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

Xue-Li JIN [1,#], Shu-Hong TANG [3,#], Zhong-Ze FANG [2], Yan-Qing QU [1], Rui LIANG [1], Zhen-Ming GAO [1], Bo TANG [1], De-Guang SUN [1], Ming LI [3], Ling YANG [2] & Li-Ming WANG [1*]

[1] *1 The Second Affiliated Hospital of Dalian Medical University, Dalian,116023,China*

[2] *Laboratory of Pharmaceutical Resource Discovery, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, 116023, China*

[3] *The Department of Oncology Medicine, The fifth hospital of Dalian, Dalian, China*

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 IC_{50} 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 C_{max} or 0.2 % using unbound C_{max} with reversible inhibition prediction equation, while the AUC of (R)-warfarin was estimated to increase by 23.1 % using C_{max} or 10.4 % using unbound C_{max} 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.

* Author to whom correspondence should be addressed. *E-mail:* wangbcc259@yahoo.com.cn

\# These two authors contributed equally to this work.

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