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Interaction of ergotamine with liver Cytochrome P450 3A in rats

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ABSTRACT

This study was conducted to investigate the effect of the ergot alkaloid, ergotamine (ET), on the induction of CYP3A and the interaction in vivo and in vitro with ET. Sprague-Dawley rats were treated intraperitoneally for 4 days as follows: control (injecting with 0.5 ml of only corn oil); dexamethasone treatment (injecting with 100mg/kg of dexamethasone in corn oil); and ergotamine treatment (injecting with 100mg/kg of ergotamine in corn oil). Liver tissues were collected from each group (n = 5, total of 30 rats) and liver microsomes were prepared. Cytochrome CYP3A activity was evaluated using ET and its isomer as substrates in medium containing liver microsomes and NADPH at 37℃ for 30 min. HPLC was used to measure the disappearance of the substrate and the appearance of the metabolites. Liver microsomes from rats pretreated with dexamethasone were five times more ($P < 0.01$) active than microsomes from the control animals in the biotransformation of ET (32.1 and 7.0 nM/min/mg protein, respectively; SE = 4.83) or ET-isomer (21.6 and 4.7 nM/min/mg protein, respectively; SE = 1.7079) into its corresponding ET metabolites. The ergotamine treatment produced no increase ($P > 0.05$) in activity of CYP3A when compared to the control group (5.2 vs. 7.0 nM ET/min/mg protein; SE = 4.83) or ET isomer (1.5 vs. 4.7 nM ET isomer/min/mg protein; SE = 1.70). When ketoconazole was used as specific inhibitor of CYP3A, ergotamine metabolisms were inhibited in a dose dependent fashion reaching a maximum at an inhibitor to substrate ratio of greater than one and LD50 at 0.5 nM of ketoconazole/mg protein. The data presented in this study suggest that although the ergot alkaloids ergotamine and its isomer are ideal substrates for the isozyme CYP3A, these compounds have no effect on the induction of CYP3A after 4 days of treatment.

KEYWORDS

Microsomes; Liver; Rat

Cite this paper

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