Gastrointestinal Dissolution, Supersaturation and Precipitation of the Weak Base Indinavir Sulfate in Healthy Volunteers: Fasted State, Fed State and Concomitant Proton Pump Inhibitor Use

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Purpose

This study investigated the intraluminal dissolution, supersaturation and precipitation behaviour of the weakly basic BCS Class II drug indinavir. Several studies have reported a reduction in the oral bio-availability of indinavir when given with a high-fat meal or in case of concomitant proton pump inhibitor (PPI) use. This study aimed to identify the underlying mechanisms responsible for the reduced bioavailability by investigating the intraluminal events prior to absorption.

Methods

Five healthy volunteers were recruited into a cross-over study, investigating indinavir behavior in fasted state, fed state and fasted state with concomitant PPI use (esomeprazole). The fed state was simulated by administrating a liquid meal (Ensure® Plus). For the PPI condition, volunteers were asked to follow a regime of one Nexium® tablet a day, starting 2 days prior to the study and taking the last tablet the morning of the study. In each condition, a Crixivan® capsule (indinavir sulfate) was orally administered with 240 mL of water. Volunteers were intubated through the mouth or nose with two double-lumen polyvinyl catheters. Gastric and duodenal fluids were aspirated through the catheters during 3 hours. The total amount of indinavir (solid + solute) was evaluated by direct dilution of the aspirates. Dissolved indinavir concentrations were assessed by diluting the supernatant following a centrifugation step. In order to evaluate indinavir supersaturation, the equilibrium solubility of indinavir was determined in all duodenal aspirates and in the gastric aspirates from the PPI condition using the shake-flask method. The bioaccessible fraction of indinavir was determined by assessing indinavir permeation from human aspirates across cellulose membrane strips. All analysis were performed on a UPLC-MS system.

Results

In a fasted stomach, a nearly complete dissolution of indinavir was observed (90 ±3.1%). Concomitant PPI use resulted in a smaller fraction of total indinavir being dissolved (58 ±23.9%). In the PPI state, drug release from the Crixivan® capsule was altered as lower total concentrations were observed compared to the fasted state. In fed state conditions a similar fraction of indinavir dissolved as in the fasted state (83 ±12.4%), though drug release from the capsule was delayed and more gradual. Gastric supersaturation was only relevant in a neutral stomach environment. Regardless of dosing conditions, less indinavir was dissolved in the duodenum compared to the stomach. Duodenal supersaturation was observed in all three testing conditions. The highest degrees of duodenal supersaturation (6.5 ±5.9) were observed in the fasted state. The average duodenal indinavir exposure decreased with 56% in the PPI condition compared to the fasted state. The PPI-induced elevation of gastric pH causes a reduced dissolution and/or increased precipitation of indinavir in the stomach, resulting in a reduced intraduodenal exposure. Most likely, this explains the reported reduction in systemic exposure. In a fed state conditions, duodenal indinavir exposure was still ongoing after three hours but already reached 70% of the fasted state exposure (on average). Thus, it seems unlikely that reports on reduced systemic exposure in the fed state can be explained by a decreased duodenal exposure. Based on a 2-hour permeation experiment, the bio-accessible fraction of indinavir appeared to be 2.6-fold lower in fed state fluids compared to fasted state fluids. The ingestion of a liquid meal will increase intraluminal concentrations of solubility-enhancing compounds (bile salts, phospholipids,…) which may hamper indinavir absorption through micellar entrapment.

Conclusion

Our data indicates that the stomach’s pH plays an important role in the reduction of indinavir’s bioavailability. Concomitant PPI administration resulted in less gastric indinavir to be dissolved, which in turn resulted in a reduced duodenal exposure. In this PPI condition, gastric supersaturation was observed in all volunteers. Duodenal supersaturation was observed in all volunteers, irrespective of dosing conditions. Furthermore, this study confirms that a reduced postprandial bioavailability of indinavir is caused by micellar entrapment. Overall, by studying the intraluminal behaviour of the weak base indinavir, new insights were gained into the underlying mechanisms of earlier reported interactions.

Acknowledgments

This study was supported by the Research Foundation – Flanders (FWO) (PhD fellowship 11Z2615N and Research grant No. G.0769.14N). This work has received support from the Innovative Medicines Initiative Joint Undertaking (http://www.imi.europa.eu) under Grant Agreement No. 115369, resources of which are composed of financial contribution from the European Union’s Seventh Framework Program and EFPIA companies' in kind contribution.