A Novel Method to Investigate Local Concentrations of Mesalamine in the Gastrointestinal Tract of Healthy Volunteers

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INTRODUCTION

- Locally-acting drugs in the gut must achieve adequate gastrointestinal (GI) concentrations to ensure therapeutic efficacy, but plasma levels may not parallel GI concentrations.
- The standard bioequivalence (BE) study methods using plasma pharmacokinetics cannot be used to ensure BE for GI locally-acting and targeted delivery drugs (1,2). To overcome these challenges, the FDA has launched critical paths for BE of locally-acting GI products (3).
- Mesalamine is a locally-acting salicylate commonly used to treat ulcerative colitis (UC). Since the pathological changes of UC are in distal regions of the GI tract, extended release formulations are used to maintain high local drug concentrations in this region.
- There are many different formulations of extended release mesalamine on the market. There is no data to support that one formulation is superior to another (4). Different formulations have distinct drug release mechanisms, and thus have different local drug concentrations, absorption profiles, and systemic drug concentration. Therefore, different formulations are not interchangeable from a BE or therapeutic efficacy standpoint (5).

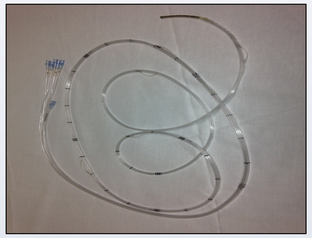
SPECIFIC AIMS

- Measure *in vivo* drug release, drug dissolution, and local drug concentration in human GI tract of 3 mesalamine products: Pentasa, Apriso, and Lialda.
- Measure GI fluid, plasma, urine, and fecal concentrations of mesalamine and its inactive metabolite N-acetyl-mesalamine.
- Correlate GI fluid, plasma, urine, and fecal levels to define distinct bioavailability and pharmacokinetic profiles for these formulations.

METHODS

- Healthy subjects underwent oral intubation of a 3 meter long, 4-lumen catheter to a mean depth of 208.2 cm.
- Fluoroscopic positioning of aspiration ports in the stomach, duodenum, jejunum, and distal jejunum/proximal ileum was performed.
- 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- GI fluid samples (1 mL) were withdrawn from each port hourly x 7 h. Blood, urine, and feces were collected for 72 h.
- Luminal fluid pH was measured and GI fluid, urine, and fecal mesalamine concentrations were quantified by LC-MS/MS. *In vivo* dissolution and pharmacokinetics of mesalamine were calculated.

Figure 1. Photo of Multi-Lumen GI Tube



Port Locations:
1. Distal Jejunum/ Proximal Ileum
2. Proximal Jejunum
3. Duodenum
4. Antrum

Figure 2. GI Tube Placement

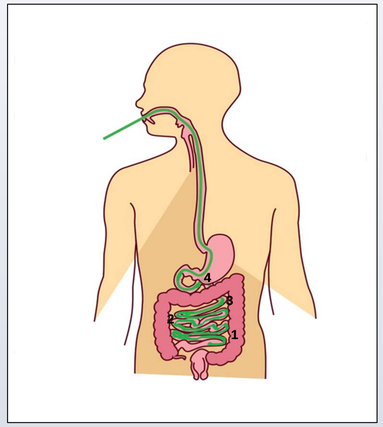
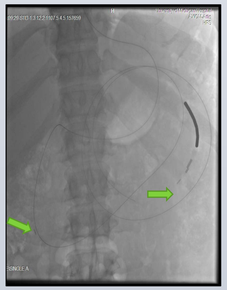
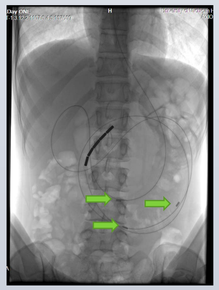


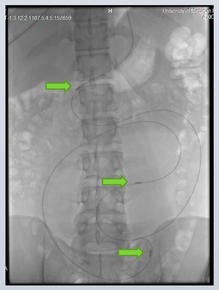
Figure 3. Fluoroscopic Photos of Final GI Tube Placement



➢ Two aspiration ports located in the Duodenum and Mid-Jejunum.



➢ Three aspiration ports located in the Antrum, Proximal Jejunum, and Distal Jejunum.



➢ Three aspiration ports located in the Antrum, Proximal Jejunum, and Distal Jejunum.

RESULTS

- Representative GI fluid mesalamine concentrations in relation to time and local pH, and cumulative urine and fecal mesalamine excretion are shown in **Table 1** from one subject who received all 3 formulations.
- Peak plasma mesalamine levels were 380 ng/mL for Pentasa at 8 h (50-500 fold less than GI fluid levels) and 800 ng/mL for Apriso at 4 h (20-1250 fold less than GI fluid levels). Mesalamine release from Lialda was not detected in GI fluids. In this subject, Cmax and AUC were highest for Lialda and lowest for Pentasa.
- **Table 2** shows GI fluid, urine, and fecal mesalamine levels for 3 subjects who received Pentasa. Peak plasma mesalamine levels ranged from 337-1940 ng/mL for Pentasa at 2-8 h (30-500 fold less than GI fluid levels).

Table 1. Mesalamine release from three formulations individually dosed in one subject

Formulation	Time After Ingestion	GI Fluid Mesalamine Concentration	Location	GI Fluid pH	72 hr Urine Mesalamine Excretion	72 hr Fecal Mesalamine Excretion
Pentasa	1 to 4 hours	60-190 ug/mL	Stomach	1.9-2.2	0.9 mg	140.4 mg
	1 to 7 hours	20-200 ug/mL	Mid-jejunum	6.15-6.52		
Apriso	4 to 6 hours	5-42 ug/mL	Stomach	1.9-2.76	6.7 mg	112.1 mg
	6 to 7 hours	200-1000 ug/mL	Duodenum	6.6-6.9		
	6 to 7 hours	50-700 ug/mL	Proximal jejunum	6.53-6.7		
	7 hours	16 ug/mL	Distal jejunum	6.4		
Lialda	up to 7 hours	not detected	---	---	15.4 mg	306.5 mg

Table 2. Average mesalamine release from one formulation individually dosed in three subjects

Formulation	Time After Ingestion	GI Fluid Mesalamine Concentration	Location	GI Fluid pH	72 hr Urine Mesalamine Excretion	72 hr Fecal Mesalamine Excretion
Pentasa	1 to 7 hours	20-1200 ug/mL	Stomach	1.2-6.13	199 mg	203 mg
	3 to 7 hours	40-400 ug/mL	Duodenum	5.25-6.69		
	2 to 7 hours	10-650 ug/mL	Jejunum	3.9-6.7		
	4 to 7 hours	10-160 ug/mL	Proximal Ileum	5.6-6.2		

CONCLUSIONS

- This study employed a novel multi-port luminal aspiration catheter for collection of GI fluid samples to quantify regional drug concentrations in the gut.
- As an example of the utility of this methodology, distinct and variable luminal release profiles were demonstrated for 3 different mesalamine formulations after ingestion which were correlated with plasma, urine, and fecal levels to characterize bioavailability and pharmacokinetic properties.
- 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 grant #HHSF223201000082C.

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