body weight. As a consequence of parallel differences in volume of distribution and clearance, half-life did not significantly differ between the sexes.

Age comparison

In elderly subjects of either sex, compared with young subjects of the same sex, intravenous C_{\max} was statistically significantly higher (27% in males, 48% in females). No statistically significant age-related differences were observed in any other pharmacokinetic parameter, although there was a tendency toward higher bioavailability and oral AUC with increased age in females.

Discussion

The pharmacokinetics of alossetron are not greatly affected by age. Although bioavailability tended to be higher with age in females, no statistically significant effect of age was observed after oral dosing. The only observed statistically significant effect of age was higher peak concentrations after intravenous dosing, which bears no direct clinical relevance for this orally administered drug.

In contrast to age, sex was associated with significant differences in the pharmacokinetics of alossetron, independent of smoking habit and body weight. The clearance of alossetron by metabolism was lower in women than in men. However, this difference in pharmacokinetics does not explain the greater efficacy of alossetron in women.

Table 2 Summary of serum alosetron pharmacokinetic parameters^a following a 2 mg dose.

	Young males	Young females	Elderly males	Elderly females
<i>Intravenous</i>				
C_{\max} (ng ml ⁻¹)	40.2 (34.2, 47.4)	43.1 (35.5, 52.3)	51.0 (42.5, 61.1)	63.7 (54.3, 74.8)
AUC(0, ∞) (ng ml ⁻¹ h)	49.3 (40.5, 59.9)	66.1 (52.4, 83.4)	49.7 (40.0, 61.8)	72.2 (59.6, 87.6)
$t_{1/2}$ (h)	1.52 (1.36, 1.69)	1.65 (1.45, 1.88)	1.69 (1.49, 1.90)	1.79 (1.61, 1.99)
CL (ml min ⁻¹)	677 (556, 823)	504 (400, 636)	670 (539, 833)	461 (381, 559)
V_{ss} (l)	82.6 (72.3, 94.2)	63.1 (53.9, 73.8)	84.5 (73.0, 97.8)	62.4 (54.8, 71.1)
<i>Oral</i>				
C_{\max} (ng ml ⁻¹)	9.35 (6.85, 12.8)	14.6 (10.1, 21.1)	8.67 (6.13, 12.2)	16.1 (11.9, 21.9)
t_{\max} (h)	1.00 (0.75, 2.00)	1.00 (0.50, 2.00)	0.75 (0.50, 2.00)	0.75 (0.50, 1.50)
AUC(0, ∞) (ng ml ⁻¹ h)	24.6 (17.5, 34.7)	36.6 (24.4, 55.0)	23.6 (16.1, 34.5)	44.2 (31.6, 61.9)
$t_{1/2}$ (h)	1.45 (1.28, 1.64)	1.44 (1.24, 1.68)	1.58 (1.37, 1.82)	1.67 (1.48, 1.89)
F	0.50 (0.41, 0.62)	0.49 (0.40, 0.61)	0.51 (0.41, 0.63)	0.63 (0.51, 0.79)

^aGeometric least-square mean (95% confidence interval), except t_{\max} : median (range); all groups $n=12$.

Table 3 Statistical comparison of serum alosetron pharmacokinetic parameters between groups.

	Sex comparison (female/male) ^a		Age comparison (elderly/young) ^a	
	Young subjects	Elderly subjects	Male subjects	Female subjects
<i>Intravenous</i>				
C_{\max} (ng ml ⁻¹)	1.07 (0.85, 1.35)	1.25 (1.01, 1.54)	1.27 (1.05, 1.53)*	1.48 (1.21, 1.81)*
AUC(0, ∞) (ng ml ⁻¹ h)	1.34 (1.02, 1.77)	1.45 (1.13, 1.87)*	1.01 (0.81, 1.26)	1.09 (0.86, 1.39)
$t_{1/2}$ (h)	1.09 (0.93, 1.26)	1.06 (0.92, 1.22)	1.11 (0.98, 1.26)	1.08 (0.95, 1.24)
CL (ml min ⁻¹)	0.75 (0.57, 0.98)	0.69 (0.53, 0.89)*	0.99 (0.79, 1.24)	0.92 (0.72, 1.16)
V_{ss} (l)	0.76 (0.63, 0.92)*	0.74 (0.62, 0.88)*	1.02 (0.88, 1.19)	0.99 (0.84, 1.16)
<i>Oral</i>				
C_{\max} (ng ml ⁻¹)	1.56 (1.01, 2.41)	1.86 (1.24, 2.78)*	0.93 (0.65, 1.32)	1.11 (0.76, 1.62)
t_{\max} (h)	0.00 (-0.25, 0.25)	0.00 (-0.25, 0.00)	-0.13 (-0.25, 0.00)	-0.25 (-0.25, 0.00)
AUC(0, ∞) (ng ml ⁻¹ h)	1.49 (0.92, 2.41)	1.87 (1.20, 2.92)*	0.96 (0.65, 1.42)	1.21 (0.79, 1.83)
$t_{1/2}$ (h)	1.00 (0.83, 1.19)	1.06 (0.90, 1.24)	1.09 (0.95, 1.26)	1.16 (0.99, 1.35)
F	0.98 (0.76, 1.27)	1.24 (0.96, 1.60)	1.01 (0.79, 1.31)	1.28 (0.99, 1.65)

^aGeometric least-square mean ratio (90% confidence interval), except t_{\max} : median difference (90% confidence interval).

*Significant difference between subject groups ($P<0.05$).

However, it may be inferred that the activity of at least one of the enzymes that metabolize alosetron differs between the sexes. Preliminary *in vitro* experiments indicate that alosetron is metabolized by several human hepatic cytochrome P450 enzymes including CYPs 2C9, 3A4, and 1A2 (unpublished data).

Although sex differences in human drug metabolism are not common, a number have been identified [5]. One particularly relevant example is the metabolism of ondansetron, which is chemically and pharmacologically related to alosetron. Ondansetron exhibits lower clearance in women, especially elderly women [6], and is also metabolized by CYP3A4 and 1A2. Sex differences in the activity of both these enzymes have been reported, with both higher [7–9] and lower [10, 11] metabolism of some CYP3A4 substrates, and lower metabolism of some

CYP1A2 substrates [12–16] in women. Thus, either or both of these enzymes may be responsible for the sex difference in alosetron metabolism.

The sex difference in alosetron metabolism was statistically significant in the elderly but not in the young. A larger sex difference in metabolism in the elderly has been reported for some substrates of CYP3A4 [5, 9] and CYP2C9 [17]. Thus, the differential effect of age on the variation between men and women in alosetron metabolism may also be related to the activity of one or more enzymes.

The involvement of CYP1A2 in alosetron metabolism had been demonstrated *in vitro*, although the *in vivo* importance of this smoking-inducible [18] enzyme is not known. The effect of smoking on alosetron clearance, independent of those of sex or other subject characteristics,

provides indirect evidence of the involvement of CYP1A2 in the *in vivo* metabolism of alosetron.

Although volume of distribution has no clinical relevance for an orally administered drug, the observed sex difference in this parameter was unexpected. This difference was not related to body weight, but may be influenced by body composition (e.g. a difference in lean body mass), which will apply to both the young and elderly.

In conclusion, alosetron provides an example of a drug that exhibits a sex difference in both metabolism and distribution, independent of smoking habit. The contribution of various CYP enzymes to the metabolism of alosetron, and the role these may play in producing the sex difference in alosetron clearance will require further investigation.

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