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Glycyrrhizin Affects the Pharmacokinetics of Omeprazole in Rats through Inducing the Activity of CYP3A4, CYP2C19, and *P-gp*

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SUMMARY. **Omeprazole and glycyrrhizin are widely used for the treatment of peptic ulcer in China clinics. This study investigates the effects of glycyrrhizin on the pharmacokinetics of omeprazole. The pharmacokinetics of orally administered omeprazole (2 mg/kg) with or without glycyrrhizin (100 mg/kg/day for 7 days) pretreatment were investigated in male Sprague-Dawley rats using LC-MS/MS. A Caco-2 cell transwell model and rat liver microsome incubation systems were also used to support the *in vivo* pharmacokinetic data and investigate its potential mechanism. The results indicated that co-administration of glycyrrhizin could decrease significantly the systemic exposure of omeprazole ($P < 0.05$), including the area under the curve (597.72 ± 148.06 *vs.* 1060.93 ± 169.82 ng·h/mL) and the maximum plasma concentration (226.96 ± 18.66 *vs.* 333.05 ± 28.67 ng/mL). The $t_{1/2}$ of omeprazole also decreased significantly (1.77 ± 0.18 *vs.* 2.23 ± 0.27 h, $P < 0.05$) with the pretreatment of glycyrrhizin. The efflux ratio of omeprazole across the Caco-2 cell transwell model increased significantly from 1.85 to 2.67 ($P < 0.05$), and the metabolic stability of omeprazole was decreased from 46.1 ± 8.1 to 25.7 ± 6.8 min with the pretreatment of glycyrrhizin ($P < 0.05$). In conclusion, glycyrrhizin could decrease the systemic exposure of omeprazole in rats when glycyrrhizin and omeprazole was co-administered, and it might exert these effects through decreasing the absorption of omeprazole by inducing *P-gp,* or through accelerating the metabolism of omeprazole in rat liver by inducing the activity of CYP3A4 or CYP2C19.**

RESUMEN. Omeprazol y glicirricina son ampliamente utilizados para el tratamiento de la úlcera péptica en las clínicas de China. Este estudio investiga los efectos de la glicirricina en la farmacocinética de omeprazol. La farmacocinética del omeprazol administrado por vía oral (2 mg/kg) con o sin pretratamiento con glicirricina (100 mg/kg/día durante 7 días) se investigó en ratas macho Sprague-Dawley usando LC-MS/MS. También se usaron sistemas de incubación de células transgénicas Caco-2 y sistemas de incubación de microsomas hepáticos de rata para respaldar los datos farmacocinéticos *in vivo* e investigar su mecanismo potencial. Los resultados indicaron que la administración concomitante de glicirricina podría disminuir la exposición sistémica de omeprazol significativamente ($P < 0.05$), incluyendo el área bajo la curva (597.72 ± 148.06 *vs*. 1060.93 ± 169.82 ng.h/mL) y la concentración plasmática máxima (226,96 ± 18,66 frente a 333,05 ± 28,67 ng/mL). El $t_{1/2}$ de omeprazol también disminuyó significativamente (1.77 ± 0.18 *vs*. 2.23 ± 0.27 h, $P < 0.05$) con el pretratamiento de la glicirricina. La relación de eflujo de omeprazol a través del modelo de transwell de células Caco-2 aumentó significativamente de 1,85 a 2,67 ($P < 0,05$) y la estabilidad metabólica de omeprazol disminuyó de 46,1 ± 8,1 a 25,7 ± 6,8 min con el pretratamiento de glicirricina ($P < 0.05$). En conclusión, la glicirricina podría disminuir la exposición sistémica de omeprazol en ratas cuando se coadministraron glicirricina y omeprazol, y podría ejercer estos efectos al disminuir la absorción de omeprazol induciendo *P-gp,* o al acelerar el metabolismo de omeprazol en hígado de rata induciendo la actividad de CYP3A4 o CYP2C19.

KEY WORDS: CYP3A4, CYP2C19, herb-drug interaction, P-gp.

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