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Effects of Dimethoate on the Activities of CYP450 Enzymes in Rats Using a Cocktail Approach

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***SUMMARY*. Dimethoate (DM) as a kind of high-effective organophosphorus pesticides (OPPs) is widely used in agricultural production; however, its residues in agro-products and foods have become a public health concern because of its toxicity. Our study investigated four CYP450 isoforms of liver by cocktail method while chronic exposured to DM in rats. Sprague-Dawley Rats were randomly divided into control-group, given physiological saline and DM-group, given DM 28 mg/kg·d. Two weeks later the rats were administered intragastrically with four probe drugs: phenacetin (CYP1A2), bupropion (CYP2B6), tolbutamide (CYP2C9), and metoprolol (CYP2D6). The results of pharmacokinetics parameter showed there were no obviously difference in $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, CL, T_{max} and C_{max} for phenacetin between two groups. However, in DM-group, the C_{max}, AUC(0-t) and $AUC_{(0-\infty)}$ of bupropion, tolbutamide and metoprolol were significantly decreased, V_Z/F of bupropion and metoprolol were both increased. In conclusion, DM could accelerate metabolism of bupropion, tolbutamide and metoprolol after exposured for two weeks.**

RESUMEN. El dimetoato (DM), una especie de plaguicida organofosforado altamente efectivo, es ampliamente utilizado en la producción agrícola; sin embargo, sus residuos en los productos agrícolas y los alimentos se han convertido en un problema de salud pública debido a su toxicidad . En este estudio se investigaron cuatro isoformas de CYP450 de hígado por el método de cóctel mediante exposición crónica a DM en ratas. Ratas Sprague-Dawley fueron divididas aleatoriamente en grupo control, al que se administró solución salina fisiológica, y grupo DM, al que se administró 28 mg/kg·d de DM. Dos semanas más tarde, a las ratas se les administró por vía intragástrica cuatro drogas sonda: fenacetina (CYP1A2), bupropión (CYP2B6), tolbutamida (CYP2C9) y metoprolol (CYP2D6). Los parámetros farmacocinéticos mostraron que no había diferencias en el $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, CL, T_{max} y C_{max} para la fenacetina entre los dos grupos. Sin embargo, en el grupo DM, la Cmax, AUC(0-t) y $AUC_{(0-\infty)}$ de bupropión, tolbutamida y metoprolol se redujo significativamente, en tanto que V_Z/F de bupropión y metoprolol aumentaron. En conclusión, DM podría acelerar el metabolismo de bupropión, tolbutamida y metoprolol luego de dos semanas de exposición.

KEY WORDS: CYP450, Dimethoate, Liver, Pharmacokinetics, Rat.

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