Direct Measurement of Mesalamine Dissolution in Human Gastrointestinal Tract

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**Purpose**
Locally-acting gastrointestinal (GI) drugs used to treat ulcerative colitis, such as mesalamine, must achieve adequate concentrations in the gut to ensure therapeutic efficacy. Different formulations of mesalamine have distinct clinical effects which may result from region-specific release profiles in the GI tract. The purpose of this study is to directly measure drug dissolution and regional concentrations of mesalamine in the stomach and different small bowel segments, after administration of three modified release mesalamine products: Pentasa, Apriso, and Lialda.

**Methods**
We employed a novel multi-tube aspiration catheter to (i) quantify mesalamine concentrations in different gut regions after ingestion of 3 formulations: Pentasa, Apriso, Lialda and (ii) correlate drug levels in GI fluid, plasma, and feces to define distinct bioavailability and pharmacokinetic profiles of each formulation. Healthy subjects underwent oral intubation of a 3 meter long, 4-lumen catheter to a mean depth of 208 cm with fluoroscopic positioning of aspiration ports in the stomach, duodenum, jejunum, and distal jejunum/proximal ileum. Subjects ingested Pentasa (1000 mg), Apriso (1125 mg), or Lialda (1200 mg). GI fluid samples (1 mL) were withdrawn from each port hourly x 7 h. Blood and feces were collected for up to 96 h. Luminal fluid pH was measured and GI fluid, plasma, and fecal concentrations of mesalamine (5-aminosalicylic acid, 5-ASA) and its primary metabolite (N-acetyl-5-aminosalicylic acid, Ac-5-ASA) were quantified by LC-MS. In vivo dissolution and pharmacokinetics of mesalamine were calculated.

**Results**
The average mesalamine and primary metabolite concentrations in different regions of the GI tract were quantified. Three modified release formulations demonstrate different concentrations in the stomach and small intestine. Pentasa releases 5-ASA throughout the GI tract, from stomach to distal jejunum, from 2 to 7 hours. Apriso starts to release 5-ASA from duodenum to jejunum from 4 to 7 hours. Lialda has minimal release of 5-ASA from stomach to jejunum from 1 to 7 hours, with a small amount released from jejunum. Luminal 5-ASA and Ac-5-ASA concentrations were at least 100-fold lower in the distal jejunum after Lialda compared to the other formulations, consistent with a more distal release profile for this preparation. The total average accumulation of mesalamine and its primary metabolite recovered in feces at the different collection times was also quantified. All three MR formulations have 5-ASA remaining in feces, largely unreleased and undissolved. Although Lialda has much larger amount of 5-ASA in feces than Pentasa and Apriso, all three formulations have similar levels of fecal Ac-5-ASA, suggesting similar levels of local release and dissolution in colon.

**Conclusion**
The three mesalamine modified release formulations exhibit distinct luminal release profiles which likely result from release differences between different formulations as well as intra- and inter-individual variability in regional gut transit. Taken together, these differences may explain the disparate clinical effects of the different mesalamine formulations. These data provide a foundation for future investigations to better understand the variable clinical responsiveness to different formulations of locally-acting drugs. This research was supported by FDA grants HHSF223201000082C and HHSF223201300460A.