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THE THERAPEUTIC EFFICACY OF THE NOVEL URICOSURIC AGENT UR-1102 FOR HYPERURICEMIA AND GOUT

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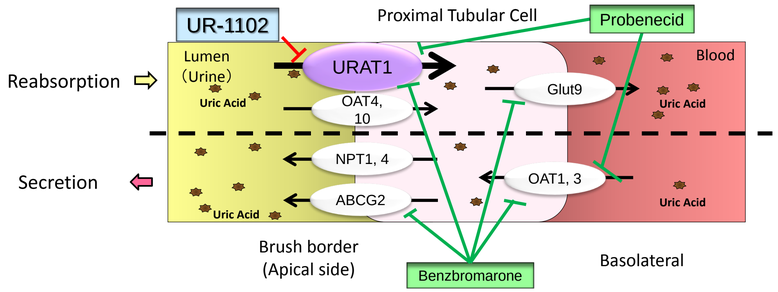
Introduction

Currently available uricosuric drugs (benzbromarone, probenecid etc.) block renal uric acid reabsorption by inhibiting uric acid transporter 1 (URAT1). Probenecid has long history but its efficacy is limited. Benzbromarone is known to be therapeutically more effective than other uricosurics, however, as fatal cases of serious liver damage have been reported, it is not available in US and major countries. In addition, due to its low selectivity to URAT1, it is not clear if more selective URAT1 inhibitor can exert better uricosuric effect and contribute to the current treatment for gout.

We have identified highly selective URAT1 inhibitor UR-1102. In this study, the therapeutic potential of UR-1102 was examined by comparing it with benzbromarone *in vitro* and *in vivo* with cebus monkeys. In addition, the risk of fulminant hepatitis, which is incidental to benzbromarone, of UR-1102 was evaluated.



Conclusion

UR-1102 is a highly selective and potent inhibitor of URAT1 and showed more potent efficacy and safety profile than benzbromarone. Its nature as the pure URAT1 inhibitor will contribute to solve the unmet medical need for current gout treatment.

Methods

➢ *In vitro* inhibitory effects of UR-1102 and benzbromarone on human URAT1, OAT1, or OAT3 were evaluated using HEK293 cells transfected with each transporter. The inhibitory effects on ABCG2 were evaluated using membrane vesicles. The RI-labeled specific substrates for those transporters (^{14}C uric acid for URAT1, ^{3}H para-aminohippuric acid for OAT1 or OAT3, and ^{14}C methotrexate for ABCG2) were used and the uptake amount of each specific substrate was measured by radioactivity.

➢UR-1102, at 3, 10, and 30 mg/kg/day, and benzbromarone, at 3, 10, 30, and 100 mg/kg/day, were administered orally to four male and two female cebus monkeys. Test and control articles were administered once daily for 3 consecutive days in one phase; there were 8 phases with 2-week intervals (cross-over design with eight groups). Blood was collected at 2, 4, 8, and 24 h after each administration; Urine from 0 to 8 h and 8 to 24 h, respectively. Plasma and urinary uric acid and creatinine were analyzed by enzymatic method.

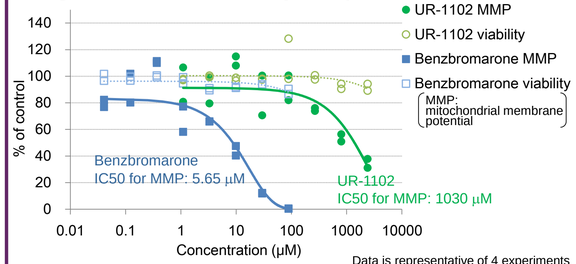
➢The risk of fulminant hepatitis was evaluated by testing HepG2 cells for mitochondrial toxicity, and by measuring the covalent binding of compounds in human liver microsomes, and their inhibitory effects on human MRP2 using membrane vesicles.

Results

Table 1. Inhibitory effects of UR-1102 and benzbromarone on URAT1, OAT1, OAT3, or ABCG2

	UR-1102	Benzbromarone
URAT1, Ki value	0.055 ± 0.034 μM	0.051 ± 0.014 μM
OAT1, Ki value (vs URAT1)	7.8 ± 2.9 μM (142 fold)	0.2 ± 0.0 μM (4 fold)
OAT3, Ki value (vs URAT1)	2.4 ± 0.3 μM (43 fold)	0.1 ± 0.1 μM (3 fold)
ABCG2, IC_{50} value (vs URAT1)	72.4 ± 10.3 μM (1316 fold)	25.7 ± 0.6 μM (504 fold)

Fig. 4. Mitochondrial toxicity in HepG2 cells (4 h)



Data is representative of 4 experiments

Fig. 5. Covalent binding in human liver microsomes

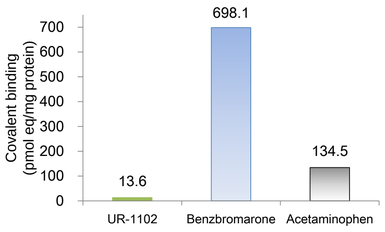


Fig. 1. Average plasma uric acid ($AUC_{0\text{-}8hr}$/8hr on day3)

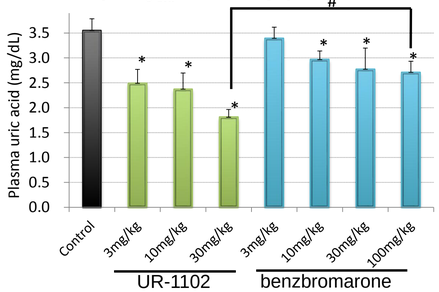
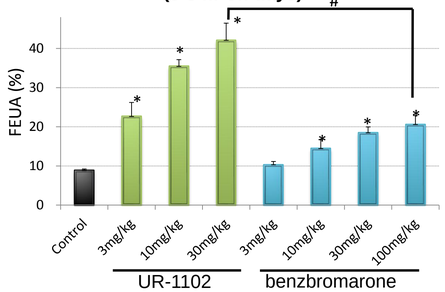
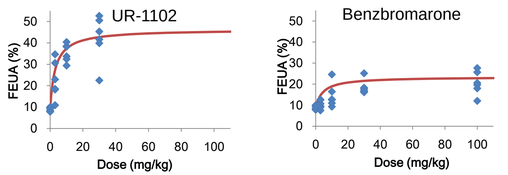


Fig. 2. Urinary fractional excretion of uric acid (0-8 hr on day3)



Mean + SE (n=6), *; p<0.05, significantly different from Control (paired t-test based on a mixed effects model)
#; p<0.05, significant difference between UR-1102 30 mg/kg and benzbromarone 100 mg/kg (paired t-test)

Fig. 3. Emax model of urinary fractional excretion of uric acid



	UR-1102	Benzbromarone
Emax (%)	46 ± 12	23 ± 7
ED50 (mg/kg)	3.1 ± 1.7	4.5± 4.3

Mean ± SE (n=6)

Table 2. PK profile of UR-1102 and benzbromarone in cebus monkeys

	UR-1102			Benzbromarone			
	3 mg/kg	10 mg/kg	30 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg	100 mg/kg
Cmax (μg/mL)	8.96 ± 1.74	42.4 ± 12.8	92.9 ± 21.0	4.25 ± 1.94	10.0 ± 2.7	21.0 ± 5.5	43.7 ± 9.7
Tmax (hr)	0.6 ± 0.2	0.5 ± 0.0	0.8 ± 0.3	1.7 ± 0.5	1.7 ± 0.5	1.5 ± 0.5	1.8 ± 0.4
T1/2 (hr)	4.7 ± 0.9	4.2 ± 1.1	3.3 ± 0.8	2.0 ± 0.9	2.0 ± 1.0	2.8 ± 0.3	2.8 ± 0.7
$AUC_{0\text{-}inf}$ (μg·h/mL)	26.2 ± 8.1	108 ± 51	257 ± 60	14.8 ± 4.6	37.2 ± 15.3	70.4 ± 22.6	172 ± 59

Mean ± SD (n=6)

Summary of results

➢ The inhibitory effect of UR-1102 on URAT1 was highly selective compared with OAT1, OAT3, or ABCG2. While the inhibitory effect of benzbromarone on URAT1 was comparable with UR-1102, the selectivity was much lower. (Table 1)

➢ In cebus monkeys, both UR-1102 and benzbromarone dose-dependently reduced plasma uric acid and increased urinary fractional excretion of uric acid. Hypouricemic and uricosuric effects were more potent for UR-1102 than for benzbromarone in both dose and maximum efficacy in cebus monkeys. (Fig. 1-3)

➢ UR-1102 showed better oral absorption than benzbromarone. Systemic exposures of UR-1102 10 or 30 mg/kg and benzbromarone 100 mg/kg were equivalent. (Table 2)

➢ The risk of fulminant hepatitis in UR-1102 was apparently lower than in benzbromarone. (Fig. 4, 5)

Discussion

The superior efficacy of UR-1102 on plasma uric acid lowering to benzbromarone may not be understood well by the oral bioavailability difference because same level of exposures were achieved for both compounds. It will be better explained by the difference in selectivity on uric acid transporters. Benzbromarone also inhibited OAT1, OAT3, and ABCG2 which are responsible for uric acid secretion in renal proximal tubule. Therefore, when high dose is administered, it will not work as a pure URAT1 inhibitor, compromising the effect of URAT1 inhibition then cannot show further uric acid excretion. This may not happen with UR-1102, a pure URAT1 inhibitor, which even at higher doses showed incremental uricosuric effects.

【COI】All authors are employees of C&C Research Lab., Chugai Pharmaceutical Co., Ltd., JW Pharmaceutical Corp., or Shin Nippon Biochemical Lab.