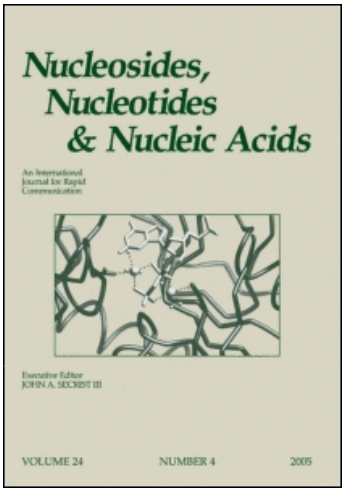

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Pharmacokinetics/Pharmacodynamics of Y-700, A Novel Xanthine Oxidase Inhibitor, in Rats and Man

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ABSTRACT

The pharmacokinetics and pharmacodynamics of a novel xanthine oxidase (XO) inhibitor, Y-700, were evaluated in rats and healthy male volunteers. In a rat model of hyperuricemia, oral Y-700 (0.3–10 mg/kg) showed a more potent and a longer-lasting hypouricemic action than allopurinol. A single oral dosing of Y-700 (5, 20 or 80 mg) to volunteers caused a dose-dependent reduction of serum uric acid levels indicating close relationship to plasma concentrations of the compound. In addition, Y-700 was hardly excreted in urine but mainly excreted in feces in rats and volunteers. These results suggested that Y-700 is a new effective inhibitor of XO in rats and humans with high oral bioavailability being predominantly eliminated via the liver unlikely to allopurinol.

Key Words: Gout; Hyperuricemia; Xanthine oxidase/dehydrogenase; Y-700.

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INTRODUCTION

Y-700, 1-(3-Cyano-4-neopentyloxyphenyl)pyrazole-4-carboxylic acid, has been introduced as a novel xanthine oxidase inhibitor, which bears no structural relationship to the known inhibitor, allopurinol.[1] The present study was conducted to evaluate the pharmacokinetics and pharmacological actions of Y-700 in rats and healthy adult male volunteers.

MATERIALS AND METHODS

Male Sprague–Dawley rats were used for animal study. A rat model of hyperuricemia was established by repeated treatment of the animals with the uricase inhibitor, potassium oxonate following our previous report.[1] ^{14}C—labeled Y-700 was used for the assessments of absorption, metabolism and excretion in rats. In a clinical study, a single dose (5, 20 or 80 mg) of Y-700 or placebo was administered orally to adult healthy male Japanese volunteers. Plasma and urinary concentrations of Y-700 and urinary amounts of xanthine and hypoxanthine were detected by a validated HPLC method.

RESULTS

Y-700 was absorbed rapidly in both species and was eliminated with t1/2 of 2.7–5.0 h for rats and 27.6–40.2 h for humans. In rats and humans, Cmax and AUC of oral Y-700 were increased dose-dependently (Table 1). Only Y-700 was detected in rats and humans plasma. Urinary excretions of Y-700 in rats and humans were 1.1% and 1.5%, respectively. In hyperuricemic rats, oral Y-700 (0.3–10 mg/kg) showed hypouricemic action in a dose-dependent manner, and was more potent and longer lasting than allopurinol. In humans, the action at doses of 20 and 80 mg were statistically significantly different from the placebo, indicating that maximal changes in serum UA levels (Emax) at doses 20 and 80 mg were −1.01 and −2.66 mg/dL, respectively. The hypouricemic action of Y-700 was maintained throughout the post dose. Urinary

Table 1. Pharmacokinetic and pharmacodynamic parameters of Y-700 after its single dosing in healthy male volunteers.

Dose	Placebo	5 mg	20 mg	80 mg
Cmax (μg/mL)	–	0.24 ± 0.04	0.92 ± 0.15	5.54 ± 1.20
AUC_{0-71h} (μg/h/mL)	–	5.5 ± 1.4	16.6 ± 1.9	106.3 ± 20.8
t1/2 (h)	–	40.2 ± 4.4	29.8 ± 1.6	27.6 ± 4.6
Emax (mg/dL)	0.25 ± 0.31	− 0.44 ± 0.4	− 1.01 ± 0.38*	− 2.66 ± 0.13**

Mean ± SD (n = 5–7).
*$p < 0.05$.
**$p < 0.01$ vs. placebo group (Dunnett's multiple comparison test).

excretion of xanthine and hypoxanthine were significantly increased after dosing of Y-700 compared with placebo group.

DISCUSSION

The present study demonstrated that Y-700 is a new effective XO inhibitor of non-renal excretion type with a potent and a long-lasting hypouricemic action in rats and humans. The distinctive elimination route of Y-700 is expected to provide a beneficial property as a new drug for the treatment of gout and hyperuricemia. Unlike the case for allopurinol, it may not be necessary to adjust the dosage of Y-700 in patients according to their degree of renal function.

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