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Effect of hydrochlorothiazide on the pharmacokinetics and pharmacodynamics of febuxostat, a non-purine selective inhibitor of xanthine oxidase

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Hyperuricaemia and gout frequently coexist with cardiovascular disorders such as hypertension and heart failure. The use of diuretics has been re-established as a first-line treatment for patients with hypertension and the effects of diuretics on serum uric acid may diminish the urate-lowering effects of febuxostat, a novel, potent, non-purine selective inhibitor of xanthine oxidase.

WHAT THIS STUDY ADDS

- Co-administration of febuxostat 80 mg and hydrochlorothiazide 50 mg had no effect on the pharmacokinetics and did not have a clinically significant effect on the pharmacodynamics of febuxostat. Dose adjustment for febuxostat is not necessary when it is administered with hydrochlorothiazide.

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Keywords

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AIM

This study examined the effect of co-administration of febuxostat, an investigational urate lowering therapy, and hydrochlorothiazide on the pharmacokinetics and pharmacodynamics of febuxostat.

METHODS

Healthy subjects (36 healthy men and women) received single doses of febuxostat 80 mg alone and febuxostat 80 mg + hydrochlorothiazide 50 mg, separated by 7 days in an open-label, randomized, crossover fashion. Plasma concentrations of febuxostat and urinary and serum concentrations of uric acid were assessed.

RESULTS

Mean febuxostat C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $t_{1/2,z}$, CL/*F* and V_{ss}/F values for regimens co-administration/febuxostat alone were 2.9/2.9 μg ml^{-1}, 9.3/9.1 μg ml^{-1} h, 9.6/9.3 μg ml^{-1} h, 6.5/6.1 h, 8.8/9.3 l h^{-1} and 45/44 l, respectively. Geometric mean ratios (co-administration : febuxostat alone) and their 90% confidence intervals for febuxostat plasma C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ were 1.00 (0.86, 1.17), 1.03 (0.98, 1.09), and 1.04 (0.98, 1.10), respectively; all of the 90% CIs were within the *no effect* range of 0.8 to 1.25. Serum uric acid $C_{mean,24h}$, $C_{mean,48h}$ and CL_R for both regimens co-administration/febuxostat alone were 216/203 μmol l^{-1}, 218/202 μmol l^{-1} and 9.1/10.1 ml min^{-1}, respectively. Although serum uric acid $C_{mean,24h}$ and $C_{mean,48h}$ values were higher and CL_R values lower after co-administration compared with dosing of febuxostat alone, with the differences being statistically significant ($P < 0.003$), none of the differences (6.5%–9.5%) was considered clinically significant.

CONCLUSION

Dose adjustment for febuxostat is not necessary when it is administered with hydrochlorothiazide.

Introduction

Approximately 6.1 million adults in the United States develop gout, with prevalence increasing with age for both men and women [1]. Hyperuricaemia (particularly, persistent asymptomatic hyperuricaemia with serum uric acid (sUA) concentrations $\geq$7 mg dl^{-1}) is the most important determining risk factor for the development of gout [2]. Long-term management of chronic gout often requires urate-lowering therapy that includes xanthine oxidase (XO) inhibitors, uricosuric agents, and recombinant urate oxidases. XO inhibitors decrease the production of UA, whereas uricosuric agents and recombinant urate oxidases increase the elimination rate of UA. Febuxostat is a novel, potent, non-purine, selective inhibitor of XO that has activity against both the oxidized and reduced forms of XO [3].

In a large, multicentre trial in 760 patients with gout and hyperuricaemia (baseline sUA of $\geq$8.0 mg dl^{-1}), febuxostat at a daily dose of 80 mg or 120 mg was more effective than allopurinol at the commonly used [4] fixed daily dose of 300 mg in lowering serum urate [5]. Absorption of febuxostat is rapid (t_{max} of approximately 1 h), and C_{max} and AUC exhibit dose proportionality over the dose range of 10 to 120 mg. Febuxostat is highly bound (>99%) to plasma proteins [6] and undergoes extensive phase 1 and phase 2 metabolism to its acyl-glucuronide metabolite and to hydroxylated metabolites [7]. Less than 5% of the dose is excreted unchanged in urine [7].

Hyperuricaemia and gout frequently coexist with cardiovascular disorders such as hypertension and heart failure [8, 9]. Recently, the use of diuretics has been re-established as a first-line treatment for patients with hypertension following the results of the ALLHAT study [10]. Of concern is that the effects of diuretics on sUA may diminish the urate-lowering effects of febuxostat.

Approximately 30% of systemic UA is excreted into the GI tract, where it is then destroyed by bacterial uricases [11]. The remaining 70% of systemic UA is excreted into the urine [12]. While in the kidney, uric acid undergoes extensive reabsorption in the nephronal proximal tubule, with only 6%-12% of filtered UA finally excreted in urine [12]. Therefore, any medication that affects tubular reabsorption can influence sUA concentration [12]. All of the loop diuretics and thiazide diuretics increase the net reabsorption of UA, thus reducing its urinary excretion and increasing its serum concentration. Such increases in sUA can be seen within 24 h of the first dose following a high dose of diuretic; this response remains stable during prolonged administration [12]. Recent work has established that some drugs (e.g. allopurinol/oxipurinol, loop and thiazide diuretics, some uricosurics and salicylates) can alter urate renal transport via a multi-drug resistance protein (MRP4) in the apical membrane of the proximal tubule. Hydrochlorothiazide and furosemide can decrease urate transport by inhibiting MRP4 [13].

In addition, diuretic use and hypertension have both been shown to be independent risk factors for gout [14]. Therefore, diuretics have the potential to alter the urate-lowering efficacy of febuxostat through their direct pharmacodynamic effects. Diuretics also have the potential to attenuate urate-lowering efficacy through more indirect pharmacokinetic interactions. The purpose of this study was to examine the effect of a thiazide diuretic, hydrochlorothiazide 50 mg, on the pharmacokinetics and pharmacodynamics of febuxostat 80 mg.

Methods

Patient population

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 $\leq$30 kg m^{-2} were recruited for this study. Lactating or pregnant women, nicotine users, patients with histories of gout, hypertension, hypotension, xanthinuria, or hypersensitivities to hydrochlorothiazide or other sulfonamide derivatives; and subjects with any clinically significant abnormalities that could interfere with the evaluation of the study medication were excluded. The following medications/substances were discontinued prior to participation: nicotine (tobacco, nicotine patches, nicotine gum) for 3 months, over-the-counter medications (e.g. Moduretic, herbals, vitamins, dietary supplements) for 7 days, prescription medications or enzyme-altering agents (except for stable oral contraceptive and hormone replacement regimens) for 4 weeks and investigational drugs for 1 month. In addition, consumption of grapefruit-, caffeine-, and xanthine-containing products was prohibited during the study. The study was approved by an Institutional Review Board and written informed consent was obtained from each subject prior to enrollment.

Study design

This study was designed as a randomized, single-centre, single-dose, open-label, two-period crossover study. A total of 36 subjects were recruited and randomly assigned in equal numbers to one of two regimen sequence groups. Upon study completion, each subject had received both regimens in a crossover fashion (febuxostat 80 mg alone and febuxostat 80 mg + hydrochlorothiazide 50 mg) separated by 7 days. The hydrochlorothiazide dose was selected as the highest recommended dose for use in hypertension. Study medication was administered following an overnight fast (at least 10 h), and subjects continued to fast for 4 h post-dose.

In each period, blood samples for the determination of febuxostat plasma concentrations were collected pre-dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dose. Blood samples for the determination of sUA concentrations were collected pre-dose, and at 6, 12, 18, 24,

and 48 h post-dose. Urine samples for the determination of UA were collected and pooled between 0 and 12 h post-dose, and between 12 and 24 h post-dose.

Safety was monitored through adverse event recording, vital signs, physical examination and laboratory evaluations.

Analytical methods

Plasma concentrations of febuxostat were determined using a validated high performance liquid chromatography method with fluorescence detection at excitation and emission wavelengths of 320 and 380 nm, respectively. In brief, after addition of the internal standard (2-naphthoic acid), plasma samples (0.5 ml) were deproteinized by the addition of 0.5 ml of acetonitrile, mixed, and 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) Capcell Pak C_{18} 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} ($r^2 >$ 0.9988). The lower limit of quantification with a 0.5 ml plasma sample was 0.01 µg ml^{-1} for febuxostat. Quality control samples (at 0.03, 1, and 15 µg ml^{-1}) analyzed with the study samples showed absolute deviations from the theoretical concentrations of 7.7% or less and coefficients of variation of less than 10% for febuxostat.

For UA, the serum and urine sample analyses were performed using standard methods at the investigative site's clinical laboratory. In brief, UA concentrations for both serum and urine were determined by an enzymatic method with colorimetric assay, using a quinine di-imine dye (SYNCHRON LX® system), measured photometrically at 520 nm. Calibration for serum and urine UA was performed using the Synchron Multi Calibrator (URIC reagent) with linear analytical ranges of 0.5–12.0 mg dl^{-1} and 5.0–120 mg dl^{-1}, respectively. Serum QC samples Level 1 and 3 (Triad®) analyzed with the study samples showed coefficients of variation of 1.4% or less. Urine QC sample Level 2 (Liquichek™) analyzed with the study samples showed coefficients of variation of 1.3% or less.

Pharmacokinetic assessments

Pharmacokinetic parameters of febuxostat were estimated using noncompartmental pharmacokinetic methods (linear trapezoidal method) with WinNonlin Professional Version 3.1 (Pharsight Co., Mountain View, CA). The following pharmacokinetic parameters were estimated: the peak plasma concentration (C_{max}), the time to reach the peak concentration (t_{max}), the apparent terminal phase elimination rate constant (λ_z), the apparent terminal phase elimination half-life ($t_{1/2}$), the area under the plasma concentration curve (AUC) from time zero to the last measurable concentration [$AUC_{(0-t)}$], the AUC from time zero to infinity [$AUC_{(0-\infty)}$], oral clearance (CL/*F*), and the apparent steady state volume of distribution (V_{ss}/F).

Pharmacodynamic assessments

Mean sUA concentrations over the 24- and 48-h post-dosing intervals ($C_{mean,24h}$ and $C_{mean,48h}$, respectively) were calculated as serum $AUC_{(0-24\ h)}/24$ and $AUC_{(0-48\ h)}/48$, respectively. The sUA parameters $AUC_{(0-24\ h)}$ and $AUC_{(0-48\ h)}$ were calculated using noncompartmental pharmacokinetic methods (linear trapezoidal method) with WinNonlin Professional Version 3.1 (Pharsight Co., Mountain View, CA). The 24 h renal clearance of UA (CL_R) was calculated by dividing the total amount UA excreted in urine over the 24 h (Ae_{24}) post-dosing period by the sUA $AUC_{(0-24\ h)}$.

Statistical methods

All statistical analyses were performed using SAS Version 8.2 on the UNIX operating system. Analyses of variance (ANOVAs) were performed on febuxostat t_{max}, and the natural logarithms of C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$, with factors for sequence, subjects nested within sequence, period and regimen. The factor of subjects nested within sequence was considered random and all other factors were fixed.

The effect of hydrochlorothiazide on the pharmacokinetics of febuxostat was assessed via geometric mean ratios and 90% confidence intervals (CIs) of the ratios for febuxostat + hydrochlorothiazide to febuxostat alone for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. The geometric mean ratios were determined by exponentiating the difference between regimen natural logarithm least square means. Similarly, the CIs were determined by exponentiating the endpoints of 90% CIs for the difference of natural logarithm least square means obtained from the ANOVA model estimates. A conclusion of *no effect* of hydrochlorothiazide on the pharmacokinetics of febuxostat was made if the 90% confidence intervals were completely contained within the interval of 0.80, 1.25 for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$.

Analyses of variance were performed on the pharmacodynamic parameters UA $C_{mean,24h}$, $C_{mean,48h}$, CL_R and Ae_{24} with factors for sequence, subject nested within sequence, period and regimen. The factor of subject nested within sequence was treated as random and all other factors were considered fixed. A significance level of 0.05 was used for all tests.

Results

Subject population

A total of 36 subjects (20 men and 16 women) were randomized and received at least one dose of study drug. The mean age was 33 years (range: 19–51 years), the mean weight was 72.1 kg (47.2–91.3 kg), the mean height was 171 cm (147–185 cm), and the mean BMI was 24.6 kg m^{-2} (19.1–29.5 kg m^{-2}) (Table 1). Four subjects prematurely discontinued the study: three subjects withdrew after receiv-

Table 1

Demographics and baseline characteristics for all subjects enrolled and for the PK/PD population

Demographic characteristics	All subjects $n = 36$		PK/PD population $n = 33$	
Gender [*n* (%)]				
Male	20	(56%)	19	(58%)
Female	16	(44%)	14	(42%)
Race [*n* (%)]				
Caucasian	22	(61%)	21	(64%)
Black	7	(19%)	7	(21%)
Hispanic	6	(17%)	4	(12%)
Asian	1	(3%)	1	(3%)
Age (years) [Mean (Range)]	33	(19–51)	33	(19–51)
Weight (kg) [Mean (Range)]	72.1	(47.2–91.3)	73.0	(47.2–91.3)
Height (cm) [Mean (Range)]	171	(147–185)	171	(152–185)
BMI (kg m^{-2}) [Mean (Range)]	24.6	(19.1–29.5)	24.7	(19.1–29.5)

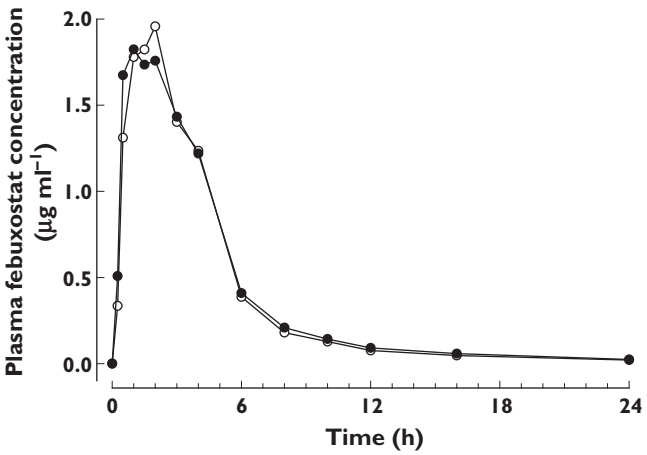

Figure 1

Mean plasma concentration–time profiles of febuxostat. Febuxostat alone (—○—); Febuxostat + hydrochlorthiazide (—●—)

ing the first dose of study medication, and one subject withdrew after completing the blood collections for both treatment periods. Two of the four subjects withdrew for personal reasons and the remaining two subjects withdrew due to adverse events, which were not considered by the investigators to be related to the study medication. Therefore, 33 subjects (19 men and 14 women) were included in pharmacokinetic or pharmacodynamic analyses. Among these 33 subjects, three subjects took acetaminophen, and one subject took oral contraceptives; none of these medications was expected to have an effect on the study outcome.

Pharmacokinetic results

As shown in Figure 1, administration of febuxostat 80 mg alone and co-administration of febuxostat 80 mg and hydrochlorothiazide 50 mg resulted in similar febuxostat plasma concentration profiles.

Pharmacokinetic results for febuxostat are provided in Table 2. Mean febuxostat C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $t_{1/2}$, CL/*F* and V_{ss}/F following co-administration appeared to be similar to values after the administration of febuxostat alone. Following febuxostat + hydrochlorothiazide co-administration and febuxostat alone; the respective peak plasma concentration mean values (C_{max}) were 2.9 and 2.9 μg ml^{-1} and the estimated total exposure mean values [$AUC_{(0-\infty)}$] were 9.6 and 9.3 μg ml^{-1} h.

Statistical analyses of the relative bioavailability of febuxostat + hydrochlorothiazide compared with febuxostat alone showed that the 90% CIs for the ratios of central values for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were all contained within the interval of 0.80 to 1.25 (Table 3). This indicated that the two treatments were bioequivalent with respect to maximum and total systemic exposure to febuxostat.

Pharmacodynamic results

Following co-administration of febuxostat and hydrochlorothiazide, mean 24 and 48 h sUA concentrations ($C_{mean,24h}$ and $C_{mean,48h}$, respectively) were higher than those with administration of febuxostat alone. The $C_{mean,24h}$ was 216 μmol l^{-1} with febuxostat + hydrochlorothiazide and 203 μmol l^{-1} with febuxostat alone, a 6.5% difference. The $C_{mean,48h}$ was 218 μmol l^{-1} with febuxostat + hydrochlorothiazide and 202 μmol l^{-1} with febuxostat alone, a 7.9% difference (Table 4). Although these differences for sUA concentration between the two regimens were statistically significant ($P < 0.001$), the differences in the means were considered not clinically relevant. The 24-h renal clearance of UA (CL_R) and the total amount of UA excreted in urine (Ae_{24}) were 9.5% and 4.4% lower, respectively, for co-administration relative to febuxostat alone. This difference for CL_R was statistically significant ($P = 0.003$) but not clinically relevant, and the difference for Ae_{24} was neither clinically nor statistically significant.

Safety results

All available data for the 36 enrolled subjects were used for safety assessments. The overall incidence of adverse events was no different between the two regimens (Table 5). The incidence of neurological signs and symptoms (e.g. dizziness) was numerically greater for subjects treated with febuxostat + hydrochlorothiazide; however, the incidence of headaches was similar between the two regimens. Also of note, known side effects for hydrochlorothiazide include dizziness.

All adverse events were mild to moderate in severity with the exception of a vaginal wall tear, which occurred during the washout period between regimens, and was considered not related to study drug by the investigator. There were no deaths reported. Two subjects prematurely discontinued due to adverse events, one of the two subjects discontinued due to pharyngitis, and the other subject discontinued due to the previously discussed vaginal wall tear.

Table 2

Arithmetic mean (±SD) febuxostat pharmacokinetic parameters following single dosing with febuxostat 80 mg alone and in combination with a single 50 mg dose of hydrochlorothiazide

Parameter	Febuxostat 80 mg alone *n* = 33		Febuxostat 80 mg + hydrochlorothiazide 50 mg *n* = 33	
t_{max} (h)	2.0	(1.28)	1.9	(1.43)
C_{max} (μg ml^{-1})	2.9	(1.44)	2.9	(1.38)
$AUC_{(0-t)}$ (μg ml^{-1} h)	9.1	(2.57)	9.3	(2.56)
$AUC_{(0-\infty)}$ (μg ml^{-1} h)	9.3	(2.61)	9.6	(2.57)
CL/F (l h^{-1})	9.3	(2.53)	8.8	(2.01)
V_{ss}/F (l)	44	(16.0)	45	(17.0)
$t_{1/2}$ (h)	6.1	(1.57)	6.5	(2.18)

Table 3

Relative bioavailability of febuxostat following single dosing with febuxostat 80 mg in combination with a single 50 mg dose of hydrochlorothiazide

Pharmacokinetic parameter	Geometric mean ratio (febuxostat 80 mg + hydrochlorothiazide 50 mg : febuxostat 80 mg alone) *n* = 33	90% confidence interval
C_{max}	1.00	(0.86, 1.17)
$AUC_{(0-t)}$	1.03	(0.98, 1.09)
$AUC_{(0-\infty)}$	1.04	(0.98, 1.10)

Table 4

Arithmetic mean (±SD) pharmacodynamic parameters for uric acid following single dosing with febuxostat 80 mg alone and in combination with a single 50 mg dose of hydrochlorothiazide

Parameter	*n*	Febuxostat 80 mg alone	Febuxostat 80 mg + hydrochlorothiazide 50 mg	*P* value*
Serum uric acid				
$C_{mean,24h}$ (μmol l^{-1})	30	203 (71.4)	216 (77.3)	<0.001
$C_{mean,48h}$ (μmol l^{-1})	30	202 (67.8)	218 (76.1)	<0.001
Urine uric acid				
Ae_{24} (mg)	33	454 (114.3)	434 (82.8)	0.129
CL_R (ml min^{-1})†	30	10.1 (2.84)	9.1 (2.79)	0.003

**P* values from ANOVA with terms for sequence, subject (sequence), period and regimen. A significance level of 0.05 was used for all tests. †The 24-h renal clearance of uric acid.

Neither of these adverse events leading to withdrawal was considered related to study drug. The subject (20 year old male) who experienced the pharyngitis adverse event also experienced a single transient elevation in liver function tests (ALT and AST), which was considered by the investigator possibly related to the study drug; however, an alternate aetiology of intercurrent illness (viral syndrome) and concomitant medication (Tylenol, Nyquil, and Augmentin) use were cited by the investigator.

Co-administration of febuxostat and hydrochlorothiazide showed notable changes in urinary electrolytes, none of which was considered clinically significant. No clinically meaningful changes from baseline were observed for serum concentrations of sodium, chloride, potassium, or bicarbonate. Group mean reductions in systolic blood pressure were observed. These reductions were unlikely to be the result of co-administration with hydrochlorothiazide, as this diuretic exerts its antihypertensive effect only with chronic use. In addition, no clinically meaningful mean changes from baseline were observed for any orthostatic or other vital signs. No trends were noted for other laboratory tests or vital signs, physical examinations or ECGs.

Discussion

The present study demonstrated that the overall rate and extent of absorption of a single dose of febuxostat 80 mg was not affected by co-administration with a single dose of

Table 5
All adverse events

Adverse event	Febuxostat 80 mg alone *n* = 34		Febuxostat 80 mg + hydrochlorothiazide 50 mg *n* = 35		Overall *n* = 36	
Any event	**14**	**(41%)**	**15**	**(43%)**	**23**	**(64%)**
Vision blurred	0	(0%)	1	(3%)	1	(3%)
Dyspepsia, eructation	1	(3%)	1	(3%)	2	(6%)
Abdominal pain	2	(6%)	0	(0%)	2	(6%)
Nausea and vomiting	2	(6%)	3	(9%)	5	(14%)
Upper respiratory tract infections	2	(6%)	2	(6%)	4	(11%)
Sunburn	1	(3%)	0	(0%)	1	(3%)
Abnormal liver function test	1	(3%)	0	(0%)	1	(3%)
Myalgia	0	(0%)	1	(3%)	1	(3%)
Muscle cramp	1	(3%)	0	(0%)	1	(3%)
Somnolence	2	(6%)	0	(0%)	2	(6%)
Headache	4	(12%)	4	(11%)	6	(17%)
Dizziness	2	(6%)	4	(11%)	6	(17%)
Menstruation with increase bleeding	0	(0%)	1	(3%)	1	(3%)
Vaginal laceration	0	(0%)	1	(3%)	1	(3%)
Dermatitis, contact	0	(0%)	1	(3%)	1	(3%)
Orthostatic hypotension	1	(3%)	1	(3%)	2	(6%)

hydrochlorothiazide 50 mg in healthy adult subjects. This lack of effect of hydrochlorothiazide on the pharmacokinetics of febuxostat is consistent with the metabolic characteristics of the two medications. Hydrochlorothiazide does not undergo biotransformation, and is primarily excreted unchanged in urine. In addition, hydrochlorothiazide is not known to affect the uridine diphosphoglucuronyl transferase enzyme or cytochrome P450 enzymes involved in the elimination of febuxostat [6]. Therefore, no effect on the biotransformation of febuxostat was expected.

Hydrochlorothiazide is known to decrease the renal clearance and subsequently increase serum concentrations of UA [12, 13]. In this study, co-administration of febuxostat and hydrochlorothiazide modestly decreased the renal clearance of UA (9.5% reduction), potentially due to a hydrochlorothiazide-induced increase in the net reabsorption of UA in the renal proximal tubules. This decrease in renal clearance of UA caused a slight increase in the mean sUA concentrations over 24 and 48 h post-dosing intervals (6.5% and 7.9%, respectively). These slight increases in sUA concentrations, despite being statistically significant, were not considered clinically significant. Therefore, diuretics are not expected to diminish significantly the overall urate-lowering effect of febuxostat.

A limitation of this study is its design as a single dose drug–drug interaction study in healthy subjects with normal renal function. However, since hydrochlorothiazide does not accumulate significantly following multiple oral dosing, the extent of its effect after multiple dosing on both the pharmacokinetics and pharmacodynamics of febuxostat is expected to resemble that after single dosing with hydrochlorothiazide. Therefore, the effects of a single dose of hydrochlorothiazide may be extrapolated to multiple dose conditions. Similarly, the percent change in the renal clearance of UA caused by hydrochlorothiazide in hyperuricaemic subjects is not expected to be substantially different from that in healthy subjects, suggesting that the findings from this study may also be applicable to hyperuricaemic patients.

Due to the long elimination half-life of systemic UA, the use of percent change in renal clearance of UA (CL_R) instead of percent change in sUA may be a more accurate measure of the overall effect of hydrochlorothiazide from this single dose study for extrapolation to multiple dose conditions. Based on the % decrease in CL_R of 9.5% from our study under single dose conditions in healthy subjects, one would expect an approximately 10% (i.e. $100 \times [1-(100/90.5)]$) increase in sUA in multiple dosing conditions. In a multiple dose study in 3693 stepped care participants in the 'Hypertension Detection and Follow-up Program' [15], among men and women with higher serum uric acid concentrations (upper quartile sub-population with sUA = 458 $\pm$ 40 μmol l^{-1} and 403 $\pm$ 45 μmol l^{-1}, respectively), following multiple dosing for 1 year with chlorthalidone or other thiazide diuretics, the mean sUA also increased by approximately 11–12% (51 $\pm$ 77 μmol l^{-1} and 47 $\pm$ 88 μmol l^{-1}, respectively).

The lack of a clinically significant pharmacodynamic interaction between febuxostat and hydrochlorothiazide suggests that febuxostat may be an effective treatment for patients who develop gout while on diuretics. In fact, diuretic use has been established as an independent risk factor for the development of gout [14]. One epidemiological study of elderly subjects (≥65 years) found that the relative risk of initiation of urate lowering therapy was

higher in subjects receiving thiazide (alone or in combination). This increase was seen for all thiazide dose groups studied (<25 mg day^{-1}, 25–49 mg day^{-1}, ≥50 mg day^{-1}) with the magnitude of the risk increasing along with dose [16]. In addition, febuxostat has a superior clinical pharmacokinetic profile for patients with other characteristics typically associated with gout and/or hyperuricaemia, requiring no dose adjustments based on age and gender and in subjects with mild-severe renal dysfunction or mild-moderate hepatic dysfunction [17–25].

Finally, the lack of a pharmacokinetic effect or a clinically significant pharmacodynamic effect of hydrochlorothiazide on febuxostat suggests that febuxostat may be a viable option for hyperuricemic gout patients who require diuretics. In addition, febuxostat 80 mg co-administered with hydrochlorothiazide 50 mg under single dose conditions was found to be safe and well-tolerated by healthy subjects. The results from this study indicate that no adjustment in the dose of febuxostat is necessary when it is co-administered with hydrochlorothiazide.

Competing interests

J-TW is an employee of Takeda Global Research & Development Center and holds stocks of Takeda. LV was an employee of TAP Pharmaceutical Products Inc at the time of the study. CL was employed by Takeda from 2002–2008. There are no other competing interests to declare.

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