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Letters to the Editor

Food consumption, cytochrome P450 3A4 (CYP3A4) presystemic inhibitors, and bioavailability of saquinavir

To the Editor:

It is accepted that the low bioavailability of orally administered saquinavir –SQV– (about 4% for the hard gelatin capsule or tablets –HGCT–, and about 12% for the soft gelatin capsule –SGC– when it is taken with food), is due to an incomplete intestinal absorption and to an extensive first-pass metabolism by cytochrome P450 3A4 (CYP3A4) in the gut and liver[1]. As well, P-glycoprotein (P-gp), an efflux pump located on the apical membrane of enterocytes, might contribute to this effect. However, the effect of P-gp on the bioavailability of SQV is contradictory to the results of a recent study of the effect of quercetin (an *in vivo* inhibitor of P-gp) on the plasma concentrations of SQV, in which coadministration of quercetin to 10 healthy adults did not increase the bioavailability of saquinavir[2].

It is also accepted that simultaneous food ingestion increases the bioavailability and the therapeutic effect of SQV[1]. Recent evidence shows that food increases the bioavailability of SQV by a different mechanism from an effect on gastric pH[3]. Thus, the increase on the plasma concentrations of SQV by food is probably due to that: a) a food-induced augment in SQV solubility; and b) a food-induced raise in the hepatic and portal vein blood flow, which may reduce the first-pass hepatic metabolism effect on bioavailability of SQV[4]. In addition, coadmistration of CYP3A4 intestinal and hepatic inhibitors resulting in an increase of plasma concentrations of SQV[1].

Food consumption and bioavailability of saquinavir. Drugs absorbed into mucosal capillaries of the intestine (e. g. SQV) are delivered to the liver through the hepatic portal vein, so a raise in the hepatic and portal vein blood flow could be associated to a significant increase of the hepatic entry rate, to a decrease of hepatic presystemic clearance, and to an increase of bioavailability of drugs. Therefore, the increase of bioavailability of SQV by food without relation to changes in gastric pH caused by ranitidine[3] is probably due to that food augments SQV solubility and reduces hepatic firs-pass effect on SQV.

Cytochrome P450 3A4 (CYP3A4) presystemic inhibitors and bioavailability of saquinavir. Drugs with low oral bioavailability due to effect of CYP3A (e. g. SQV) are very susceptible to presystemic enzymatic inhibition processes, which is reflecting in a markedly increase in their plasma concentrations without changes in the elimination half-life. For instance, ritonavir 100 mg twice a day (a potent inhibitor of CYP3A) when is coadministered with SQV 1,000 mg twice a day results in an increase by 300-800% in SQV area under the concentration-time curve (AUC) compared with SQV without ritonavir[1]. So ritonavir acts as a pharmacokinetic enhancer by inhibiting hepatic and intestinal CYP3A4 isoenzymes. SQV increases in AUC and maximum observed plasma concentration (C_{max}) in presence of different inhibitors of CYP3A4 are shown in table I.

Moreover, it could be hypothesized that: a) the improvement of bioavailability of SQV, when is coadministered with ranitidine[3], cimetidine[5], and omeprazole with ritonavir[6], is due to a diminish of presystemic clearance associated to the coadministration of these drugs, which may reduce the CYP3A isoenzymes activity and effect on hepatic and intestinal presystemic clearance, although in lesser magnitude than ritonavir; and b) CYP3A enzymes in liver (not in gut-wall) are mainly determinant of low bioavailability of SQV, an assumption that is according to recently published results indicating that the contribution of intestinal CYP3A4 in the low bioavailability of SQV is lower than what has been previously assumed[7], and the contribution of P-gp is this effect is conflicting[2].

Table I. Increases for saquinavir in AUC and C_{max} in presence of different inhibitors of CYP3A4

Dosage for saquinavir HGCT or SGC	*Coadministered inhibitor*	*N*	*% Increase for saquinavir*	
			AUC (95% CI)	*C_{max} (95% CI)*
SGC 1,200 mg tid for 7 days	Clarithromycine[1] 500 mg bid for 7 days	12 V	177 (108-269)	187 (105-300)
SGC 1,200 bid for 13 days	Cimetidine[6] 400 mg bid for 13 days	12 V	120 (46-32)	153 (35-962)
Saquinavir SGC/ritonavir 1,000/100 mg bid for 15 days	Omeprazol[7] 40 mg daily on day 11-15	18 V	82 (37-144)	75 (31-134)
HGCT 1,000 mg bid	Ritonavir[1] 100 bid	24 P	176	153
HGCT 600 mg daily for 1 day	Ranitidine[3] 150 mg evening before and 150 mg on the day study	12 V	87	112
SGC 1,200 mg tib	Ketoconazole[1] 400 mg daily	12 V	190	171
SGC 600 mg daily for 1 day	Grapefruit juice 400 mL for 1 day	8 V	50	93

HGCT: hard gelatin capsules or tables; SGC: soft gelatin capsules; AUC: area under the concentration-time curve; C_{max}: maximum observed plasma concentration; V: voluntaries; P: patients; Bid: twice a day; Tid: three times a day.

Besides, food, ranitidine[3] (maybe as others CYP3A inhibitors shown in table I) coadministration increase significantly the bioavailability of oral SQV by reducing presystemic clearance of SQV independently of change on gastric pH[3], because: a) food augments SQV solubility and reduces first-pass hepatic via increasing the splanchic-hepatic and portal vein blood flow and increasing the rate of drug delivery to the liver; and b) ranitidine enhances this effect via reducing presystemic clearance, mainly hepatic. This kind of drug interaction looks like an interesting therapeutic approach, which could be assessed in clinical trial studies designed to determinate the benefits and risk of this plausible boosting effect of others CYP3A inhibitors different than ritonavir, in which food intake control must be carried out during the entire study and the use of one-daily, 1,600 mg, or twice-daily, 1,000 mg, SQV hard-gelatin capsules or tablets, could be tested, a formulation which is stable a room temperature and has better economic access than soft-gelatin capsules[8].

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