Regional In Vivo Dissolution of Immediate Release Ibuprofen in Human Gastrointestinal Tract and Its Relationship to Luminal pH, GI Motility, and Systemic Absorption


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Purpose
Extensive information on in vitro drug dissolution is required for approval of new drugs, but the ability to measure in vivo dissolution and bioavailability is limited. Drug dose, dissolution, gastric emptying, gastrointestinal (GI) motility, solubility, and intestinal content influence systemic drug absorption. Regional GI tract in vivo drug dissolution must be better understood to refine in vitro methodologies to predict drug bioavailability. We aimed to quantify plasma and GI luminal concentrations of the highly absorbable drug ibuprofen in different regions of the stomach and small bowel in relation to fasting vs. fed status and to luminal pH, GI motility, and fluid dynamics using a novel multi-lumen aspiration catheter in healthy humans.

Methods
Specialized manometry catheters with 4 aspiration ports were orally inserted with fluoroscopic positioning of collection sites in the stomach, duodenum, and jejunum (N=16 procedures in 11 healthy humans). Subjects were randomized to fasting or fed (Pulmocare, Abbott Nutrition, 710 cal before drug dosing) conditions and then ingested immediate release ibuprofen 800 mg tablet with non-absorbable phenol red marker in 250 mL of water. GI fluid samples were collected x 7 h and venous blood was obtained x 28 h post dosing. GI fluid and plasma ibuprofen concentrations were measured by LC-MS/MS and were related to GI fluid pH levels.

Results
Ibuprofen was detected immediately after ingestion in the stomach under fasting and fed conditions; overall gastric concentrations remained higher during the fed vs. fasting state until 7 h after oral dosing (Figure 1). Duodenal and jejunal ibuprofen concentrations increased after gastric levels were detected and persisted x 7 h. Ibuprofen plasma levels were higher during fasting vs. after feeding x 8 h and remained detectable x 28 h under both conditions (Figure 2). Gastric pH increased to near neutrality after feeding before decreasing to pH 2 at 7 h; higher pH levels related to greater gastric ibuprofen levels but lower plasma levels during the fed period. Finally, analysis of GI motility in the fed state showed Cmax occurring shortly after Phase III MMCs (peak GI motility) events.

Conclusion
This novel in vivo methodology involving time-dependent fluid sampling in several sites in the stomach and small intestine was employed to characterize dissolution, distribution in different regions of the upper GI tract, and absorption of immediate release ibuprofen in healthy human volunteers. Ongoing manometric studies and determinations of gastric and small bowel transit using phenol red measurements showed a correlation of ibuprofen Cmax with GI motility. Taken together, these data show the importance of GI motility, gastric emptying, pH, and fed vs. fasting state in Cmax values and overall drug efficacy. These observations will be useful to validate current in vitro dissolution methods. We expect this approach will support computational and mathematical modeling efforts to develop drug product optimization processes that may maximize oral drug safety and efficacy.