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Strong Inhibition of UDP-Glucuronosyltransferase (UGT) 1A1 by Levothyroxine Indicates the Potential UGT-Inhibition Based Adverse Effect of Levothyroxine

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***SUMMARY*. UDP-glucuronosyltransferase (UGT) 1A1, one of the most important UGT isoforms, can metabolize a variety of endogenous substances and xenobiotics. UGT1A1-catalyzed glucuronidation reaction plays a key role in many clinical events, including Gilbert syndrome and irrinotecan-induced diarrhea toxicity. The present study aims to investigate the inhibition of UGT1A1 by levothyroxine which is clinically used to treat thyroid hormone deficiency, and occasionally to prevent the recurrence of thyroid cancer. The recombinant UGT1A1was used as enzyme source, and 4-methylumbelliferone (4-MU) was utilized as a non-specific probe substrate. The results showed that levothyroxine inhibited the UGT1A1-catalyzed 4-MU glucuronidation in a dose-dependent manner. Furthermore, Lineweaver-Burk and Dixon plots showed that the inhibition of UGT1A1 by levothyroxine was best fit to the competitive inhibition type, and the inhibition kinetic parameter (K_i) was calculated to be 1 μM. Taken together, the competitive of levothyroxine towards UGT1A1 was demonstrated in the present study, which might induce severe clinical results, including potential drug-drug interaction and metabolic disorders of endogenous substances.**

KEY WORDS: Levothyroxine, UDP-glucuronosyltransferase (UGT) 1A1, Drug-drug interaction.

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