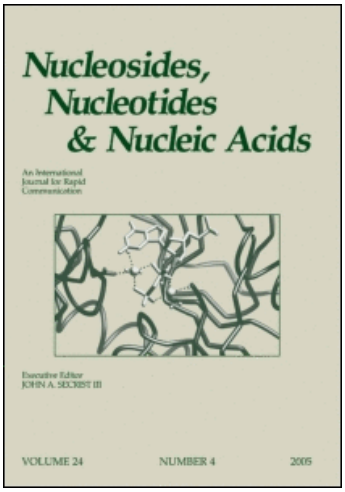

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Pharmacokinetics and Pharmacodynamics of Febuxostat (TMX-67), a Non-Purine Selective Inhibitor of Xanthine Oxidase/Xanthine Dehydrogenase (NPSIXO) in Patients with Gout and/or Hyperuricemia

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ABSTRACT

The diurnal change of sUA and the effect of febuxostat on this change were investigated in 10 patients with gout and/or hyperuricemia. The diurnal sUA change after the last dose during the 4-week treatment phase (20 mg, QD) was almost the same as the pre-treatment value. Considering the dose, the AUC_{obs} and C_{max} of unchanged drug in patients with gout and/or hyperuricemia were estimated to be similar to those of healthy male adults. The results show that a 6-week treatment with febuxostat is safe and well-tolerated in the target patient population for this drug.

Key Words: Febuxostat; XOD/XDH Inhibitor; Pharmacokinetics; Pharmacodynamics; Hyperuricemia; Gout.

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INTRODUCTION

Febuxostat (TMX-67), a non-purine selective inhibitor of xanthine oxidase/xanthine dehydrogenase (NP-SIXO), is in clinical development as an orally administered agent for the treatment of hyperuricemia and gout.[1–3] Results from in vivo animal studies reveal that febuxostat lowers serum urate (sUA) levels more potently than allopurinol,[4,5] and it binds to these enzymes by means of a different mechanism from that used by a metabolite of allopurinol oxypurinol. This study was conducted to investigate the pharmacodynamics (PD), represented by diurnal changes in the sUA level, and the pharmacokinetics (PK) of febuxostat before and after repeated administration to patients with gout and/or hyperuricemia.

SUBJECTS AND METHODS

The study was conducted as Phase II, an open label clinical study. One investigation site participated in the study. Ten patients with gout and/or hyperuricemia (sUA level: 9.51 ± 1.79 mg/100 mL, range: 8.0–13.7 mg/100 mL; hyperuricemia: $n = 10$; gout: $n = 3$), among 22 patients who gave their written consent, were treated with 10 mg of febuxostat during a 2-week introductory phase, and then with 20 mg during a 4-week treatment phase. All drugs were administered orally once daily (QD) after breakfast. On the day before the first administration of febuxostat (Day–1) and on the day of the final administration (Day 41), each patient was admitted to the hospital in order to conduct laboratory tests and PK and PD evaluations.

The sUA levels were determined 24, 22, 20, 18, 16, 12 h and just before the first administration and just before and 2, 4, 6, 8, 12, and 24 h after the final administration. sUA levels were measured by the uricase-peroxidase methods.

The levels of unchanged drug and oxidative metabolites (67 M-1, 67 M-2 and 67 M-4) of febuxostat in plasma, and of unchanged drug, oxidative metabolites and glucuronic acid conjugates of febuxostat (67-Glu) in urine were determined by HPLC and LC-MS/MS methods just before and 1, 2, 4, 6, 8, 12, and 24 h after the final administration. PK parameters were then calculated from these data.

The safety of febuxostat was evaluated based on adverse events that included both clinical laboratory test results outside the normal range and patient symptoms.

RESULTS

The mean sUA levels were 8.60, 8.56, 8.37, 8.53, 8.46, 8.62 and 9.11 mg/100 mL at 24, 22, 20, 18, 16, 12 h and just before the first administration. After the 4-week treatment phase, the levels were 5.96, 5.82, 5.61, 5.53, 5.51, 5.56 and 6.40 mg/100 mL just before and 2, 4, 6, 8, 12, and 24 h after the final dose. For the 24-h period before the first administration, the difference between maximum and minimum sUA level was 0.84 ± 0.34 mg/100 mL and for the 24-h period after the final administration the value was 0.96 ± 0.25 mg/100 mL. These results suggest that the diurnal change in sUA remains small even after febuxostat treatment for 4 weeks. All ten patients showed

Table 1. PK Parameters for Febuxostat after a 4-week treatment of patients.

Plasma unchanged drug				
AUC_{obs} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	
2092.30 ± 463.20	541.77 ± 227.79	2.2 ± 1.6	8.17 ± 2.41	
C_{max} Ratio (metabolite/unchanged drug)				
67 M-1 (%)	67 M-2 (%)	67 M-4 (%)		
1.38 ± 0.54	0.91 ± 0.86	1.49 ± 0.64		
Urinary excretion rate				
fe (% of dose)				
Unchanged drug (Febuxostat)	67 M-1	67 M-2	67 M-4	67-Glu
2.21 ± 1.56	3.55 ± 1.28	3.60 ± 1.67	2.05 ± 1.16	40.06 ± 7.65
CL/F and CL_R of unchanged drug				
CL/F (mL/h)	CL_R (mL/h)			
9930.14 ± 1922.17	211.15 ± 140.57			

Data represent the mean ± SD.

similar diurnal changes in sUA level in the 24 h after the final administration. The mean AUC of sUA for the 24 h before the first administration was 8.7 mg/100 mL, and for the 24 h after the final administration was 5.8 mg/100 mL. These results indicate that febuxostat reduces sUA levels by 33.3%.

The AUC_{obs} of unchanged drug in patients was 2092.30 ± 463.20 ng · h/mL and the C_{max} was 541.77 ± 227.79 ng/mL (Table 1). The t_{max} of the unchanged drug was 2.2 ± 1.6 h.

In almost all patients, the t_{max} of each metabolite was nearly equal to the t_{max} of the unchanged drug. The $t_{1/2}$ was 8.17 ± 2.41 h. Considering the dose, the AUC_{obs} and

Table 2. Adverse events.

Body system classification	No. of events	Adverse event (no. of case)
Gastrointestinal system disorder	2	Indigestion* (2)
Liver and biliary system disorder	1	GOT increase (1)
Metabolic and nutritional disorder	4	CPK increase (1), Triglyceride increase (2), Al-P increase (1)
Endocrine disorder	1	TSH increase (1)
Urinary system disorder	2	Urinary occult blood (2)

*Two moderate adverse events occurred in one patient.

C_{max} of the unchanged drug in patients with gout and/or hyperuricemia were estimated to be similar to those of healthy male adults.[3]

Ten adverse events (8 mild, 2 moderate in severity) were observed in 4 patients (Table 2). Since three events were ''not related'' and seven were ''probably not related'' to febuxostat, none of the events is thought to be an adverse drug reaction.

DISCUSSION

The diurnal change of sUA and the effect of febuxostat on this change were investigated in 10 patients with gout and/or hyperuricemia. A QD treatment with febuxostat does not affect the diurnal change in sUA to a great extent. Because it is thought that acute changes in sUA levels are involved the development of a gouty attack, the possibility of the onset of an attack might be reduced by QD treatment of febuxostat. In addition, the sUA-lowering effect of febuxostat is almost the same as that observed during an early phase II study.[1] Considering the dose, the AUC_{obs} and C_{max} of unchanged drug in patients with gout and/or hyperuricemia were estimated to be similar to those of healthy male adults.[3] Although the t_{max} of unchanged drug was slightly delayed, and the $t_{1/2}$ was slightly prolonged in patients with hyperuricemia in comparison with healthy male adults,[3] the delay in t_{max} and the prolongation in $t_{1/2}$ were considered to be not clinically significant considering the respective range of variation. In conclusion, the results show that a 6-week treatment with febuxostat is safe and well-tolerated in patients with gout and/or hyperuricemia, the target patient population for this drug.

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