Effect of food and gender on the pharmacokinetics of tucaresol in healthy volunteers

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Aims The potential effects of food and gender on the pharmacokinetics of tucaresol were investigated in healthy volunteers.

Methods Ten males (mean weight 76.5 kg, age 27–42 years) and eight females (mean weight 58.9 kg, age 18–44 years) received a single oral dose of 200 mg tucaresol on two occasions in random order. On one occasion, tucaresol was given after an overnight fast and on the other, immediately after ingestion of a standard breakfast.

Results There were no significant differences in standard pharmacokinetic parameters between the two occasions but the rate of tucaresol absorption was faster after food intake. Female subjects had higher $C_{\max}$ (ratio 1.25 with 95% CI 1.10–1.44) and AUC (ratio 1.25 with 95% CI 1.05–1.49) values than males but the differences were due to the higher body weights of the males; weight-adjusted apparent total clearance values (CL/F) were not different between genders (ratio 1.03 with 95% CI 0.87–1.21).

Conclusions Food intake and gender have no significant effect on the exposure to orally administered tucaresol.

Keywords: food, gender, human, interaction, pharmacokinetics, tucaresol

Introduction

Tucaresol is a substituted benzaldehyde originally designed as a potential treatment for sickle cell disease by its preferential binding via Schiff base formation to the oxy conformation of haemoglobin [1]. Tucaresol was well tolerated in single doses in a dose-escalation study in healthy volunteers [2]. It had dose-proportional pharmacokinetics and an elimination half-life of 4–5 days. However, in placebo-controlled multiple dose studies of up to 10 days duration in healthy volunteers and sickle cell patients [3, 4], with levels of haemoglobin modification >10%, there was a characteristic syndrome of fever, rash and cervical lymphadenopathy in about a third of the drug-treated subjects studied. Further studies in animals have now indicated that these symptoms may be associated with the potentiation of an antigen-induced immune response [5] due to Schiff base formation and tucaresol is currently undergoing investigation in melanoma, HIV and hepatitis B patients at lower doses to explore its immunopotentiating properties. In this study we investigated the potential effects of food and gender on the pharmacokinetics of tucaresol in healthy volunteers.

Methods

Study design

Nineteen healthy volunteers (10 men aged 27–42 years, weight 62–95.5 kg, mean 76.5 kg and 9 women aged 18–44 years, weight 50.5–68 kg, mean 58.9 kg) participated in an open two occasion crossover study with at least 5 weeks between occasions. All subjects gave written, informed consent and the protocol was approved by the independent Wellcome Protocol Review Committee and the King's Health Care Ethics Review Committee. On both occasions subjects received a single 200 mg dose of tucaresol with 200 ml water; on one occasion this was taken after an overnight fast and on the other it was taken immediately prior to a standard breakfast (orange juice, milk, cornflakes, bacon, sausage, fried egg, toast, butter, marmalade, tea or coffee; protein 127 kcal, carbohydrate 383 kcal, fat 457 kcal). The breakfast was consumed within 15 min of dosing. Based on data from a previous single dose study [2], it was estimated that 10 subjects would give 90% power to detect a 32% increase or a 24% decrease in AUC in women compared with men. Assuming the worst case that the effect of food was different in men and women, 10 subjects gave 90% power to detect a 19% increase in AUC or a 16% decrease ($\alpha=5\%$). Blood samples were taken for drug assay (6 ml, Li heparin) predose and 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 h and 2, 3, 4, 7, 10, 14, 21 and 28 days after dosing. To determine haemolysate concentrations, 1 ml blood was added to 4 ml distilled water, mixed and frozen at -20°C until assayed. Plasma was separated from the remainder of

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Table 1 Mean (s.d.) pharmacokinetic parameters of tucaresol after a single 200 mg dose, and their comparison between men and women and after food compared to fasting.

	Men (n = 10)		Women (n = 8)		Fed/fasted (%) and 95% CI	Female/male (%) and 95% CI
	Fed	Fasted	Fed	Fasted		
Plasma						
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	9.44 (1.42)	9.55 (1.27)	11.8 (1.81)	11.9 (2.25)	99 (92, 106)	126 (110, 144)
$t_{\max}$ (h)*	5.10 (3.11)	6.90 (2.02)	5.75 (3.01)	5.75 (1.49)	−1.5 (−2.5, 1.0)	
AUC ($\mu\text{g ml}^{-1}$ h)	1440 (274)	1410 (244)	1750 (336)	1760 (414)	101 (96, 105)	125 (105, 149)
$t_{1/2,z}$ (h)	111 (16.9)	113 (16.8)	105 (12.2)	107 (20.6)	99 (95, 102)	96 (83, 100)
V/F (1 kg^{-1})	0.295 (0.032)	0.304 (0.025)	0.296 (0.036)	0.299 (0.029)	98 (94, 102)	99 (90, 107)
CL/F ($\text{ml min}^{-1} \text{ kg}^{-1}$)	0.0315 (0.0064)	0.0318 (0.0054)	0.0331 (0.0062)	0.0330 (0.0054)		103 (87, 121)
Red cell						
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	45.9 (9.43)	44.2 (10.41)	69.2 (15.63)	64.5 (12.5)	106 (98, 114)	149 (121, 183)
$t_{\max}$ (h)*	9.60 (5.56)	11.9 (6.61)	7.88 (2.8)	7.88 (2.7)	−1.5 (−5.0, 1.0)	
AUC ($\mu\text{g ml}^{-1}$ h)	5720 (1490)	5440 (1400)	7080 (1800)	7040 (1490)	103 (96, 109)	128 (102, 161)
$t_{1/2,z}$ (h)	83.5 (19.2)	84.3 (18.3)	72.9 (13.7)	76.2 (11.2)	97 (91, 102)	90 (75, 108)
V/F (1 kg^{-1})	0.057 (0.012)	0.062 (0.017)	0.051 (0.009)	0.054 (0.006)	94 (86, 103)	90 (74, 109)
CL/F ($\text{ml min}^{-1} \text{ kg}^{-1}$)	0.0082 (0.0028)	0.0087 (0.003)	0.0083 (0.0016)	0.0083 (0.0014)		101 (79, 128)

*median (range) and median difference (95% CI).

the blood and frozen. Tucaresol concentrations were determined in plasma and haemolysate samples using h.p.l.c. with u.v. detection at 280 nm [2, 4]. The limit of quantification was $0.2 \mu\text{g ml}^{-1}$ in plasma and $1.0 \mu\text{g ml}^{-1}$ in haemolysate.

Data analysis

Red blood cell concentrations (C_{RBC}) were calculated from plasma (C_{P}) and haemolysate concentrations (C_{B}) and the haematocrit value (H) either measured at the same plasma sample time or calculated as the average of the two haematocrit determinations bracketing the plasma sample, using the formula: $C_{\text{RBC}} = (C_{\text{B}} - C_{\text{P}}(1-H))/H$. Plasma and red cell pharmacokinetic parameters were calculated by standard methods [6]. C_{max} is the maximum measured concentration, t_{max} is the time to C_{max} , $t_{1/2,z}$ is the terminal elimination half-life from the log-linear regression of the last 4–8 concentration points, AUC is the linear trapezoidal area under the concentration time curve, extrapolated to infinity, CL/F is the apparent total clearance and V/F is the apparent volume of distribution. Parameters were compared by analysis of variance on log transformed data (except t_{max} , GLM procedure of SAS for Windows, version 6.10, SAS Institute, Cary, NC 27513, USA).

The Wilcoxon Rank Sum test in the manner suggested by Koch to account for any occasion effect was used to analyse t_{max} data [7].

Results

Ten women were recruited but one withdrew before treatment and another withdrew after her first occasion after developing cervical lymphadenopathy, associated with mild catarrh, headache and cough. These events were considered possibly drug-related; there was no serological evidence of infection with Epstein-Barr virus, cytomegalovirus, influenza or adenoviruses. Thus eight women and 10 men completed the study and were included in the statistical analysis. Initial statistical analyses of all data for males and females indicated that there were no significant food:gender interactions and the data were reanalysed using combined male and female data to compare fed and fasted parameters and combined fed and fasted data to test for gender differences. The arithmetic mean and standard deviations for the parameters and the ratios of least squares mean parameters with associated 95% confidence intervals are given in Table 1. There were no statistically significant differences in any parameters between the fasted and fed states. C_{max} and AUC values for female subjects were significantly higher than for males but this difference is related to the greater body weight for male subjects (mean weight for males, 76.5 kg and for females; 58.9 kg); the mean apparent total clearance values for males and females, adjusted for body weight, were not significantly different. Figure 1 shows the mean plasma (and red cell) concentrations for male and female data combined for the first 24 h. In the fasted state the absorption of tucaresol was slower than when given immediately after a standard breakfast and the shape of the absorption profile showed greater variability between subjects.

Figure 1 Mean (s.d.) plasma (circles) and red blood cell (squares) tucaresol concentrations after a single 200 mg oral dose fasting (open symbols) and with food (closed symbols). (For clarity, data are shown for the first 24 h only; there was no differences between fed and fasted curves thereafter).

Discussion

Previous studies have shown that the pharmacokinetics of tucaresol are dose dependent, with a slower elimination half-life for increased body load [2, 4]. Parameters for the present data are in good agreement with data obtained in the fasted state for the same dose in a dose escalation study [2] but define the pharmacokinetics much better since the 200 mg dose was only administered to two subjects previously and concentration measurements were only taken up to 168 h after dosing. In sickle cell patients [4], two female patients achieved higher plasma and red cell concentrations after dosing for 10 days at 300 mg daily than male subjects given the same doses and this was evident also after a single dose. The present study shows that differences in pharmacokinetics between genders are entirely accounted for by differences in body weight and that tucaresol exposure is not affected by food intake. Absorption is slow in both fasted and fed states with no significant difference in t_{max} . However, initial rate of absorption appears faster after food. This may be related to the solubilising effect of the fatty components of the meal since tucaresol shows poor aqueous solubility at or below neutral pH. This may be of clinical relevance for the immunopotentiating effect of the drug. The process of tucaresol binding proteins requires the formation of covalent bonds and is likely to be slow. Thus it can be speculated that the faster rise in concentrations when tucaresol is dosed after food, compared to fasting, may be associated with transiently higher free drug concentrations. It is not known if this will translate into clinically important differences.

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