Effect of food or antacid on pharmacokinetics and pharmacodynamics of febuxostat in healthy subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Febuxostat is a novel nonpurine selective inhibitor of xanthine oxidase.

WHAT THIS STUDY ADDS

- This is the first manuscript to address the effect of food and antacid on the pharmacokinetics and/or pharmacodynamics of febuxostat.
- The study will determine whether the drug can be administered regardless of food or antacid.
- It will therefore influence how the drug should be administered.

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AIMS

To evaluate the effects of food or antacid on the pharmacokinetics and/or pharmacodynamics of febuxostat.

METHODS

Four Phase I, two-period, crossover studies were performed in healthy male and female subjects. Subjects either received single 40-mg ($n = 24$), multiple 80-mg ($n = 24$) and single 120-mg ($n = 20$) doses of febuxostat in fasting and nonfasting conditions, or received single 80-mg ($n = 24$) doses alone or with antacid.

RESULTS

Food caused a decrease in $C_{\max}$ (38–49%) and AUC (16–19%) of febuxostat at different dose levels following single or multiple oral dosing with febuxostat. However, a slightly greater percent decrease in serum uric acid concentrations (58% vs. 51%) after multiple dosing with 80 mg of febuxostat under nonfasting conditions was observed, which was statistically ($P < 0.05$) but not clinically significant. Antacid caused a decrease in $C_{\max}$ (32%), but had no effect on AUC of febuxostat. Febuxostat was safe and well tolerated in all studies.

CONCLUSIONS

Even though food caused a decrease in the rate and extent of absorption of febuxostat, this decrease was not associated with a clinically significant change in febuxostat pharmacodynamic effect. Despite a decrease in the absorption rate of febuxostat, antacid had no effect on the extent of febuxostat absorption. Therefore, febuxostat can be administered regardless of food or antacid intake.

Introduction

Gout is the most common form of inflammatory joint disease in men aged >40 years and is commonly characterized by hyperuricaemia and recurrent attacks of acute arthritis [1, 2]. Sustained hyperuricaemia is considered to be the precursor and the underlying cause of gout [3]. The management of hyperuricaemia associated with gout is therefore one of the most important cornerstones in the management of gout. Management of hyperuricaemia is achieved by the use of drugs that increase uric acid total body clearance (e.g. uricosurics or uricase) or drugs that decrease uric acid production (e.g. xanthine oxidase inhibitors).

Febuxostat is a novel nonpurine selective inhibitor of xanthine oxidase (NP-SIXO) which is currently under investigation for the management of hyperuricaemia in patients with gout [4]. Phase II and III data indicate that febuxostat effectively decreases serum uric acid in hyperuricaemic patients with gout [5, 6]. Febuxostat is absorbed extensively (84%) from the gastrointestinal tract with a time to reach maximum plasma concentration of approximately 1 h [7–9]. It is highly protein bound (~99%) and has a low to medium volume of distribution of approximately 0.7 l kg⁻¹ [8, 9]. Although the drug appears to have a low hepatic extraction ratio, it undergoes extensive metabolism via phase II (i.e. glucuronidation) and phase I metabolism (i.e. oxidation) [7–9]. Less than 5% of the dose is excreted in urine as intact drug, indicating that renal clearance contributes to a small extent to the total body clearance of febuxostat. Febuxostat is a weak acid (pK_a = 3.42), 'practically insoluble' in water (solubility of 0.0129 mg ml⁻¹), and considered to be a Class II compound on the Biopharmaceutics Classification Scale [10].

Food and antacids can alter the rate and extent of absorption of different drugs. They may affect the physicochemical (e.g. dissolution rate, degradation rates and intraluminal diffusion) as well as physiological parameters (e.g. gastrointestinal transit time, bile and enzyme secretions, region-dependent absorption, intraluminal volume and splanchnic blood flow) involved in the absorption of a drug [11]. Certain food contents can delay the gastric emptying [12, 13], increase gastric pH [14, 15] and the intraluminal fluid volume [16], enhance bile salt solubilization of lipophilic drugs [15, 17, 18], enhance adsorption of the drug to food contents [19], or impede the intraluminal diffusivity of the drug [20–22]. Similarly, antacids can affect the absorption of different drugs by affecting the gastric pH, gastric emptying time and urinary pH or through adsorption and chelation mechanisms [23].

Therefore, food or antacid can cause a decrease or an increase in the total plasma exposure to drugs, which may require dose adjustments to maintain their pharmacological effects or to avoid any potential toxic effects. Since febuxostat may be administered with food or antacids, drug interaction studies were performed to study the

effect of food and antacid on the pharmacokinetics and pharmacodynamics of febuxostat.

Materials and methods

Patient population

In one antacid and three food effect studies, healthy adult male and female subjects between the ages of 18 and 55 years with normal creatinine clearance (79–149 ml min⁻¹) and a body mass index <30 kg m⁻² were recruited. Lactating or pregnant women, nicotine users, subjects with histories of gout, xanthinuria, subjects with any known drug allergies and subjects with any clinically significant abnormalities that could have interfered with the evaluation of the study medication were excluded. The following medications were discontinued prior to participation: any prescription medications, enzyme altering agents, investigational drugs, and nicotine at least 4 weeks prior to dosing; over-the-counter (OTC) anti-inflammatory agents, aspirin at least 14 days prior to dosing; and OTC medications (including vitamins, and herbal or dietary supplements) at least 7 days prior to dosing. In addition, consumption of high-purine-, grapefruit-, caffeine- or alcohol-containing products was not allowed. Each study was approved by an Institutional Review Board (Independent Investigational Review Board, Inc. Plantation, FL, USA; MDS Harris Institutional Review Board, Lincoln NE, USA; Quorum Review Inc. Seattle, WA, USA) and written informed consents were obtained prior to enrolment for each study.

Study design

These four studies were designed as randomized, single-centre, two-way crossover studies. Healthy male and female subjects received either 40 mg (single dose), 80 mg (multiple doses) or 120 mg (single dose) of febuxostat under fasting and nonfasting (i.e. high-fat breakfast) conditions; or received 80 mg (single dose) of febuxostat alone and with an antacid [i.e. 800 mg Mg(OH)₂ + 900 mg Al(OH)₃]. In each study, subjects were randomly assigned to one of two regimen sequences which identified the order in which each subject received febuxostat under fasting (reference) or nonfasting (test) conditions for food effect studies and alone (reference) or with antacid (test) for the antacid study. In each study, the two periods were separated by a 7–16-day wash-out interval. The specific details of each study are presented in Table 1.

In the food effect studies, for the fasting regimen, subjects remained fasting from food starting at 22.00 h on the day before dosing until 2 h post dosing on the next day. For the nonfasting regimen, subjects received a standard high-fat breakfast (30.5 g protein) containing two eggs fried in butter, two strips of bacon, two slices of toast with butter, 113 g of hash brown potatoes and 227 g of whole milk approximately 30 min before the dosing. In the antacid

Table 1

Summary information for each study

Study type	Dose, mg	Dosing	Dosing interval	Wash-out interval	No enrolled	PK analysis	PD analysis	Safety analysis
Food Effect	40	Single dosing	1 day	7 days	24	Yes	No	Yes
	80	Multiple dosing	6 days	16 days	24	Yes	Yes	Yes
	120	Single dosing	1 day	7 days	20	Yes	No	Yes
Antacid effect	80	Single dosing	1 day	7 days	24	Yes	No	Yes

PK, Pharmacokinetics; PD, pharmacodynamics.

study, subjects were fasting from food starting at 21.30 h on the day prior to dosing until approximately 4.5 h post dosing on the next day.

In the multiple dose food effect pharmacokinetic and pharmacodynamic study, in order to ensure that the daily protein intake was similar between the nonfasting and fasting regimen [24], an afternoon snack, between noon and dinner, was provided for subjects receiving the fasting regimen. The snack (30.6 g protein) included one piece of American cheese, 85 g of turkey breast and two slices of bread.

Blood samples for the determination of plasma concentrations of febuxostat were collected at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post dose on day 1 of each period for single-dose studies and on day 6 for the multiple-dose study. In the multiple-dose study, additional predose blood samples were also obtained on days 1–6 of each period. In the multiple-dose study, for determination of serum uric acid concentrations, additional blood samples were obtained at 12, 18 and 24 h predose on day –1, predose on days 1–6 and at 6, 12 and 24 h post dose on day 6. The transferred plasma (for febuxostat concentration measurements) or serum (for uric acid concentration measurements) samples were frozen at approximately –20°C and shipped on dry ice to the bioanalytical lab where they were stored at approximately –20°C until analysed.

Safety was monitored through adverse events, concurrent medication utilization, vital signs, physical examinations and laboratory evaluations.

Analytical methods

Plasma concentrations of febuxostat were measured using a validated high-performance liquid chromatography with fluorescence detection method at excitation and emission wavelengths of 320 and 380 nm, respectively. In brief, after addition of internal standard (2-naphthoic acid), plasma samples (0.5 ml) were deproteinized by addition of 0.5 ml of acetonitrile, mixed, centrifuged, and the resulting supernatant was acidified with 50 µl of glacial acetic acid. Febuxostat and the internal standard were resolved from the matrix components using a Phenomenex (Torrance, CA, USA) Capcell Pak C₁₈ column with a mobile phase composed of 0.032% glacial acetic acid in water:acetonitrile

(55:45, v:v). The calibration curve range for febuxostat was linear from 0.01 to 20 µg ml⁻¹ with a correlation coefficient of >0.996. Quality control (QC) samples at 0.03, 1 and 15 µg ml⁻¹ were analysed with the plasma samples from each study. The lower limit of quantification with a 0.5-ml plasma sample was 0.01 µg ml⁻¹ for febuxostat. QC samples showed interday coefficients of variation of ≤10.0% and ≤19.2%, and absolute relative errors of ≤7.7% and ≤4.3% for single- and multiple-dose studies, respectively. In the multiple-dose study, there was one anomalous value for the 0.03 µg ml⁻¹ QC on one of the standard curves, which caused the coefficient of variation to be 19.2% for that QC level. However, the standard curve met the standard and QC acceptance criteria and was included in the dataset. At other QC levels, 1 and 15 µg ml⁻¹, in the multiple-dose study, the interday coefficients of variation were 3.3% and 3.6%, respectively. After exclusion of the anomalous value at 0.03 µg ml⁻¹ QC level, the coefficients of variation and the relative errors at all QC levels in the multiple-dose study were ≤4.7% and ≤4.3%, respectively.

Serum uric acid analyses were performed using standard methods at the investigative site's clinical laboratory.

Pharmacokinetic assessments

For all four studies, pharmacokinetic parameters of febuxostat were estimated using noncompartmental pharmacokinetic methods with WinNonlin Professional Version 3.1 (Pharsight Co., Mountain View, CA, USA). The pharmacokinetic parameters estimated included: the observed maximum plasma concentration (C_{max}); the time to reach the observed maximum plasma concentration (t_{max}); the apparent terminal elimination half-life ($t_{1/2}$); the area under the plasma concentration–time curve from time zero to the last quantifiable sampling time point (AUC_t), from time zero to 24 h post dose (AUC_{24} , for the multiple-dose study), or from time zero to infinity (AUC_{∞}); and the oral clearance (CL/F).

Pharmacodynamic assessments

In the multiple-dose study, the area under the serum concentration–time curve for serum uric acid was estimated using standard noncompartmental methods using

Table 2

Summary of demographic data for subjects completing each study

Study	Gender (M/F)*	Race (W/H/B/A)‡	Age† (years)	Height† (cm)	Weight† (kg)	Body mass index (kg m ⁻²)
Food effect studies						
40 mg single dose	11/12	22/1/0/0	39.9 ± 10.0 (22–54)	174 ± 11 (157–193)	77.8 ± 13.1 (51.3–98.1)	25.6 ± 3.1 (19.7–30.0)
80 mg multiple doses	14/9	15/2/5/1	38.8 ± 10.8 (20–55)	173 ± 9 (155–191)	77.4 ± 14.9 (50.4–103.5)	25.8 ± 3.6 (18.8–29.8)
120 mg single dose	8/11	2/15/2/0	36.5 ± 10.9 (19–51)	166 ± 7 (150–178)	69.2 ± 9.3 (55.8–86.3)	25.0 ± 2.9 (20.5–30.7)
Antacid effect study						
80 mg single dose	10/14	1/21/2/0	36.0 ± 9.3 (19–53)	166 ± 9 (147–191)	68.7 ± 13.1 (45.9–100.3)	24.9 ± 3.5 (17.8–30.4)

*Number of male/female subjects completing each study. †Data presented are mean ±SD (range). ‡Number of White/Hispanic/Black/Asian subjects completing each study.

WinNonlin Professional™ V.3.1. The 24-h mean serum concentration ($C_{\text{mean},24}$) was calculated by dividing the area under the serum concentration–time curve from time zero to 24 h by 24. The pharmacodynamic parameters that were estimated included days –1 and 6 $C_{\text{mean},24}$ and the percent change of $C_{\text{mean},24}$ from baseline (day –1) to day 6 of each period.

Statistical methods

All statistical analyses were performed using SAS Versions 6.2 or 8.2 (SAS Inc., Cary, NC, USA). Analyses of variance (ANOVAs) were performed on t_{max} and the natural logarithms of C_{max} and AUCs with factors for sequence, subjects nested within sequence, period and regimen (test or reference regimen). The factor of subjects nested within sequence was considered as random and all other factors were considered fixed.

The effect of food or antacid on febuxostat pharmacokinetics was assessed via 90% confidence intervals (CI) for the ratio of test regimen (i.e. nonfasting regimen or febuxostat with antacid regimen) to reference regimen (i.e. fasting regimen or febuxostat alone regimen) geometric means for febuxostat C_{max} and AUCs. A conclusion of no effect of food or antacid on the pharmacokinetics of febuxostat was made if the 90% CIs were within the range of 0.80–1.25 for febuxostat C_{max} and AUCs.

In the multiple-dose study, the effect of food on serum uric acid $C_{\text{mean},24}$ and percent change in serum uric acid $C_{\text{mean},24}$ from baseline was analysed using an ANOVA with factors for sequence, subjects nested within sequence, period and regimen. The factor of subjects nested within sequence was treated as random and all other factors were fixed. The statistical tests within the ANOVA framework were performed at a significance level of 0.05. A 95% CI was determined for the difference between regimens in the percent change in serum uric acid $C_{\text{mean},24}$ from the baseline.

Results

Subject population

Twenty to 24 subjects were enrolled in each of the studies (Table 1). There was one subject in each of the food effect studies who did not complete the study and therefore was excluded from the pharmacokinetic and/or pharmacodynamic parameters statistical analyses. The demographic data for subjects who completed each of the four studies are provided in Table 2.

Pharmacokinetics

Food effect The pharmacokinetic parameters for febuxostat when administered under fasting conditions (reference) or nonfasting conditions (test) are presented in Table 3. The mean plasma concentration profiles of febuxostat under fasting or nonfasting conditions at different dose levels are depicted in Figure 1A–C. Following administration of different doses of febuxostat under nonfasting conditions, there was a delay of 12–66 min in febuxostat mean t_{max} compared with administration of febuxostat under fasting conditions. The difference in febuxostat t_{max} between the two treatment groups was statistically significantly different from zero ($P < 0.001$) at the 40 mg dose level. In addition, there was a decrease in febuxostat C_{max} and AUC geometric mean values under nonfasting conditions compared with fasting conditions, ranging from 38 to 49% and 16 to 19%, respectively, with differences being statistically significantly different from zero ($P < 0.001$) on the natural logarithm scale. The 90% CI for C_{max} and AUC test to reference geometric mean ratio extended below the no effect range of 0.80–1.25 at all three dose levels. The nonfasting harmonic mean $t_{1/2}$ for febuxostat under nonfasting conditions was within 87–114% of that under fasting conditions. There was a 21–24% increase in CL/F under nonfasting conditions compared with fasting conditions, with differences being statistically significantly dif-

Table 3

Plasma febuxostat mean ($\pm$ SD) pharmacokinetic parameters, test to reference geometric mean ratios (GMR) and the 90% confidence intervals (90% CI) for the ratios in the food effect studies

Parameters	Reference (fasting)	Test (Nonfasting)	GMR	90% CI
40 mg single dose				
$t_{\max}$ (h)	0.8 $\pm$ 0.6	1.9 $\pm$ 0.9**		
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	1.82 $\pm$ 0.57	1.00 $\pm$ 0.38**	0.54	(0.48, 0.61)
AUC_t ($\mu\text{g h}^{-1} \text{ml}^{-1}$)	4.47 $\pm$ 1.59	3.65 $\pm$ 1.39**	0.81	(0.77, 0.85)
AUC_{∞} ($\mu\text{g h}^{-1} \text{ml}^{-1}$)	4.61 $\pm$ 1.61	3.75 $\pm$ 1.42**	0.81	(0.77, 0.85)
$t_{1/2}$ (h)	5.5 $\pm$ 2.3 (4.7)†	4.6 $\pm$ 1.5 (4.1)†		
CL/F (l h^{-1})	9.6 $\pm$ 2.9	11.9 $\pm$ 3.7**‡		
80 mg multiple dose				
$t_{\max}$ (h)	1.6 $\pm$ 1.1	1.8 $\pm$ 1.0		
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	3.26 $\pm$ 0.84	1.80 $\pm$ 0.85**	0.51	(0.44, 0.60)
AUC_{24} ($\mu\text{g h}^{-1} \text{ml}^{-1}$)	9.21 $\pm$ 3.59	7.67 $\pm$ 3.29**	0.82	(0.78, 0.87)
$t_{1/2}$ (h)	6.8 $\pm$ 2.7 (5.9)†	5.9 $\pm$ 1.6 (5.6)†		
CL/F (l h^{-1})	9.8 $\pm$ 3.4	11.9 $\pm$ 4.1**§		
120 mg single dose				
$t_{\max}$ (h)	1.7 $\pm$ 1.1	2.3 $\pm$ 1.2		
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	5.27 $\pm$ 1.78	3.44 $\pm$ 1.49**	0.62	(0.52, 0.74)
AUC_t ($\mu\text{g h}^{-1} \text{ml}^{-1}$)	15.47 $\pm$ 3.94	13.06 $\pm$ 3.62**	0.84	(0.78, 0.90)
AUC_{∞} ($\mu\text{g h}^{-1} \text{ml}^{-1}$)	15.64 $\pm$ 3.95	13.28 $\pm$ 3.67**	0.84	(0.79, 0.90)
$t_{1/2}$ (h)	4.4 $\pm$ 0.9 (4.2)†	5.1 $\pm$ 1.4 (4.8)†		
CL/F (l h^{-1})	8.2 $\pm$ 2.3	9.9 $\pm$ 3.4**‡		

$C_{\max}$, Maximum observed concentration for febuxostat; $t_{\max}$, time to reach the observed $C_{\max}$; AUC_t , area under the plasma concentration–time curve from time zero to the time for the last measurable concentration for febuxostat; AUC_{∞} , area under the plasma concentration–time curve from time zero to infinity for febuxostat; AUC_{24} , area under the plasma concentration–time curve over 24 h (dosing interval) for febuxostat; $t_{1/2}$, apparent terminal phase half-life; CL/F, oral clearance. †Harmonic mean is in parentheses. **Statistically significantly (P -value < 0.001) different compared with the fasting regimen (on the natural logarithm scale for $C_{\max}$, AUC and CL/F). ‡Based on the test for $\ln(\text{AUC}_{\infty})$. §Based on the test for $\ln(\text{AUC}_{24})$.

ferent from zero ($P < 0.001$) on the natural logarithm scale (based on the test for $\ln(\text{AUC})$).

With the exception of sequence effect for $C_{\max}$ at the 40 mg dose level and period effect for $t_{\max}$ and AUC_{24} at the 80 mg dose level, which were statistically significant ($P < 0.05$), there was no statistically significant ($P > 0.05$) period or sequence effect for febuxostat pharmacokinetic parameters analysed. Since the wash-out periods in these studies were sufficiently long, the significant sequence effect was probably not due to unequal carryover effect, but rather due to randomness. The existence of the period effect did not affect the comparison between the test and the reference, but rather confirmed the appropriateness of the crossover design.

Antacid effect The pharmacokinetic parameters for febuxostat when administered alone (reference) or with antacid (test) are presented in Table 4. The plasma concentration profiles of febuxostat when given alone or with antacid are depicted in Figure 1D. Following administration of febuxostat with antacid, mean $t_{\max}$ occurred at 1.8 h, which was approximately 1 h longer compared with that from administering febuxostat alone ($P < 0.05$). In conjunction with the delay in $t_{\max}$, there was also a 32% decrease in $C_{\max}$ and a 15% decrease in AUC geometric

mean, with differences being statistically significantly different from zero ($P < 0.001$) on the natural logarithm scale. The 90% CI for the ratio of $C_{\max}$ geometric means extended below the 0.80–1.25 no effect range, whereas, for AUC geometric mean ratios, the 90% CI remained within the 0.80–1.25 no effect range. Within the framework of the ANOVA, the sequence and period effects were not statistically significant for any of the parameters analysed.

Pharmacodynamics

Food effect only The day –1 and day 6 pharmacodynamic parameters for febuxostat when administered under fasting or nonfasting conditions in the multiple-dose study are presented in Table 5. The predose and the 24-h plasma profiles of uric acid are shown in Figure 2. The predose and 24-h mean serum concentrations of uric acid appear to be slightly lower under nonfasting compared with fasting conditions. Although the percent decrease in serum uric acid under nonfasting conditions was statistically significantly ($P < 0.05$) different (i.e. greater) from that under fasting conditions (Table 5, 58% vs. 51%), the 95% CI of 4–10% for the differences was not considered to be clinically significant.

Figure 1
Mean (SD) plasma concentration–time profile of febuxostat in food effect and antacid studies in healthy subjects

Table 4
Plasma febuxostat mean (± SD) pharmacokinetic parameters, test to reference geometric mean ratios (GMR), and the 90% confidence intervals (90% CI) for the ratios in the antacid effect study

Parameters	Reference (alone)	Test (with antacid)	GMR	90% CI
t_{max} (h)	0.9 ± 0.4	1.8 ± 1.5*		
C_{max} (µg ml ⁻¹)	3.29 ± 1.15	2.28 ± 1.01**	0.68	(0.58, 0.79)
AUC_t (µg h ⁻¹ ml ⁻¹)	8.82 ± 2.74	7.51 ± 2.29**	0.85	(0.80, 0.90)
AUC_{∞} (µg h ⁻¹ ml ⁻¹)	9.03 ± 2.70	7.71 ± 2.27**	0.85	(0.81, 0.90)
$t_{1/2}$ (h)	6.5 ± 3.1 (5.5)‡	6.3 ± 3.0 (5.3)‡		
CL/F (l h ⁻¹)	9.7 ± 3.0	11.4 ± 3.9**†		

C_{max} , Maximum observed concentration for febuxostat; t_{max} , time to reach the observed C_{max} ; AUC_t , area under the plasma concentration–time curve from time zero to to the time for the last measurable concentration for febuxostat; AUC_{∞} , area under the plasma concentration–time curve from time zero to infinity for febuxostat; $t_{1/2}$, apparent terminal phase half-life; CL/F, oral clearance. †Harmonic mean is in parentheses. *Statistically significantly (P-value < 0.05) different compared with febuxostat alone regimen. **Statistically significantly (P-value < 0.001) different compared with febuxostat alone regimen on the natural logarithm scale. ‡Based on the test for ln(AUC_{∞}).

Table 5

Serum uric acid mean ($\pm$ SD) pharmacodynamic parameters, test and reference least squares means (LSM) difference, and the 95% confidence interval (95% CI) for the difference following multiple dosing with 80 mg of febuxostat

Parameters	Reference (fasting)	Test (non-fasting)	LSM difference	95% CI
Day -1 $C_{\text{mean},24}$ (mg dl ⁻¹)	5.11 $\pm$ 1.59	5.26 $\pm$ 1.51		
Day 6 $C_{\text{mean},24}$ (mg dl ⁻¹)	2.61 $\pm$ 1.29	2.24 $\pm$ 1.01		
% decrease in serum uric acid $C_{\text{mean},24}$	51 $\pm$ 14	58 $\pm$ 12*	7	(4,10)

$C_{\text{mean},24}$, 24-h mean concentration. *Statistically significantly (P-value < 0.05) different compared with the fasting regimen.

Figure 2

Predose and 24-h mean serum concentration–time profiles of uric acid following once-daily multiple oral doses of febuxostat 80 mg under fasting or nonfasting conditions in healthy subjects

Safety

Food effect studies In the 40-mg single-dose study, the majority of adverse events reported were mild and self-limiting. No serious adverse events were reported in this study. The most frequently reported adverse events considered by the investigator to be related to study drug were headache, and nausea (Table 6). The incidence of adverse events that were possibly, probably or definitely related to study drug was higher in the fasting (17%) compared with the nonfasting regimen (4%).

In the 80-mg multiple-dose study, the majority of the adverse events reported were mild or moderate in severity; two subjects reported severe adverse events (one subject with severe abdominal cramps and somnolence, one with severe nausea). The overall incidence of treatment-related adverse events with febuxostat 80 mg administration was higher in the fasting (50%) than in the nonfasting regimen (35%) with the increase noted in gastrointestinal and musculoskeletal adverse events during the fasting period (Table 6).

In the 120-mg single-dose study, all adverse events were mild in intensity. No treatment-related adverse

events were observed under the fasting regimen and only one subject had a treatment-related adverse event (headache) on the nonfasting regimen (Table 6). All events were transient and self-limiting.

Antacid effect study In the antacid interaction study, one adverse event was reported. The event, ecchymosis, occurred after dosing with febuxostat with antacid, was mild in severity, and was considered to have no relationship to the study drug.

Discussion

Administration of febuxostat with food caused a delay in t_{max} and was associated with a lower maximum and total exposure to febuxostat, indicating a decrease in the absorption rate constant and an increase (21–24%) in the oral clearance (i.e. CL/F) of febuxostat. Administration of febuxostat under nonfasting conditions (i.e. high-fat meal) did not appear to affect the apparent terminal phase elimination half-life of febuxostat, supporting a lack of effect of

Table 6

Most frequent* treatment-related adverse events observed during each study

Adverse event	Reference	Test
Food effect studies		
40 mg single dose		
Subjects with at least 1 related adverse event	4 (17%)	1 (4%)
Headache	3 (13%)	1 (4%)
Nausea	2 (8%)	0 (0%)
80 mg multiple doses		
Subjects with at least 1 related adverse event	12 (50%)	8 (35%)
Somnolence	3 (13%)	3 (13%)
Abdominal pain upper, abdominal pain NOS	2 (8%)	1 (4%)
Nausea	2 (8%)	1 (4%)
Diarrhoea NOS	2 (8%)	0 (0%)
Headache	0 (0%)	2 (9%)
Arthralgia	2 (8%)	0 (0%)
Myalgia	0 (0%)	2 (9%)
120 mg single dose		
Subjects with at least 1 related adverse event	0 (0%)	1 (5%)
Headache NEC†	–	–
Antacid study		
80 mg single dose		
Subjects with at least 1 related adverse event	0 (0%)	0 (0%)
None	–	–

*Reported by two or more subjects in either regimen. †The headache not elsewhere classified (NEC) was the only event assessed by the investigator as being possibly related to study drug, and it was experience by only one subject.

food on the total body clearance of febuxostat. Therefore, the increase in febuxostat oral clearance following its administration under nonfasting conditions was probably the result of a slight decrease in the total bioavailability of febuxostat (i.e. F) and not its total body clearance (i.e. CL).

Regardless of the slight decrease in the total bioavailability of febuxostat under nonfasting conditions, the febuxostat pharmacodynamic effect was not diminished. Indeed, the percent change from baseline in serum uric acid $C_{\text{mean},24}$ on day 6 was slightly greater under nonfasting conditions (58.5% decrease) than under fasting conditions (51.2% decrease). The slight decrease in the total bioavailability of febuxostat with food was associated with a potential decrease in its absorption rate constant, which led to lower febuxostat plasma exposures during the 0–6-h time interval and higher exposures during the 6–24-h interval than those under the fasting conditions (Figure 1). Therefore, the concentrations of febuxostat under nonfasting conditions were higher than those under fasting conditions for a longer period of time. Considering that febuxostat is a potent inhibitor of xanthine oxidase (plasma K_i value of approximately 27 ng mL^{-1}) [4], capable of inhibiting the enzyme at lower plasma concentrations

beyond 6 h postdose, the change or shift in febuxostat plasma profile under nonfasting conditions may have contributed to this slightly higher percent decrease in serum uric acid concentrations despite lower maximum and total plasma exposure to febuxostat under nonfasting compared with fasting conditions. Nevertheless, this small difference in the pharmacodynamic effect of febuxostat was not considered clinically significant even though it was statistically significant ($P < 0.05$). Therefore, administration of febuxostat with food does not require any dose adjustments for febuxostat.

Following administration of febuxostat with antacid, there was also a delay in febuxostat t_{max} and a decrease in febuxostat C_{max} ; however, the change in febuxostat AUC was neither statistically nor clinically significant. Based on the relative bioavailability data from this study, it is very unlikely that cationic complex formation (i.e. a chelation mechanism) was the mechanism for the lower C_{max} . In the case of complex formation, one would have expected at least a significant decrease in the total exposure to febuxostat. It is therefore probable that a decrease in the absorption rate constant of febuxostat upon coadministration with antacid contributed to the delay in t_{max} and the decrease in C_{max} . These changes in febuxostat pharmacokinetic profile are not expected to be associated with any clinically significant changes in the pharmacodynamics of febuxostat.

The incidence of treatment-related adverse events was higher under fasting conditions compared with nonfasting conditions; however, all events were self-limiting and probably the result of the act of fasting itself.

Therefore, based on the pharmacokinetic, pharmacodynamic and safety data, febuxostat can be administered without regard to food or antacid intake.

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