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Effect of Rutin Combined with Nimodipine on the Pharmacokinetics of Nimodipine

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***SUMMARY*. Through *in vivo* and *in vitro* experiments, the pharmacokinetic interaction of rutin with nimodipine was studied. The pharmacokinetic of nimodipine (25 mg/kg) with or without rutin (20 mg/kg/day) was studied. Meanwhile, the transport and metabolic stability of nimodipine was studied in the Caco-2 model and rat liver microsomes. Rutin dramatically suppressed the C_{max} (22.41 ± 1.93 vs. 36.55 ± 6.87 ng/mL) and $t_{1/2}$ (from 4.13 ± 0.30 to 2.65 ± 0.17 h) of nimodipine. The efflux ratio of nimodipine was significantly increased from 1.56 to 1.93. Moreover, the metabolic stability of nimodipine was significantly increased with the intrinsic clearance rate increased from 36.69 ± 1.71 to 50.66 ± 2.31μL/min/mg protein by rutin. The *in vivo* pharmacokinetic study showed a decrease in the system exposure of nimodipine, which might be the results of the inducing of CYP3A4 and P-*gp* activity by rutin.**

RESUMEN. Mediante experimentos *in vivo* e *in vitro*, se estudió la interacción farmacocinética de la rutina con nimodipina. Se estudió la farmacocinética de nimodipina (25 mg/kg) con o sin rutina (20 mg/kg/día). Mientras tanto, se estudió el transporte y la estabilidad metabólica de la nimodipina en el modelo Caco-2 y en microsomas de hígado de rata. La rutina suprimió drásticamente la $C_{máx}$ (22,41 ± 1,93 frente a 36,55 ± 6,87 ng/mL) y $t_{1/2}$ (de 4,13 ± 0,30 a 2,65 ± 0,17 h) de nimodipina. La relación de salida de nimodipina aumentó significativamente de 1,56 a 1,93. Además, la estabilidad metabólica de la nimodipina aumentó significativamente con la tasa de aclaramiento intrínseco incrementada de 36,69 ± 1,71 a 50,66 ± 2,31 μL/min/mg de proteína por rutina. El estudio farmacocinético *in vivo* mostró una disminución en la exposición del sistema de nimodipina, que podría ser el resultado de la inducción de la actividad de CYP3A4 y P-*gp* por la rutina.

KEY WORDS: CYP3A4, Drug-drug interaction, Nimodipine, *P-gp*, Rutin

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