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Effect of Aconitine on Three Cytochrome P450 Isoforms in Rats

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***SUMMARY*. Aconitine (AC) is a highly toxic diester-diterpene alkaloid from *Aconitum* species of the Ranunculaceae family. The purpose of this study was to find out whether AC influences the effect on rat cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C19 and CYP3A4) by using cocktail probe drugs *in vivo*. A cocktail solution at a dose of 5 mL/kg, which contained phenacetin (20 mg/kg), omeprazole (20 mg/kg) and midazolam (10 mg/kg), was oral administrated to rats treated with 10 days oral administration of AC. Blood samples were collected at a series of time-points and the concentrations of probe drugs in plasma were determined by HPLC-MS/MS. Our study showed that treatment with multiple doses of AC had inductive effect on rat CYP1A2. However, AC had significant inhibition effect on CYP2C19 and CYP3A4 enzyme activities after multiple doses of AC treatment. Therefore, caution is needed when AC is co-administration with some CYP substrates in clinic, which may result in herb-drug interactions.**

RESUMEN. La aconitina (AC) es un alcaloide diéster-diterpeno altamente tóxico presente en especies de *Aconitum* de la familia Ranunculaceae. El propósito de este estudio fue averiguar si la AC influye en el efecto sobre las enzimas del citocromo P450 (CYP) de rata (CYP1A2, CYP2C19 y CYP3A4) por el uso de cóctel de drogas *in vivo*. Una solución cóctel de 5 ml/kg conteniendo fenacetina (20 mg/kg), omeprazol (20 mg/kg) y midazolam (10 mg/kg), se administró por vía oral a ratas tratadas durante 10 dias con CA por vía oral. Se recogieron muestras de sangre a diversos tiempos y las concentraciones de los fármacos en el plasma se determinaron mediante HPLC-MS/MS. Nuestro estudio mostró que el tratamiento con dosis múltiples de AC tuvo efecto inductor sobre CYP1A2 rata. Sin embargo, AC tuvo efecto inhibidor significativo en las actividades de las enzimas CYP2C19 y CYP3A4 tras dosis múltiples de tratamiento con AC. Por lo tanto, es necesario tener precaución cuando AC es co-administrada con algunos sustratos del CYP en la clínica, que pueden dar lugar a interacciones hierba-droga.

KEY WORDS: Aconitine, Cytochrome P450 (CYP), Herb-drug interactions.

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