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EFFECT OF THE CYP 3A4 INHIBITOR ERYTHROMYCIN ON THE PHARMACOKINETICS OF LIGNOCAINE AND ITS PHARMACOLOGICALLY ACTIVE METABOLITES IN SUBJECTS WITH NORMAL AND IMPAIRED LIVER FUNCTION

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Aims. The objectives of this study were: a) to evaluate the effect of a cytochrome P 450 (CYP) 3A4 inhibitor, erythromycin, on the pharmacokinetics of intravenous lignocaine and its two pharmacologically active metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX); b) to assess whether the effects of the erythromycin inhibitory action on lignocaine clearance and the results of the MEGX liver function test depend on the liver functional status; c) to determine the effects of both moderate and severe liver dysfunction on the disposition kinetics of lignocaine.
Methods: The study was carried out on 10 healthy volunteers, 10 Child's class A and 10 Child's class C cirrhotic patients, according to a double-blind, randomized, 2-way crossover design. On day 1 of the investigation, all subjects received three oral doses of erythromycin (600 mg of the ethylsuccinate ester) or placebo, and two further doses on day 2. One hour after the fourth dose, subjects were given 1 mg kg^{-1} lignocaine intravenously. Timed plasma samples were then obtained until 12 h for determination of the concentrations of lignocaine, MEGX and GX.
Results. Erythromycin caused statistically significant, although limited, modifications of lignocaine and MEGX pharmacokinetic parameters. In healthy volunteers, lignocaine clearance was decreased from 9.93 to 8.15 ml kg^{-1} min^{-1} [mean % ratio (95% CI), 82 (65-98)] and the half-life was prolonged from 2.23 to 2.80 h [mean % ratio (95% CI), 130 (109-151)]; the MEGX area under the concentration-time curve from 0 to 12 h was increased from 665 to 886 ng ml^{-1} h [mean % ratio (95% CI), 129 (102-156)]. Quantitatively similar modifications were observed in the two cirrhotic groups. GX levels were lowered in all study groups, although not to statistically significant extents. Erythromycin coadministration caused no appreciable interference with the results of the MEGX test. Only in patients with Child's grade C liver cirrhosis were lignocaine kinetic parameters significantly altered with respect to healthy volunteers: clearance was about halved, steady-state volume of distribution was increased, and terminal half-life was more than doubled.
Conclusions. Although erythromycin only modestly decreases lignocaine clearance, it causes a concomitant elevation of the levels of its pharmacologically active metabolite MEGX. A pharmacodynamic study following lignocaine infusion to steady-state appears necessary to assess the actual clinical relevance of these combined effects. The degree of liver dysfunction has no influence on the extent of the erythromycin-lignocaine interaction, whereas it markedly influences the extent of the changes in lignocaine pharmacokinetics. These changes indicate that no dose adjustment is needed in patients with moderate liver cirrhosis, whereas the lignocaine dose should be halved in patients with severe cirrhosis.