THE MAGNITUDE OF INHIBITORY DRUG INTERACTIONS IS DEPENDENT ON LIVER FUNCTIONAL STATUS

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Background and objectives: In vivo inhibition of cytochrome P450 (CYP) 1A2 by the reversible inhibitor fluvoxamine causes a reduction in the clearance of the CYP1A2 substrates lidocaine (1) and theophylline (2), which decreases in proportion to the degree of liver dysfunction. The objective of this study was to evaluate the effect of liver cirrhosis on the inhibition of the metabolic disposition of quinine, a probe of CYP3A4 (3), by the mechanism-based inhibitor erythromycin, to assess whether decreased sensitivity to metabolic inhibition in liver disease is a general characteristic, regardless of the type of CYP involved and the mechanism of the inhibitor.
Methods: The study was carried out in 10 healthy volunteers and 20 cirrhotic patients, 10 with mild (Child grade A) and 10 with severe (Child grade C) liver dysfunction, according to a randomized, double-blind, 2-phase, crossover design. In one phase all participants received placebo for 3 days; in the other phase they received three 600-mg erythromycin doses, 8 hours apart, for 3 days. On day 2, 500 mg of quinine were administered orally 1 hour after the morning erythromycin dose. Concentrations of quinine and its metabolite 3-OH-quinine were measured in plasma and urine up to 48 hours.
Results: The effects of erythromycin co-administration were dependent on liver function. Inhibition of quinine clearance decreased from about 40% in healthy subjects, to 33% in patients with mild liver dysfunction, with proportional increases in terminal half-lives, whereas virtually no effect was produced in patients with severe liver dysfunction. Analogous effects were observed on the formation clearance of 3-OH-quinine.
Conclusions: The effect of liver dysfunction on the inhibition of CYP-mediated drug metabolism is a general phenomenon, independent of the type of CYP involved and the mechanism of the metabolic inhibitor. Therefore, for any CYP substrate, the clinical consequences of enzyme inhibition are expected to become less and less important as liver function worsens.

References:
1. Orlando R, Piccoli P, De Martin S, Padrini R, Floreani M, Palatini P. (2004) Clin Pharmacol Ther 75: 80-88.
2. Orlando R, Padrini R, Perazzi M, De Martin S, Piccoli P, Palatini P. (2006) Clin Pharmacol Ther 79 (5): 489-499.
3. Wanwimorluk S, Paine MF, Pusek SN, Watkins PB. (2002) Br J Clin Pharmacol 54: 643-651.