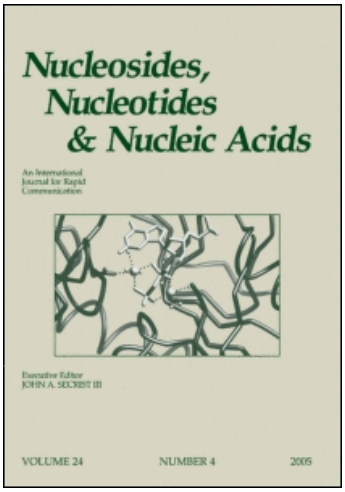

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Febuxostat (TMX-67), a Novel, Non-Purine, Selective Inhibitor of Xanthine Oxidase, Is Safe and Decreases Serum Urate in Healthy Volunteers

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ABSTRACT

In order to evaluate the safety, pharmacological properties, and urate-lowering efficacy of febuxostat, a non-purine, selective inhibitor of xanthine oxidase, a Phase 1, 2-week, multiple-dose, placebo-controlled, dose-escalation study was conducted in 154 healthy adults of both sexes. Daily febuxostat doses in the range 10 mg to 120 mg resulted in proportional mean serum urate reductions ranging from 25% to 70% and in proportional increases in maximum febuxostat plasma concentrations and area under plasma concentration versus time curves. Accompanying the hypouricemic effect were increases in serum xanthine concentrations, decreases in urinary uric acid excretion, and increases in urinary xanthine and hypoxanthine excretion, confirming inhibition of xanthine oxidase activity by febuxostat. Hepatic conjugation and oxidative metabolism were the major pathways of elimination of febuxostat from the body, and renal elimination did not appear to play a significant role. Although not uncommon, adverse events were mild and self-limited, and no deaths or serious

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adverse events were observed. Febuxostat is a safe and potent hypouricemic agent in healthy humans.

Key Words: Hyperuricemia; Gout; Febuxostat; Xanthine oxidase; Xanthine oxidase inhibition.

INTRODUCTION

Febuxostat is a 2-arylthiazolecarboxylic acid derivative chemically engineered as a novel, non-purine, selective inhibitor of xanthine oxidase (NP-SIXO),[1,2] which is being developed as an orally administered agent for the treatment of hyperuricemia associated with gout. Febuxostat has been shown to effectively reduce serum urate levels in preclinical and clinical studies.[3–5] A Phase 1 clinical study was designed to determine the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of febuxostat during administration to healthy volunteers.

MATERIALS AND METHODS

This Phase 1, 2-week (dosing for 13 days), multiple-dose, placebo-controlled, dose-escalation study was conducted in 154 healthy adults of both sexes, ages 19 to 54 years. The study included 12 dose groups, each with 12 subjects randomized at a 5:1 febuxostat to placebo ratio. In the course of dose escalation, a report of possible traces of xanthine crystals in the urine (later not substantiated) led to a repetition of the 50 mg febuxostat dose group study. Febuxostat or placebo was administered orally once daily in a test drug dose range from 10 to 240 mg, except for 1 group that received either 30 mg febuxostat or placebo twice daily.

RESULTS

The study shows that the dose-adjusted pharmacokinetics of febuxostat were neither time- nor dose-dependent in the 10 mg to 120 mg dosage range. The maximum febuxostat plasma concentration (C_{max}) and the area under the plasma concentration versus time curve (AUC) for febuxostat increased proportionally to the dose in the 10 mg to 240 mg and 10 mg to 120 mg daily dose ranges, respectively (Table 1; Fig. 1). Time to maximum concentration (t_{max}) was relatively constant at about 1 hour (Table 1), indicating prompt gastrointestinal absorption. At steady state, approximately 25% to 45% of orally administered febuxostat was excreted in urine as unchanged febuxostat or its conjugate, but only 1–6% of the dose was excreted as unchanged drug. In addition, 2 to 8% of the drug was excreted in urine as unchanged or conjugated oxidative metabolites of febuxostat. Conjugation and oxidative metabolism were, therefore the major pathways of elimination of febuxostat from the body, and renal elimination did not play a significant role in elimination of febuxostat. Enterohepatic recirculation of febuxostat metabolites is supported by greater than dose

Table 1. Mean PK parameters after single and multiple oral dosing with different doses of febuxostat.

		AUC (μg·h/ml)[a]		C_{max} (μg/ml)		t_{max} (h)		$t_{1/2}$ (h)[b]	
Dose (mg)	N.	Single	Multiple	Single	Multiple	Single	Multiple	Single	Multiple
40 QD	10	4.00	4.30	1.53	1.82	1.4	1.2	3.8	6.3
50 QD	20	4.41	4.38	1.97	1.79	0.8	1.1	4.5	6.7
70 QD	10	6.93	6.95	3.08	2.69	1.0	1.1	4.7	8.5
90 QD	10	9.09	9.65	3.48	4.06	1.0	1.0	6.8	10.0
120 QD	10	11.31	11.96	4.47	5.31	1.0	1.1	9.1	11.9

[a]AUC refers to AUC ∞ and AUC_{24} after single and multiple oral dosing, respectively.
[b]Harmonic mean.

proportional increases in AUC observed in the groups receiving febuxostat doses ranging from 120 to 240 mg daily (Fig. 1).

Hypouricemic effects of febuxostat were confirmed by PD measurements. Progressive decreases in mean serum urate levels were nearly linearly related to the administered dose of the drug in the range of 10 to 120 mg daily (Fig. 2). Accompanying the hypouricemic effect were increases in serum xanthine concentrations. There were also corresponding decreases in urinary uric acid excretion and a marked increase in urinary xanthine and a lesser increase in hypoxanthine excretion. Each of these effects appears to reach a plateau at febuxostat doses exceeding 120 mg daily (Table 2). These findings confirm that in healthy humans febuxostat is an inhibitor of xanthine oxidase activity. Of additional note, the summed daily urinary excretion of uric acid, xanthine, and hypoxanthine was minimally reduced as compared

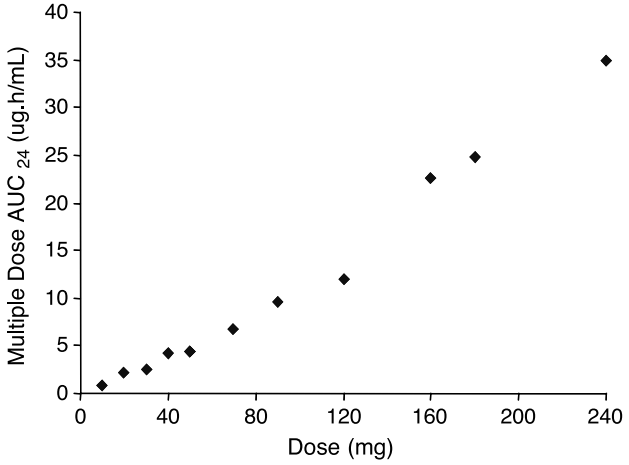

Figure 1. Area under the curve after multiple oral dosing with febuxostat.

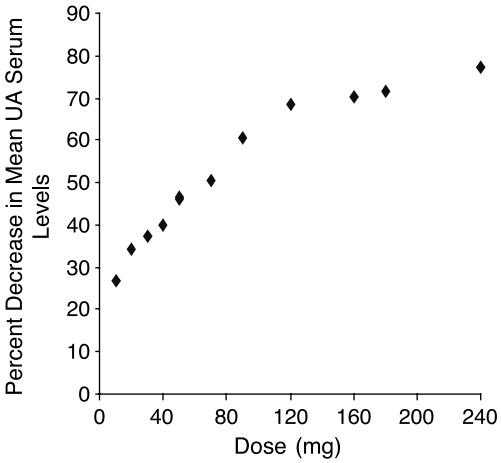

Figure 2. Percent decrease in mean serum urate (UA).

to that of untreated subjects during administration of febuxostat (Table 2), indicating little or no reduction of rates of purine nucleotide synthesis.

Headache, nausea, flushing or vasodilatation, and dizziness were the most common treatment-related adverse events (Table 3). All adverse events were self-limited. Nine subjects were withdrawn due to adverse events, including fever, myalgia,

Table 2. Total daily urinary excretion (AE_{24}) after multiple dosing with different doses of febuxostat.

Dose (mg)	Uric acid (mmol)	Xanthine (mmol)	Hypoxanthine (mmol)	% (Mean) placebo UA + X + H
Placebo	2.290	0.035	0.055	100
10 QD	1.232	0.309	0.140	92
20 QD	1.497	0.522	0.208	94
30 QD	1.196	0.661	0.185	94
40 QD	1.293	0.526	0.175	84
50 QD*	1.293	0.830	0.218	98
70 QD	1.095	0.886	0.295	96
90 QD	0.817	1.110	0.331	95
120 QD	0.780	1.264	0.289	98
160 QD	0.636	1.244	0.292	91
180 QD	0.747	1.544	0.294	109
240 QD	0.540	1.368	0.335	94
30 BID	0.871	1.037	0.326	94

Data collected on day 8.
UA = uric acid; X = xanthine; H = hypoxanthine.
*N = 20 all other treatment groups N = 10.

Table 3. Most common treatment-related adverse events in TMX-99-001.

Adverse event	PBO N = 26	10 QD N = 10	20 QD N = 10	30 QD N = 10	40 QD N = 10	50 QD N = 20	70 QD N = 10	90 QD N = 10	120 QD N = 10	160 QD N = 10	180 QD N = 10	240 QD N = 10	30 BID N = 10
At least 1 treat-related adverse event	11	4	3	2	4	8	3	2	8	9	6	8	3
Headache	7	4	3	2	2	3	2	2	5	7	6	0	3
Nausea	1	1	0	1	2	3	0	1	2	2	5	4	1
Vasodilatation (flushing, feeling of warmth)	2	0	0	0	2	0	0	1	1	5	2	4	0
Dizziness	0	0	0	0	3	0	0	1	1	5	0	0	0

All treatment-related adverse events occurring in at least 10 subjects overall.

confusion, asthenia, abdominal pain, and tachycardia. No deaths or serious adverse events occurred.

DISCUSSION

In summary, febuxostat is safe and well-tolerated when administered to healthy subjects over a 2-week period at doses ranging from 10 to 240 mg daily. Febuxostat effectively decreases serum urate concentration in a nearly dose-linear manner with once-daily dosing of up to 120 mg. Doses in excess of 120 mg daily did not appear to provide significant additional hypouricemic effect. Febuxostat did not appear to cause a significant reduction in total purine synthesis as a mechanism contributing to its hypouricemic effect. In conjunction with the lack of change in total purine synthesis and the decrease in serum and urine uric acid, the increase in serum and urine xanthine concentrations confirm that xanthine oxidase inhibition is the primary and perhaps the sole mechanism of action of this agent on purine metabolism.

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