Reversible and Time-Dependent Inhibition of CYP3A4-Mediated Nifedipine Oxidation by Noscapine

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SUMMARY. Substrate-dependent inhibition of CYP3A4 might influence the extrapolation of drug interactions from the in vitro to in vivo situation. The aim of the present study is to investigate reversible and time-dependent inhibition of CYP3A4-mediated nifedipine oxidation by noscapine. Furthermore, in vitro-in vivo extrapolation (IVIVE) was performed using in vitro parameters. The results showed that CYP3A4-mediated nifedipine oxidation activity was strongly inhibited with an IC50 of 25.7 ± 5.4 μM. Kinetic analysis showed that inhibition of CYP3A4-mediated nifedipine oxidation by noscapine was best fit to a non-competitive manner with Ki value of 10.9 μM. IC50 shift experiment showed that IC50 was significantly decreased from 25.7 ± 5.4 μM to 0.34 ± 0.07 μM after pre-incubation with noscapine for 30 min, which indicated that time-dependent inhibition existed for inhibition of CYP3A4 by noscapine. The AUC of (R)-warfarin was predicted to increase by 0.5 % using Cmax or 0.2 % using unbound Cmax with reversible inhibition prediction equation, while the AUC of (R)-warfarin was estimated to increase by 23.1 % using Cmax or 10.4 % using unbound Cmax with TDI prediction equation. Inhibition of CYP3A4 by noscapine showed substrate-dependent inhibition behaviour. However, the results obtained from IVIVE are very similar using testosterone or nifedipine as probe substrates.

KEY WORDS: Drug-drug interaction (DDI), Nifedipine, Noscapine, Substrate-dependent inhibition, Time-dependent inhibition (TDI), Warfarin.

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