**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 transporters (URAT1). Probenecid has long history but its efficacy is limited. Benzbromarone is known to be therapeutically more effective than other uricosuric agents, 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 potential therapeutic efficacy 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 incidentally to benzbromarone, of UR-1102 was evaluated.

**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 HEK293 cells. The H1-labeled specific substrates for those transporters (14C uric acid for URAT1, 3H para-aminohippuric acid for OAT1 or OAT3, and 14C 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 administrated orally to four male and two female cebus monkeys in 8 phases with 2 days per phase (one crossover 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

<table>
<thead>
<tr>
<th>Substrate/Transporter</th>
<th>UR-1102 (μM)</th>
<th>Benzbromarone (μM)</th>
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<tbody>
<tr>
<td>URAT1</td>
<td>0.055 ± 0.034</td>
<td>0.051 ± 0.014</td>
</tr>
<tr>
<td>OAT1</td>
<td>7.8 ± 2.9</td>
<td>142 fold</td>
</tr>
<tr>
<td>OAT3</td>
<td>2.4 ± 0.3</td>
<td>48 fold</td>
</tr>
<tr>
<td>ABCG2</td>
<td>72.4 ± 10.3</td>
<td>1316 fold</td>
</tr>
</tbody>
</table>

**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.

**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 oral dose 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 show further uric acid excretion. This may not happen with UR-1102.

**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. Hyperuricemic 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)