Retrospective Analysis of Mesalamine Delayed-Release Tablets in Healthy Males and Females Volunteers: Effects of Food and Gender on Pharmacokinetic Parameters

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PURPOSE

- Mesalamine (5-ASA) is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis, and for the treatment and maintenance of remission of ulcerative colitis.
- There are various approved formulations of 5-ASA on the market with different release mechanisms and thus, different pharmacokinetic profiles. The present study focuses on the delayed-release 1.2 g tablet designed to release the active ingredient in a delayed and prolonged fashion following oral administration.
- Although the exact mechanism of action of 5-ASA is believed to be topical (in the colon) rather than systemic, the FDA Draft Guidance recommends relative bioavailability studies with pharmacokinetic (PK) endpoints on both fast and fed conditions rather than clinical efficacy endpoint studies.
- For both fasting and fed studies, the following PK parameters are recommended to be evaluated:
  1) Log-transformed AUC_{8-48}, AUC_{0-t}, and C_{max};
  2) Extensive sampling points around T_{max};
  3) At least four non-zero measurements of concentration before T_{max};
  4) At least four non-zero measurements between T_{max} and 24 hours.
- The PK of 5-ASA is known to be highly variable. The PK profile is often erratic; the rate of absorption (C_{max} and T_{max}) and the systemic exposure (AUC) not well characterized, leading to high failure rate in meeting bioequivalence criteria.
- A retrospective study was conducted to identify some key factors which may explain this variability in order to better design studies, and help meeting bioequivalence criteria for generic products.

METHODS

STUDY IDENTIFICATION

A review of the Algorithme Pharma study database was performed to identify clinical trials that met the following criteria:

- Mesalamine 1.2 g delayed-release tablets;
- Pivotal bioequivalence studies with PK endpoints;
- Randomized, partial or fully reference-replicated crossover, single dose design;
- Dosing after an overnight fast of 10 hours (fast) or 30 minutes after a high-fat, high-calorie meal (fed);
- Washout period of 7 days;
- Serial blood samples drawn up to 72 hours.

Other study characteristics :

- Validated HPLC method with MS/MS detection;
- Analytical range of 2.60 - 1500.00 ng/mL for 5-ASA;
- Non-compartmental PK analysis using proprietary Kinetic software (Version 9.01; Algorithme Pharma, Laval, Canada).

STATISTICAL ANALYSIS

- Studies were combined to perform a meta-analysis with SAS® software (version 9.2; SAS Institute Inc., Cary, NC, USA).
- AUC_{8-48}, C_{max} and T_{max} were analyzed using an Analysis of Variance (ANOVA) model. Subject effect (nested within study), and a study identifier were entered as random effects. Gender, and food (fast/fed) were entered as fixed effects.

RESULTS

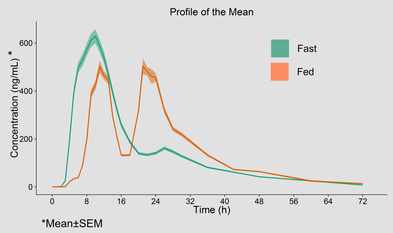
STUDY SELECTION

- Clinical trials were conducted at Algorithme Pharma between 2011 and 2013
- Eligible studies involved 604 healthy volunteers
  - ◊240 healthy volunteers under fasting conditions
  - ◊364 healthy volunteers under fed conditions
- All subjects received the reference product on two occasions
- The number of male and female volunteers was well balanced

FASTING AND FED CONDITION DIFFERENCES

- 5-ASA presents different pharmacokinetic profiles under fasting and fed conditions.

Panel 1. Effect of Food

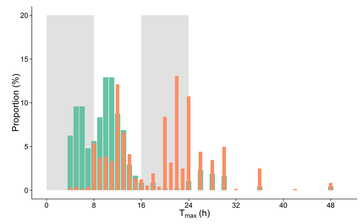


*Mean±SEM

	Fasting Mean	SEM	Fed Mean	SEM	P-value
C_{max} (ng/mL)	1217.19	168.50	1879.31	130.46	0.013
T_{max} (h)	10.75	0.87	18.88	0.67	<.0001
AUC_{8-48} (ng·h/mL)	7519.84	504.78	9054.26	394.26	0.0409

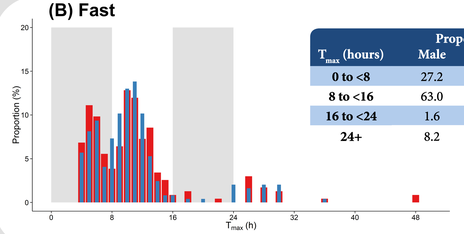
Panel 2. Effects of Food and Gender on the Distribution of T_{max}

(A) Overall



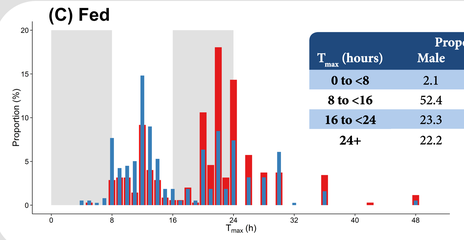
T_{max} (hours)	Proportion (%) Fast	Fed
0 to <8	30.2	1.2
8 to <16	60.0	40.4
16 to <24	2.1	31.2
24+	7.7	27.1

(B) Fast



T_{max} (hours)	Proportion (%) Male	Female
0 to <8	27.2	33.3
8 to <16	63.0	56.8
16 to <24	1.6	2.6
24+	8.2	7.3

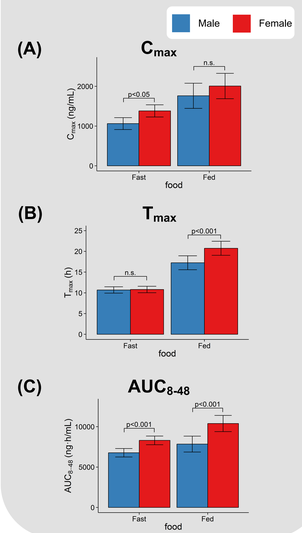
(C) Fed



T_{max} (hours)	Proportion (%) Male	Female
0 to <8	2.1	0.3
8 to <16	52.4	27.5
16 to <24	23.3	39.8
24+	22.2	32.4

Fast
Fed
Male
Female

Panel 3. Effect of Gender



- Mean 5-ASA profile displayed one major peak concentration at about 10 hours under fasting conditions; two major peaks were observed under fed conditions, at approximately 11 and 21 hours, suggesting two possible population subsets. Examination of individual profiles under fed conditions revealed one major peak in approximately 90% of the cases. Observation of two distinct peaks of similar magnitude under fed conditions represented the remaining 10% of profiles.
- Peak concentration (C_{max}) and Area Under the Curve (AUC_{8-48}) under fed conditions increased by about 1.5- and 1.2-fold respectively as compared to those under fasting conditions.
- T_{max} was significantly delayed by approximately 8 hours under fed conditions (p<0.0001).

DISTRIBUTION OF T_{MAX} OVER THE SAMPLING SCHEDULE

- Distinct distribution profiles of T_{max} were revealed under fasting and fed conditions (Panel 2A).
- Under fasting conditions, distribution of T_{max} shows similarity throughout the sampling schedule between males and females. The proportion of males and females within 8-hour intervals is also similar over the sampling time (Panel 2B) with the highest proportion observed within the 8-15 hour interval.
- Under fed conditions, distinct distribution profiles of T_{max} were evident between males and females. When categorized in 8-hour intervals, a higher proportion of T_{max} occurred within the first 16 hours in males (55%), whereas the distribution of T_{max} was shifted further to the right in females, with a higher proportion between 16 and 24 hours (40%) (Panel 2C).
- Approximately 20% of males and 30% of females exhibited late absorption peak at/or exceeding 24 hours under fed conditions compared to less than 10% under fasting conditions for both males and females.

PHARMACOKINETIC EVALUATION OF 5-ASA BY GENDER UNDER FASTING AND FED CONDITIONS

- Under fasting conditions, significant statistical differences were observed for C_{max} and AUC_{8-48} (p<0.05 and p<0.001, respectively) despite similar T_{max} (Panel 3B). Females had higher peak 5-ASA concentrations and exposure than males (Panels 3A and 3C, respectively).
- Under fed conditions, the peak concentration in females occurred significantly later than males (p<0.001). In general, female subjects also had a higher C_{max} than males (although not statistically significant) and greater exposure than males (p<0.001).

DISCUSSION AND CONCLUSION

- Statistically significant differences in bioavailability (BA) (as described by C_{max} and AUC_{8-48}) were shown under fasting conditions between males and females, despite similarity in their overall PK profile.
- Following a high-fat, high-calorie breakfast, the BA of mesalamine; represented by C_{max} and AUC_{8-48} increased by approximately 54% and 20%, respectively with a delay in the absorption of approximately 8 hours. These pooled results contrast with the percent increase in C_{max} following the ingestion of food reported in the monograph (91%).
- The distinct distribution of T_{max} between males and females observed under fed conditions suggests that the sampling schedule should be optimized to account for differences between genders.
- The broad range of time to peak concentration and delayed exposure found under fed conditions contribute to the difficulty of meeting the FDA's recommendations of four timepoints between the T_{max} and 24 hours, including the fact that a non-negligible proportion of T_{max} has been observed around 24 hours or later.
- These results challenge the FDA Draft Guidance on mesalamine concerning the same BE recommendations for studies conducted under fast and fed conditions.

REFERENCES

1) FDA. CDER. Clinical Pharmacology and Biopharmaceutics Review(s). Mesalamine. NDA 22-000. Shire Development Inc.
2) FDA. Office of Generic Drugs. Draft Guidance on Mesalamine. September 2012.