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Effect Assessment of Isoniazid on CYP450 Activity by Cocktail Approach

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***SUMMARY*. Isoniazid (INH) is a drug used as first-line medication in treatment of tuberculosis (TB). Although, the inhibition of INH on the CYP450 has been confirmed, the period of inhibition and isoforms of CYP450 are still unclear. Herein, twenty rats were involved and randomly divided into Control group and INH-group given INH 50 mg/kg.d by gavage. The activities of CYP450 isoforms were evaluated by cocktail method at day 15 and 30, which is simultaneously administered probe drugs of CYP450, phenacetin (CYP1A2), midazolam (CYP3A4), tolbutamide (CYP2C9), and omeprazole (CYP2C19). The results showed there was no obviously statistical difference in pharmacokinetic parameters for phenacetin and midazolam. The AUC, $t_{1/2}$, C_{max} of tolbutamide and omeprazole were significantly increased in INH-group compared with Control-group ($p < 0.05$) either at 15 or 30days. There was no pharmacokinetic difference of four probe drugs observed at day 15 and 30 in INH-group. In conclusion, INH may be a strong inhibitor of CYP2C9 and CYP2C19, and its inhibition effect appeared quickly but not strengthened with time.**

RESUMEN. La isoniazida (INH) es un fármaco que se utiliza como medicación de primera línea en el tratamiento de la tuberculosis (TB). Aunque la inhibición de INH en el CYP450 ha sido confirmada, el período de inhibición y las isoformas de CYP450 aún no están claros. En este trabajo, veinte ratas se dividieron aleatoriamente en grupo-Control y grupo-INH a quieren se administraron 50 mg/kg.d INH por sonda. Las actividades de las isoformas del citocromo P450 fueron evaluadas por el método de cóctel los días 15 y 30, administrando simultáneamente medicamentos sonda de CYP450: fenacetina (CYP1A2), midazolam (CYP3A4), tolbutamida (CYP2C9) y omeprazol (CYP2C19). Los resultados mostraron que no había diferencias significativas en los parámetros farmacocinéticos para la fenacetina y el midazolam. El AUC, $t_{1/2}$, $C_{máx}$ de tolbutamida y omeprazol se incrementaron significativamente en el grupo-INH en comparación con el grupo-Control ($p < 0,05$), ya sea en 15 o 30 días. No había ninguna diferencia farmacocinética de los cuatro fármacos sonda observadas entre 15 y 30 días en grupo-INH. En conclusión, INH puede ser un fuerte inhibidor de CYP2C9 y CYP2C19, y su efecto de inhibición apareció rápidamente, pero no fortalecido con el tiempo.

KEY WORDS: CYP450, Isoniazid, Pharmacokinetics, Rat.

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