Pharmacokinetic Interactions of Concomitant Administration of Febuxostat and NSAIDs

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To evaluate the effect of febuxostat on the pharmacokinetics of indomethacin and naproxen and vice versa, 2 multiple-dose, 3-period crossover studies were performed in healthy subjects. In study 1, subjects received febuxostat 80 mg once daily, indomethacin 50 mg twice daily, or both. In study 2, subjects received febuxostat 80 mg, naproxen 500 mg twice daily, or both. Twenty-four-hour blood samples were collected on day 5 in study 1 and day 7 in study 2. In study 1, 90% confidence intervals of geometric mean ratios for maximum plasma concentration (C_{max}) and area under the curve (AUC) were within the 0.80 to 1.25 no-effect range for febuxostat and indomethacin. In study 2, 90% confidence intervals for febuxostat C_{max} and AUC extended above that range, with increases of 28% and 40% in C_{max} and AUC_{24}, respectively. However, 90% confidence intervals for naproxen C_{max} and AUC were within the 0.80 to 1.25 range. Febuxostat had no effect on the plasma pharmacokinetics of indomethacin and naproxen. Similarly, indomethacin had no effect on the plasma pharmacokinetics of febuxostat. Although naproxen caused an increase in plasma exposure to febuxostat, this increase is not expected to be clinically significant. Therefore, based on the plasma pharmacokinetic data in healthy subjects, febuxostat may be administered with indomethacin or naproxen with no dose adjustments for febuxostat, indomethacin, or naproxen.

Keywords: *Febuxostat; drug-drug interaction; NSAID; indomethacin; naproxen; pharmacokinetics*

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Gout is the most common form of inflammatory arthritis in men older than 40 years and is characterized by recurrent attacks of acute inflammation in 1 or more joints because of deposition of monosodium urate crystals in the joint cavity.[1,2] Elevated serum concentrations of uric acid (hyperuricemia) are seen in more than 90% of patients with gout, and hyperuricemia is considered the precursor of gout.[1] The condition generally occurs after years of sustained hyperuricemia, and a clear relationship between serum uric acid and the risk of developing gout has been demonstrated.[1,3] According to the most recent National Health and Nutrition Examination Survey (NHANES III), gout is estimated to affect approximately 5.1 million people in the United States, and its prevalence is increasing rapidly because of an increase in 2 important risk factors of hyperuricemia: aging and obesity.[4,5]

The 2 important cornerstones of gout management are (1) management or control of hyperuricemia and (2) treatment or prevention of acute attacks of gout.[6] Management or control of hyperuricemia in gout involves inhibitors of xanthine oxidase, uricosuric agents, or uricase. These agents lower uric acid concentrations in serum by inhibiting production of uric acid (ie, inhibitors of xanthine oxidase) or by increasing clearance of uric acid from the body (ie, uricosurics or uricase). In the United States, inhibitors of xanthine oxidase are the most widely prescribed category of drugs for hyperuricemia management in patients with gout. For treatment or prevention of acute gout attacks (including those caused by the initiation of antihyperuricemic therapy), 3 categories of drugs commonly have been used: antimitotics (eg, colchicine), nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic steroids (eg, prednisone).[6] Because of the adverse events associated with colchicine therapy, NSAIDs (eg, indomethacin and naproxen), where they are not contraindicated, are the drugs of choice in treating or preventing acute

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attacks of gout. Systemic steroids are recommended only when patients do not respond to colchicine or NSAIDs or when colchicine or NSAIDs are contraindicated.

Febuxostat (2-[3-cyano-4-(2-methylpropoxy)-phenyl] -4-methylthiazole-5-carboxylic acid) is a potent novel nonpurine selective inhibitor of xanthine oxidase (NP-SIXO) and was shown to have great efficacy in lowering serum uric acid concentrations in animals.[7-11] Results of phase I, II, and III studies in healthy subjects and subjects with hyperuricemia associated with gout have confirmed the ability of febuxostat to reduce serum uric acid concentrations in humans in a dose-dependent manner.[12-15] In healthy human subjects, orally administered febuxostat is rapidly absorbed with the time to reach the observed maximum plasma concentration (t_{max}) of approximately 1 hour. The drug is highly bound to albumin in blood (~99%) and appears to have a low to medium apparent volume of distribution at steady state of approximately 0.7 L/kg. Febuxostat is metabolized mainly to its acyl-glucuronide metabolite (via uridine diphosphoglucuronosyltransferases [UGT] 1A1, 1A3, 1A7, 1A8, 1A9, 1A10, and 2B7; unpublished data) and, to a lesser extent, its active oxidative metabolites (via cytochrome P-450 1A1, 1A2, 2C8, and 2C9; unpublished data).[16-18] Approximately 33% and 11% of the orally administered dose is recovered in urine as the acyl-glucuronide of febuxostat and as the oxidative metabolites and their glucuronide conjugates, respectively.[18] Only a small fraction (< 2%) of the orally administered dose was excreted renally as unchanged febuxostat, indicating that renal elimination plays a minor role in the elimination of febuxostat from the body.[18]

During initiation of antihyperuricemic therapy, a rapid decrease in serum uric acid concentrations may precipitate an acute attack of gout. Therefore, febuxostat may need to be administered with NSAIDs such as indomethacin or naproxen. Similar to febuxostat, indomethacin and naproxen also undergo glucuronidation and are highly protein bound.[19-24] According to the literature, probenecid, a uricosuric agent, inhibits the glucuronidation of both indomethacin and naproxen.[25,26] In addition, results of in vitro and in vivo studies have shown that naproxen and/or indomethacin themselves may cause inhibition of the glucuronidation of other drugs.[27-29] Therefore, we decided to investigate the effect of febuxostat on the pharmacokinetics of indomethacin and naproxen and vice versa.

METHODS

Subjects

Two studies were conducted to investigate the effect of febuxostat on the pharmacokinetics of indomethacin and naproxen and vice versa. Enrollment for both studies started after investigational review board (Quorum Review Inc; Seattle, Wash) approval. Eligible healthy male and female subjects between 18 and 55 years of age, inclusive, were allowed to enroll in each study after signed informed consent was obtained. Subjects were required to have a body mass index less than 30 kg/m^2, a normal serum creatinine level, no history of drug sensitivity or allergic reaction to any drug, no hypersensitivity to aspirin and NSAIDs, and no comorbid, uncontrolled metabolic or psychiatric conditions. Exclusion criteria included a diagnosis of gout, a history of xanthinuria or recurrent gastrointestinal lesions, evidence of occult blood in stool, clinically significant abnormal laboratory test or electrocardiographic results, a concurrent disease state that required long-term daily medication, a history of cancer with less than 5 years of remission, and positive test results for hepatitis B, hepatitis C, or human immunodeficiency virus antibody. In addition, subjects were excluded from the study if they had taken any over-the-counter or prescription medication within 1 and 4 weeks, respectively, of the initial dose of study drug; used tobacco or other nicotine-containing products within 3 months before the initial dose of study drug; or had a history of alcohol or drug abuse. Female subjects were excluded from the study if they were pregnant or breastfeeding. Both studies were conducted at Seaview Research, Inc (Miami, Fla).

Experimental Design

Both studies were phase I, single-center, open-label, multiple-dose, randomized, 3-period crossover studies. In each study, an attempt was made to enroll equal numbers of subjects of each sex. Subjects were assigned randomly to 1 of 3 regimen sequences, as shown in Figure 1.

During confinement to the testing facility, subjects abstained from all food and beverage except for scheduled meals provided by the testing facility. Caffeine, alcohol, high-purine foods, and grapefruit and grapefruit juice were not to be consumed. Subjects were instructed to abstain from eating high-purine foods a week before confinement. During confinement, all

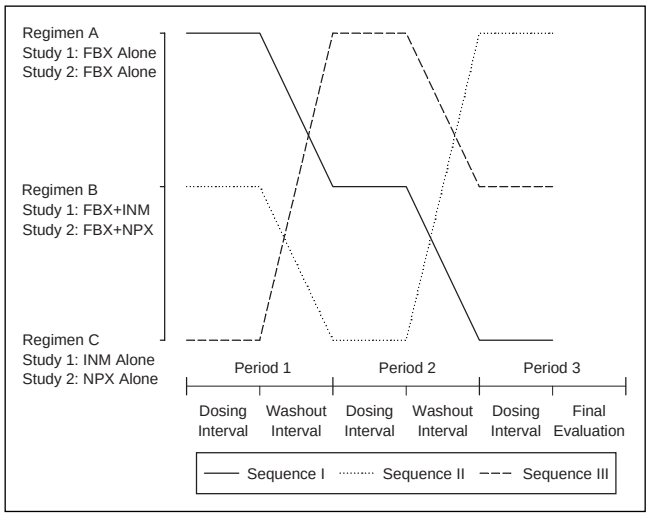

Figure 1. Diagram of regimen orders for sequences I, II, and III in studies 1 and 2. FBX, febuxostat 80 mg once daily; INM, indomethacin 50 mg twice daily; NPX, naproxen 500 mg twice daily. Dosing interval: 5 days in study 1 and 7 days in study 2. Washout interval: 2 days in study 1 and 7 days in study 2. Final evaluation: the day after the dosing interval in period 3 in studies 1 and 2 for subjects who completed the study.

subjects were served meals relative to the time of dosing with approximate times of breakfast at 0730 hours, lunch at 1300 hours, dinner at 1800 hours, and an evening snack at 1930 hours. Breakfast and snack were to be finished within 30 minutes. No food was allowed from 2000 hours until 0730 hours the next morning. Water was allowed as desired except 1 hour before and 1 hour after drug administration.

In study 1, subjects were confined to the testing facility and supervised for approximately 21 consecutive days. Confinement began at approximately 1100 hours on day –1 of period 1 to obtain all the necessary laboratory test results and ended when all study procedures were completed on day 6 of period 3. On dosing days, days 1 to 5 of each period (ie, dosing interval; Figure 1), the doses were administered according to the regimen assigned for the period. For regimen A, four 20-mg tablets of febuxostat were administered at 0800 hours with 240 mL of water. For regimen B, four 20-mg tablets of febuxostat and a single 50-mg capsule of indomethacin were administered at 0800 hours with 240 mL of water. A single 50-mg capsule of indomethacin was administered at 2000 hours with 240 mL of water. For regimen C, a single 50-mg capsule of indomethacin was administered at 0800 hours and at 2000 hours with 240 mL of water. There were 2 days between the last dose in a period and the first dose of the subsequent period when no doses were administered (ie, washout interval; Figure 1). However, subjects remained confined on these days. On days 1 through 5 of each period, venous blood samples were collected within 5 minutes before the morning administration of study drugs for the determination of febuxostat and/or indomethacin concentrations in plasma. On day 5 of regimens A and B, venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the morning administration of febuxostat for the determination of febuxostat in plasma. Venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.25, 12.5, 13, 13.5, 14, 15, 16, 18, and 24 hours after the day 5 morning administration of indomethacin in regimens B and C for the determination of indomethacin concentrations in plasma. On day 6 of period 3, final study procedures were conducted after the 24-hour sample was obtained. Blood samples also were obtained for clinical laboratory testing (eg, hematology/serum chemistry) at screening and days –1 and 6 of each period for subjects who completed the study.

In study 2, subjects were confined to the testing facility and supervised for approximately 9 days in each period. Confinement began for each period at approximately 1100 hours on day –1 and ended at approximately 1000 hours on day 8. On dosing days, days 1 to 7 of each period (ie, dosing interval; Figure 1), the doses were administered according to the regimen assigned for the period. For regimen A, four 20-mg tablets of febuxostat were administered at 0800 hours with 240 mL of water. For regimen B, four 20-mg tablets of febuxostat and a single 500-mg capsule of naproxen were administered at 0800 hours with 240 mL of water. In addition, a single 500-mg capsule of naproxen was administered at 2000 hours with 240 mL of water. For regimen C, a single 500-mg capsule of naproxen was administered at 0800 hours and at 2000 hours with 240 mL of water. There were 7 days between the last dose in a period and the first dose in the subsequent period when no doses were administered (ie, washout interval; Figure 1). Subjects were not confined on these days. On days 1, 3, 6, and 7 of each period, venous blood samples were collected within 5 minutes before the morning administration of study drugs for the determination of febuxostat and/or naproxen concentrations in plasma. On day 7 of the periods in which febuxostat was administered, venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and

24 hours after the morning administration of study drugs for the determination of febuxostat in plasma. On day 7 of the periods in which naproxen was administered, venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.25, 12.5, 13, 13.5, 14, 15, 16, 18, and 24 hours after the morning administration of study drugs for the determination of naproxen concentrations in plasma. On day 8 of period 3, final study procedures were conducted after the 24-hour sample was obtained. Blood samples also were obtained for clinical laboratory testing (eg, hematology/serum chemistry) at screening and days –1, 4, and 8 of each period for subjects who completed the study.

In both studies, the blood specimen was placed on ice immediately after collection. The sealed specimen was kept on ice until centrifuged at approximately 5°C within 2 hours of collection. The plasma was then separated and transferred to a polypropylene vial. All samples were frozen at approximately –20°C until shipped on dry ice to the bioanalytical lab, where they were stored at approximately –20°C until analyzed.

Analytical Methods

Plasma concentrations of febuxostat were measured using a validated method of high-performance liquid chromatography (HPLC) with fluorescence detection 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, 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, Calif) 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 ($R^2 > 0.996$). Quality control (QC) samples (at 0.03, 1, and 15 µg/mL) were analyzed with the plasma samples from each study. The lower limit of quantitation with a 0.5-mL plasma sample was 0.01 µg/mL for febuxostat. In study 1, QC samples showed absolute deviations from the theoretical concentrations of 22.0% or less and coefficients of variation of 106.6% or less for febuxostat. There was 1 anomalous value for the 0.03-µg/mL QC on 1 of the calibration curves, which caused the coefficient of variation to be 106.6% for that QC level. However, the calibration curve met the standard and QC acceptance criteria and was included in the data set. In study 2, QC samples showed absolute deviations from the theoretical concentrations of 7.0% or less and coefficients of variation of 10.3% or less for febuxostat.

Plasma concentrations of indomethacin were determined using a validated HPLC method with UV detection at a wavelength of 260 nm. Briefly, after addition of the internal standard (diclofenac), plasma samples were mixed with the extraction solvent (pentane/methylene chloride; 2:1, v:v), centrifuged, and flash frozen, and the resulting organic phase was evaporated to dryness and reconstituted with the mobile phase (sodium acetate buffer/methanol/acetonitrile;67:13:20, v:v:v). Indomethacin and the internal standard were resolved on a CSC (Montreal, Canada) analytical column (CSC-S ODS-1, 5 µm, 15 cm × 0.46 mm). The calibration curve range for indomethacin was linear from 24.9 to 19920.0 ng/mL ($R^2 > 0.997$). The lower limit of quantitation with a 0.5-mL plasma sample was 24.9 ng/mL for indomethacin. The QC samples (at 75, 7960, and 15 920 ng/mL) analyzed with the plasma samples from this study showed absolute deviations from the theoretical concentrations of 9.4% or less and coefficients of variation of 5.4% or less for indomethacin.

Plasma concentrations of naproxen were determined using a validated HPLC method with fluorescence detection with excitation and emission wavelengths of 230 and 370 nm, respectively. In brief, after addition of the internal standard (2-napthylacetic acid), plasma samples were mixed with the extraction solvent (methylene chloride), centrifuged, and flash frozen, and the resulting organic phase was evaporated and reconstituted with the mobile phase (acetonitrile and phosphoric acid). A Waters (Milford, Mass) symmetry C18 column was used to separate the peaks. The calibration curve for naproxen was linear from 0.1 to 100 µg/mL ($R^2 > 0.993$). The lower limit of quantitation with a 0.1-mL plasma sample was 0.1 µg/mL for naproxen. The QC samples (at 0.25, 3, and 70 µg/mL) analyzed with the plasma samples from this study showed absolute deviations from the theoretical concentrations of 3.3% or less and coefficients of variation of 12.1% or less for naproxen.

Data Analysis

Pharmacokinetic parameters for febuxostat, naproxen, or indomethacin in plasma were determined with standard noncompartmental methods using WinNonlin Professional V.3.1 software (Pharsight Corp, Mountain View, Calif). The pharmacokinetic parameters estimated

Table I Demographic Data for Subjects Completing Studies 1 and 2

Study	Sex,[a] M/F	Age,[b] Y	Race,[c] H/W	Height,[b] cm	Weight,[b] km	Body Mass Index,[b] kg/m²
1 (n = 26)	13/13	36.3 ± 8.7 (21-52)	22/4	166 ± 10 (150-185)	72.7 ± 8.8 (58-95)	26.4 ± 2.2 (22.5-29.7)
2 (n = 24)	11/13	38.0 ± 9.4 (21-53)	21/3	166 ± 9 (150-183)	71.1 ± 10.4 (49-90)	25.7 ± 2.9 (19.5-28.9)

a. Number of male/female subjects completing studies 1 and 2.
b. Data presented are mean ± SD (range).
c. Number of Hispanic/white subjects.

included the observed maximum plasma concentration (C_{max}); t_{max}; the apparent terminal elimination half-life ($t_{1/2}$); the area under the plasma concentration-time curve (AUC) from time 0 to 12 hours after dose (AUC_{12}) for indomethacin or naproxen and from time 0 to 24 hours after dose (AUC_{24}) for febuxostat, indomethacin, or naproxen; the oral clearance (CL/F); and the steady-state apparent volume of distribution (V_{ss}/F).

To assess the effect of indomethacin (study 1) and naproxen (study 2) on the pharmacokinetics of febuxostat, data from the 2 regimens with febuxostat (ie, regimens A and B) were used. Analyses of variance were performed on t_{max} and the natural logarithms of C_{max} and AUC_{24} of febuxostat, with factors for sequence, subjects nested within sequence, period, and regimen. The factor of subjects within sequence was considered random, and all other factors were fixed. The effect of indomethacin and naproxen on the pharmacokinetics of febuxostat was assessed via point estimates and 90% confidence intervals for the ratio of central values of regimen B to regimen A for febuxostat C_{max} and AUC_{24}. In addition, to assess the effect of febuxostat on the pharmacokinetics of indomethacin and naproxen, data from the 2 regimens with indomethacin and naproxen were used (ie, regimens B and C). Analyses of variance were performed on $_{AM}t_{max}$ and the natural logarithms of $_{AM}C_{max}$, $_{AM}AUC_{12}$, and AUC_{24} of indomethacin and naproxen, with factors for sequence, subjects nested within sequence, period, and regimen. The factor of subjects within sequence was considered random, and all other factors were fixed. The effect of febuxostat on the pharmacokinetics of indomethacin and naproxen was assessed via point estimates and 90% confidence intervals for the ratio of central values of regimen B to regimen C for $_{AM}C_{max}$, $_{AM}AUC_{12}$, and AUC_{24} of indomethacin and naproxen. A conclusion of *no effect* was made if the 90% confidence intervals for the ratios of central values were within the 0.80 to 1.25 range.

RESULTS

Study Subjects

In study 1, 26 (13 male, 13 female) of the 27 subjects enrolled completed the study; 1 subject prematurely discontinued from the study because of an adverse event (contact dermatitis). In study 2, 24 (11 male, 13 female) of the 27 subjects enrolled completed the study; 3 subjects prematurely discontinued from the study because of adverse events (angioedema, abnormal liver function test results, or increased cough). In study 2, 25 of the 27 subjects enrolled completed regimens A and B, whereas 24 of the 27 subjects enrolled completed regimens B and C. A summary of the demographic data for subjects who completed studies 1 and 2 is presented in Table I.

Pharmacokinetics

Effect of Indomethacin on Pharmacokinetics of Febuxostat

In study 1, pharmacokinetic parameters for febuxostat when administered alone (reference) or with indomethacin (test) are presented in Table II. The plasma concentration profile of febuxostat when administered alone and when administered with indomethacin is depicted in Figure 2. The plasma profiles for both regimens overlapped each other, and the mean pharmacokinetic parameters of the 2 regimens were similar. After administration of febuxostat with indomethacin, the median febuxostat t_{max} value remained unchanged, and the mean estimates for other pharmacokinetic parameters, including febuxostat C_{max}, AUC_{24}, $t_{1/2}$, CL/F, and V_{ss}/F, were within 11% of the respective parameters in the febuxostat-alone regimen (Table II). The effects of period and sequence were not statistically significant ($P > .05$) for any of the febuxostat pharmacokinetic parameters

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