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In Vitro Inhibitory Effects of Cepharanthine on Human Liver Cytochrome P450 Enzymes

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***SUMMARY*. Cepharanthine (CEP) extracted from the roots of *Stephania cepharantha* Hayata, has a range of therapeutic potential in clinic. Whether it affect the activity of human liver cytochrome P450 (CYP) enzymes remains unclear. The effects of CEP on eight human liver CYP isoforms (*i.e.*, 1A2, 3A4, 2A6, 2E1, 2D6, 2C9, 2C19, and 2C8) were investigated *in vitro* using human liver microsomes. The results showed that the activity of CYP3A4, CYP2E1, and CYP2C9 was inhibited by CEP, with IC50 values of 16.29, 25.62, and 24.57 μM, respectively, but other CYP isoforms were not affected. In addition, CEP was a non-competitive inhibitor of CYP3A4, but competitively inhibit CYP2E1 and CYP2C9, with K_i values of 8.12, 11.78, and 13.06 μM, respectively. CEP is a time dependent inhibitor for CYP3A4 with K_I/K_{inact} value of 10.84/0.058 min$^{-1}\mu$M^{-1} These results indicate that CEP may cause pharmacokinetic drug interactions with drugs metabolized by CYP3A4, CYP2E1 and CYP2C9.**

RESUMEN. Cepharanthina (CEP) extraída de las raíces de *Stephania cepharantha* Hayata, tiene un rango de potencial terapéutico en la clínica. Aún no está claro si afecta la actividad de las enzimas del citocromo P450 (CYP) del hígado humano. Los efectos de CEP en ocho isoformas de CYP de hígado humano (es decir, 1A2, 3A4, 2A6, 2E1, 2D6, 2C9, 2C19 y 2C8) se investigaron *in vitro* utilizando microsomas de hígado humano. Los resultados mostraron que la actividad de CYP3A4, CYP2E1 y CYP2C9 fue inhibida por CEP, con valores de CI50 de 16.29, 25.62 y 24.57 μM, respectivamente, pero otras isoformas de CYP no se vieron afectadas. Además, CEP era un inhibidor no competitivo de CYP3A4, pero inhibía competitivamente CYP2E1 y CYP2C9, con valores de K_i de 8.12, 11.78 y 13.06 μM, respectivamente. CEP es un inhibidor dependiente del tiempo para CYP3A4 con un valor de K_I/K_{inact} de 10.84/0.058 min$^{-1}\mu$M^{-1}. Estos resultados indican que CEP puede causar interacciones farmacocinéticas con medicamentos metabolizados por CYP3A4, CYP2E1 y CYP2C9.

KEY WORDS: Cepharanthine, CYP3A4, CYP2E1, CYP2C9, drug-drug interaction

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