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Tacrolimus (Tacro) Strongly Inhibits Intestinal UDP-glucuronosyltransferase (UGT) 1A8

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***SUMMARY*. Tacrolimus (Brand name: Prograf), a kind of immunosuppressants, has been reported to induce drug-drug interaction with many clinical drugs. Tacrolimus-mycophenolic acid (MPA) interaction has been widely and frequently reported. Intestinal UDP-glucuronosyltransferase (UGT) 1A8-mediated metabolism plays a key role in the elimination of MPA, and alteration of the activity of UGT1A8 resulting from gene polymorphisms could significantly influence the catalyzing activity of MPA glucuronidation. The aim of the present study is to investigate the inhibitory potential of tacrolimus towards UGT1A8, which was speculated to be a potential cause for tacrolimus-MPA interaction. The recombinant UGT1A8 was used as enzyme source, and a nonspecific substrate 4-methylumbelliferone (4-MU) was utilized as substrate. The results showed that 100 μM of tacrolimus inhibited UGT1A8-mediated 4-MU glucuronidation activity by 82.3 %. Further inhibition kinetic investigation showed that the inhibition of UGT1A8 by tacrolimus was best fit to competitive inhibition type, and the inhibition kinetic parameter (Ki) was determined to be 6.1 μM. All these results indicated that tacrolimus could exhibit strong inhibition towards UGT1A8, which should be paid more attention when explaining clinical tacrolimus-MPA interaction.**

KEY WORDS: Drug-drug interaction (DDI), Mycophenolic acid (MPA), Tacrolimus, UDP-glucuronosyltransferase (UGT) 1A8.

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