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Influence of ritonavir on the pharmacokinetics and pharmacodynamics of loperamide

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Loperamide, a synthetic opioid drug widely used as an over-the-counter (OTC) antidiarrhoeal agent, is the drug of choice in the treatment of both HIV-induced and protease inhibitor-associated diarrhea. The absence of marked central opioid effects like respiratory depression or analgesia has been attributed to its low availability in blood and the poor penetration of the blood brain barrier (BBB). High pre-systemic metabolism and the function of the intestinal efflux pump P-glycoprotein (Pgp) result in low systemic plasma and brain concentrations. Compared to mice of the Pgp wild type (*mdr1a+/+*), loperamide concentration was significantly increased in blood and tissues (e.g. brain) in knock-out mice (*mdr1a-/-*) presenting a defective *MDR1* gene. Accordingly, the modulation of Pgp at the BBB increases brain loperamide penetration.

This thesis reports the influence of ritonavir - a potent P-glycoprotein and CYP3A inhibitor - on the pharmacokinetics and pharmacodynamics of loperamide. We performed a randomized, double-blind, placebo-controlled cross-over study in 12 healthy individuals after a single high oral dose of loperamide (8 capsules of Imodium[®] 2 mg, Janssen-Cilag, Germany), with and without ritonavir (6 capsules of Norvir[®] 100 mg, Abbott Laboratories).

Venous blood samples (7.5 ml) were drawn before loperamide administration and up to 72 hours after dosing. Fractional urine was collected in four intervals. A selective and very sensitive LC/MS/MS method was used for the determination of loperamide and its two demethylated metabolites, desmethylloperamide and didesmethylloperamide, in plasma and urine. Potential opioid effects were measured by means of the transcutaneous pCO₂, pO₂, pupil diameter, and the cold pressor test for pain threshold and pain sensitivity assessment.

Ritonavir plasma concentrations were determined by LC/MS/MS after liquid/liquid extraction.

In comparison to placebo a major pharmacokinetic interaction between loperamide and ritonavir was observed. After concomitant ritonavir administration, plasma loperamide concentration increased significantly (C_{\max} : 12.1 ± 4.9 pmol/mL vs. 8.3 ± 4.1 pmol/mL; $p < 0.01$). The area under the curve (AUC) of loperamide increased about 3-fold during ritonavir treatment and therefore the apparent oral clearance decreased by a factor 3. The renal clearance, however, remained unchanged during ritonavir compared to placebo.

There was only a slight increase of the AUC of the main metabolite desmethylloperamide, and the metabolic ratio for the primary metabolic step of loperamide was significantly increased during ritonavir. This interaction is probably a result of the inhibition of CYP metabolism. The sum of total amounts of loperamide and metabolites excreted into urine was not different in both phases suggesting that intestinal Pgp could not have played an important role for the increase in loperamide bioavailability. No central pharmacodynamic effects of loperamide were observed after placebo and ritonavir, suggesting that brain concentrations of loperamide necessary to elicit opioid effects have not been reached.

In view of the results of this study we believe it is safe to treat this very common side effect of ritonavir with loperamide, although we performed only a single-dose study and repetitive administration of ritonavir might alter the situation.

In conclusion, we observed a significant increase of loperamide bioavailability after oral administration of ritonavir, which is likely caused by substantial metabolic inhibition. The fact that no evidence was found for significant inhibition of drug transport systems or altered access of loperamide to the brain suggests that the combination of loperamide with ritonavir does not pose particular risks to the patient. Because the amount of active parent compound was substantially increased and because the site of antidiarrheal action is outside the CNS compartment, it appears likely that loperamide will be sufficiently effective even when reduced doses are administered. This, however, will have to be confirmed in studies in patients with diarrhea.