EFFECT OF HERBAL BIOENHANCERS ON SAQUINAVIR IN HUMAN Caco-2 CELL MONOLAYERS AND PHARMACOKINETICS IN RATS

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ABSTRACT

Purpose: Membrane-bound efflux transporters, such as P-glycoprotein (P-gp), may limit the entry and distribution of HIV-1 protease inhibitors saquinavir (SQN) and may be the reason for low and variable oral bioavailability. The purpose is to investigate *in vitro* mechanisms of gastrointestinal absorption of saquinavir mesylate, in presence and absence of herbal bioenhancers using human Caco-2 cells. To investigate the correlation of Caco-2 out come with animal pharmacokinetic studies for bioavailability enhancement.

Method: Confluent epithelial layers of human Caco-2 cells mimicking the intestinal barrier. Pharmacokinetic studies using Male Sprague-Dawley (SD) rats.

Results: Saquinavir showed polarized transport through Caco-2 cell monolayers in the basolateral to apical direction (secretory pathway). Saquinavir has shown an efflux ratio (B-A / A-B) of > 25 and reduced to ~ 2 when saquinavir co-administered with herbal bioenhancers. Active efflux was temperature dependent, saturable and inhibited by verapamil. In presence of herbal bioenhancers the permeability of saquinavir was increased. Oral bioavailability was also increased in rat by ~ 10 folds.

Conclusions: Saquinavir is a substrate for an efflux mechanism in the gut, most likely P-glycoprotein, which acts as a counter-transporter for the drug. This may partially account for the low and variable oral bioavailability of saquinavir. After co-administration with herbal enhancers the permeability of saquinavir was increased. These herbal bioenhancers may be acting as an inhibitor of P-gp and may help by improving the oral bioavailability of saquinavir.

KEY WORDS: Saquinavir; Piperine, Gallic acid; Cinnamic acid; Herbal bioenhancers; Caco-2 cells; Pharmacokinetics