Contrasting Regional Availability of Different Mesalamine Products in the Gastrointestinal Tract in Healthy Humans Using a Novel Multi-Port Luminal Aspiration System and Correlation With Systemic Absorption

Ann F. Fioritto,[1] Jason R. Baker,[2] Kristen Collins,[2] Bo Wen, Ph.D.,[1] Ying Wang, Ph.D.,[1] Ruijuan Luo, Ph.D.,[1] Barry Bleske, Pharm.D.,[1] Mark Johnson,[1] Mark Koenigsknecht, Ph.D.,[1] William L. Hasler, M.D.,[2] Duxin Sun, Ph.D.[1]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109, USA

[2]Department of Internal Medicine, Division of Gastroenterology, University of Michigan Health System, Ann Arbor, MI 48109, USA

BACKGROUND

- 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 gastrointestinal (GI) tract, therapeutic efficacy requires maintenance of high local drug concentrations in this region.
- When mesalamine is released and dissolution occurs in the GI tract, mesalamine rapidly crosses intestinal epithelial cells and is metabolized into inactive metabolite by GI mucosa. Therefore, the standard bioequivalence (BE) study methods using plasma pharmacokinetics cannot be used to ensure BE of different mesalamine products, and currently there are no generic mesalamine products available. To overcome these challenges, the FDA has launched critical paths for BE of GI locally-acting products (1).
- 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 (2). 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 (3).

AIM OF STUDY

- There are no accurate computational models to predict *in vivo* performance of drugs acting locally in the gut or by extended-release. Such models are needed to define bioequivalence to ensure future drug safety and efficacy.
- We previously showed abilities of novel catheters with 4 aspiration ports – gastric and proximal to distal small bowel – to measure regional mesalamine levels in humans.
- In this study, we expanded this initial proof of concept to contrast local release and absorption characteristics of 3 commercially-available extended-release mesalamine products in normal subjects.

METHODS

- Healthy human subjects underwent oral placement of 3 meter 4-lumen catheters.
  - 8 subjects: 6 male, 2 female; mean age 35; mean BMI 25.0
  - Race: 7 Caucasian, 1 Asian; Ethnicity: 7 not Hispanic/Latino, 1 Hispanic/Latino
  - n=11 procedures; mean catheter depth 164 cm
- Fluoroscopic positioning of aspiration ports (**Figure 1**) in the stomach (pH 1.51-2.74), duodenum/proximal jejunum, mid-jejunum, and distal jejunum/ileum (intestinal pH 5.02-7.15) was performed.
- Gastrointestinal fluid samples (1 mL) were drawn from each port hourly x 7 h after administration of oral Pentasa (1000 mg), Apriso (1125 mg), or Lialda (1200 mg). Plasma was obtained x 96 h after taking the 3 drugs.
- Samples were analyzed for mesalamine (5-aminosalicylic acid, 5-ASA) and its metabolite (N-acetyl-5-aminosalicylic acid, Ac-5-ASA).

Figure 1. Fluoroscopic Photos of Gastrointestinal Tube with Aspiration Ports

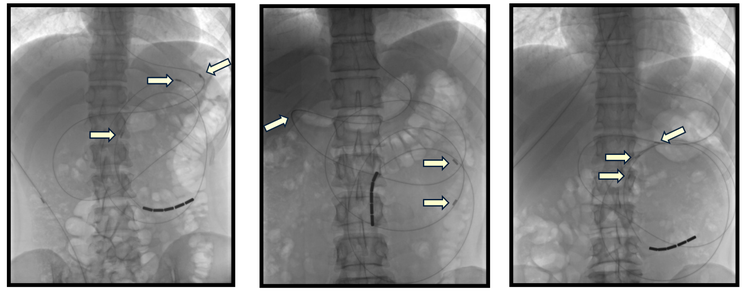
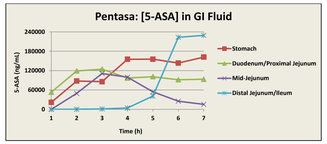
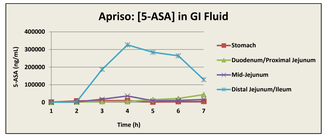


Figure 2. GI Fluid 5-ASA Levels After Ingesting 3 Oral Mesalamine Preparations





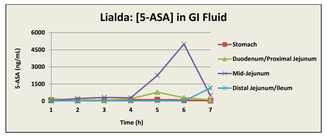
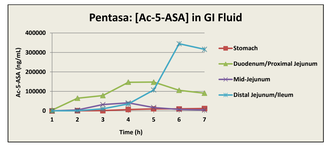
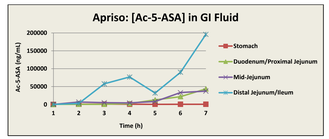


Figure 3. GI Fluid Ac-5-ASA Levels After Ingesting 3 Oral Mesalamine Preparations





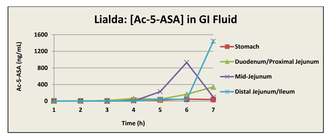


Table 1. Plasma 5-ASA and Ac-5-ASA Levels After Ingesting 3 Oral Mesalamine Preparations

Parameter	Pentasa		Apriso		Lialda	
	5-ASA	Ac-5-ASA	5-ASA	Ac-5-ASA	5-ASA	Ac-5-ASA
Mean time to initial plasma increase	0.7±0.3 h	0.5±0.0 h	3.0±1.2 h	1.4±0.8 h	6.5±1.9 h	5.3±1.5 h
Mean time to peak plasma level	5.7±4.5 h	8.7±2.3 h	6.3±0.5 h	6.5±0.6 h	11.5±1.0 h	14.5±6.4 h
Peak plasma level (ng/mL)	240±150	1270±233	1499±1016	3622±2784	523±411	1284±461

RESULTS

- Measurable GI fluid 5-ASA levels were noted within 1 h after ingesting all 3 mesalamine products; Ac-5-ASA levels increased after 1 h for Pentasa and Apriso and 3 h for Lialda.
- Prominent 5-ASA and Ac-5-ASA release after Pentasa was observed at all GI sites, including gastric. Gastric 5-ASA levels were >170-fold higher after Pentasa vs. Lialda.
- Peak small bowel GI 5-ASA (**Figure 2**) and Ac-5-ASA (**Figure 3**) levels were 15 to 1000+ fold lower for Lialda vs. Pentasa and Apriso, emphasizing greater colon release for Lialda.
- In addition, peak GI Ac-5-ASA levels were seen earlier with Pentasa (4.0+2.0 h) vs. Apriso (7.0+0.0 h) and Lialda (6.0+1.4 h).
- Plasma 5-ASA and Ac-5-ASA levels were lower vs. GI fluids consistent with luminal actions (**Table 1**).
- As in GI fluids, plasma 5-ASA and Ac-5-ASA appeared earliest for Pentasa and latest for Lialda.
- Peak plasma levels occurred 12 h after Lialda, reflecting again mostly colon absorption.

CONCLUSIONS

- Using novel multiport catheters to aspirate GI fluids for regional drug release analysis, we showed variable time-dependent appearance and absorption of 3 mesalamine products.
- Release of 5-ASA and its metabolite occurred earliest and most proximally with Pentasa, including gastric release. Small bowel release and absorption were slower and more distal with Apriso and were minimal with Lialda.
- Such innovative *in vivo* techniques will be used to validate *in vitro* dissolution methods and support computational models for future processes that are applicable to developing luminally-acting and extended-release drugs.

This research was funded by FDA grants HHSF223201000082C and HHSF223201300460A.

REFERENCES

1. Lionberger RA. FDA critical path initiatives: opportunities for generic drug development. AAPS J. 2008;10(1):103-9. doi: 10.1208/s12248-008-9010-2.
2. Baker DE. Therapeutic equivalence of mesalamine products. Rev Gastroenterol Disord. 2004;4(1):25-8.
3. Forbes A, Cartwright A, Marchant S, McIntyre P, Newton M. Review article: Oral, modified-release mesalazine formulations--proprietary versus generic. Aliment Pharmacol Ther. 2003;17(10):1207-14. doi: 1578 [pii].