Effects of purine/nonpurine type xanthine oxidoreductase inhibitors (Allopurinol/Topiroxostat) on high hypoxanthine phosphoribosyltransferase activity-uricase knockout mice

Takuji Hosoya^{1,3}, Syunya Utida², Shigeru Shibata², Naoko H. Tomioka¹, Makoto Hosoyamada¹

¹Dept. Human Physiol Pathol., Fac. Pharm-Sci., Teikyo Univ, ²Dept. Int Med., Fac. Med., Teikyo Univ, ³Dept. Pharm Res group 2, Biol Res Dept, Fuji Yakuhin Co., Ltd

The differences of purine metabolism of mice from that of human are known to be not only conserved uricase (Uox), but also low hypoxanthine phosphoribosyltransferase (HPRT) activity. The aim of this study is the establishment of high HPRT activity-Uox knockout mice as mouse model for the study of purine metabolism in human and the investigation of the effect of Allopurinol and Topiroxostat on HPRT. Allopurinol 30 mg/kg (Allo) and Topiroxostat 1 mg/kg (Top) were administered to the model mice for 7 days by feeding diet. Oxypurines (urate (UA), hypoxanthine (HX) and xanthine (XA)) and creatinine (Cr) in plasma and urine were measured by HPLC. Plasma UA value and urinary UA/Cr ratio significantly decreased in Allo and Top. Although the plasma UA-lowering effect was equivalent in Allo and Top, the urinary HX+XA/Cr ratio in Top 1 was significantly lower than those in Allo. Moreover, urinary oxypurine/Cr ratio demonstrated a significant lowering effect in Top, but not in Allo. In conclusion, Topiroxostat has a potent plasma UA-lowering effect and didn't affect the salvage pathway unlike Allopurinol, efficiently resulted in decreased total oxypurine excretion.