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Pharmacokinetic and Pharmacodynamic Interaction of Glibenclamide with Imatinib Mesylate in Rats

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SUMMARY. **This study investigated the effect of imatinib on the pharmacokinetics and pharmacodynamics of glibenclamide in alloxan-induced diabetic rats, as both drugs were reported to be CYP2C9 substrates. The control and test groups (n = 5) were treated for seven consecutive days with vehicle and imatinib (50 mg/kg), respectively. On day seven, 1 h after the last dose of imatinib, both groups were administered glibenclamide (10 mg/kg). Blood samples were collected in heparinized tubes at different time points (1, 2, 4, 8, and 12 h) from the retro-orbital plexus to determine blood glucose and glibenclamide plasma concentrations by glucose test strips and a UPLC-MS/MS analytical method, respectively. Imatinib increased the glibenclamide peak plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC_{0-t}) by 2.75 and 2.29 fold, respectively ($P < 0.05$). Blood glucose level was significantly reduced. Imatinib significantly increased glibenclamide plasma concentration and the glibenclamide hypoglycemic effect. Inhibition of CYP2C-mediated glubenclamide metabolism may be involved.**

RESUMEN. Este estudio investigó el efecto del imatinib en la farmacocinética y la farmacodinamia de la glibenclamida en ratas diabéticas inducidas por alloxan, ya que ambos fármacos son sustratos del CYP2C9. Los grupos de control y de prueba (n = 5) se trataron durante 7 días consecutivos con vehículo e imatinib (50 mg/kg), respectivamente. El día 7º, 1 h después de la última dosis de imatinib, a ambos grupos se les administró glibenclamida (10 mg/kg). Se recogieron muestras de sangre en tubos heparinizados a diferentes tiempos (1, 2, 4, 8 y 12 h) del plexo retroorbitario para determinar las concentraciones plasmáticas de glucosa en sangre y glibenclamida mediante tiras reactivas de glucosa y UPLC-MS/MS, respectivamente. Imatinib aumentó la concentración plasmática máxima de glibenclamida (C_{max}) y el área bajo la curva de concentración plasmática-tiempo (AUC_{0-t}) en 2,75 y 2,29 veces, respectivamente ($P < 0,05$). Nivel de glucosa en sangre se redujo significativamente. Imatinib aumentó significativamente la concentración plasmática de glibenclamida y el efecto hipoglucemiante de glibenclamida. La inhibición del metabolismo de la glubenclamida mediada por CYP2C puede estar involucrada.

KEY WORDS: drug-drug interactions, glibenclamide, imatinib mesylate, pharmacodynamics, pharmacokinetics.

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