The investigation of variability of the pharmacokinetics of mesalamine from various mesalamine formulations in randomized clinical trials

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Abstract

Purpose: Mesalamine, which is also called 5-aminosalicylic acid or 5-ASA, is an amino-salicylate anti-inflammatory drug indicated for the treatment of ulcerative colitis. There are several oral delayed release and sustained release mesalamine formulations. The pharmacokinetic profiles of Asacol®, Pentasa®, and Lialda® are included in this investigation.

Methods: Six comparative bioavailability trials in healthy volunteers with different mesalamine formulations were selected. Five studies were randomized two-way crossover with two periods, two sequences in healthy volunteers, and one study was the three-way crossover with two study products and one product given twice. The sample sizes employed in those clinical studies were from 12 to 50. The quantification of pharmacokinetic data included at a minimum, 5-ASA from all 6 trials, and its major metabolite N-Acetyl-5ASA from 2 trials. Pharmacokinetic data (Tmax, Cmax, AUC, and ka) of 5-ASA, and its major metabolite N-Acetyl-5ASA (if available) were calculated. The pharmacokinetic analyses were carried out by either WinNonlin or SAS.

Results: Different oral mesalamine dosage forms result in widely different mesalamine plasma profiles. The median Tmax of mesalamine was around 10 to 12 hours for Asacol® and Lialda®; while the maximum plasma concentration of mesalamine was reached around 2 to 3 hours after the administration of Pentasa®. The summary results for peak and systemic absorption of 5-ASA from all three formulations showed large variability for the parent compound 5-ASA. The intra-subject variability for both Cmax and AUC was above 50% from the delayed release formulations of both Asacol® and Lialda®; the intra-subject variability for both Cmax and AUC was above 50% and 38% respectively for extended release formulation Pentasa®.

Conclusion: The systemic and peak exposure to 5-ASA, which are main parameters of the comparative bioavailability assessment, showed large variability for all 6 trials. The delayed release products showed higher variability than the extended release product. Such variability introduces the complexity for the planning of the comparative bioavailability study in terms of the determination of the sample size. Caution needs to be taken.

Mesalamine (5-ASA)

5-aminosalicylic acid (5-ASA) extended-release formulations are indicated for the treatment of ulcerative colitis and for long-term maintenance therapy in order to maintain remission and prevent relapse of active disease.

Mesalamine has a relatively small volume of distribution of approximately 18 L, confirming minimal extravascular penetration of systemically available drug. Protein binding of mesalamine is approximately 50% and of acetyl-mesalamine is about 80%. After intravenous administration, the plasma half-life of mesalamine is approximately 40 minutes and for acetyl-mesalamine is approximately 80 minutes.

Both mesalamine and acetyl-mesalamine are excreted in the urine and faeces. The urinary excretion consists mainly of acetyl-mesalamine and the faecal excretion consists mainly of mesalamine.

The only major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid, which is pharmacologically inactive. Its formation is brought about by N-acetyltransferase (NAT) activity in the liver and in the cytosol of intestinal mucosal cells, primarily by NAT-1. The enzyme is known to be subject to genetic polymorphism.

Mesalamine Formulations and PK variability of Different Formulations

Mesalamine is known having high variability of the absorption in human subjects with different mesalamine formulations due to the fast absorption and biotransformation.

Certain information available about the coefficient of variation of mesalamine when given to human subjects in the range of 50% to over 100%.

However, there was no or limited information about the intra-subject variability of mesalamine from either delayed or extended release formulations to be considered for comparative bioavailability studies.

Studies Selected

6 studies included in the presentation with 3 different mesalamine formulations.

5 studies were randomized two-way crossover with two periods, two sequences in healthy volunteers,

1 study was the three-way crossover with two study products and one product (innovator) given twice.

All studies are under fasting condition except for study 4 was under the fed condition.

The sample sizes employed in those clinical studies were from 12 to 50.

Study	Product	Study Design	Sample Size	Compound of Interest
1	Lialda DR	Single-dose, Randomized, 3-way, 2-treatment, 2-sequence, replicate	18	5-ASA
2	Lialda DR	Single-dose, Randomized, 2-period, 2-sequence, 2-treatment, crossover	12	5-ASA n-acetyl- 5-ASA
3	Pentasa ER	Single-dose, Randomized, 2-period, 2-sequence, 2-treatment, crossover	>30	5-ASA
4	Pentasa ER	Single-dose, Randomized, 2-period, 2-sequence, 2-treatment, crossover	>30	5-ASA
5	Pentasa ER	Single-dose, Randomized, 2-period, 2-sequence, 2-treatment, crossover	>30	5-ASA
6	Asacol DR	Single-dose, Randomized, 2-period, 2-sequence, 2-treatment, crossover	18	5-ASA n-acetyl- 5-ASA

Pharmacokinetic Assessment for Mesalamine Formulations

The quantification of pharmacokinetic data included at a minimum, 5-ASA from all 6 trials, and its major metabolite Acetyl-5ASA from 2 trials.

Pharmacokinetic data (Tmax, Cmax, AUC, and ka if applicable) of 5-ASA, and its major metabolite N-Acetyl-5ASA (if available) were calculated.

The pharmacokinetic analyses were carried out by either WinNonlin or SAS.

PK Parameters (Exposure) for (5-ASA)

Study #	Dosage (mg)	Cmax Mean +/- SD (CV%) (ng/mL)	AUCt Mean +/- SD (CV%) (ng.h/mL	AUCinf Mean +/- SD (CV%) (ng.h/mL)
1	1200	967.0 +/- 652.5 (67.48%)	8062 +/- 3998 (49.58%)	8938 +/- 4857 (54.34%)
6	800	347.1 +/- 346.4 (99.79%)	3788 +/- 2899 (76.54%)	5968 +/- 2872 (48.12%)
2	1200	1383 +/- 2521 (182.25%)	9504 +/- 20406 (214.71%)	-
3	500	574.3 +/- 301.7 (50.54%)	1649 +/- 759.0 (46.02%)	1366 +/- 715.0 (52.32%)
4	500	822.5 +/- 691.9 (84.12%)	1848 +/- 1342 (72.64%)	2040 +/- 1269 (62.19%)
5	1000	1217 +/- 724.0 (59.45%)	3879 +/- 2194 (56.55%)	4829 +/- 3086 (63.90%)

PK Parameters (Exposure) for N-acetyl-5-ASA

Study #	Dosage	Cmax Mean +/- SD (CV%) (ng/mL)	AUCt Mean +/- SD (CV%) (ng.h/mL)	AUCinf Mean +/- SD (CV%) (ng.h/mL)
6	800 mg	977.9 +/- 522.2 (56.48%)	20030 +/- 12014 (59.98%)	23318 +/- 10128 (43.43%)
2	1200 mg	1812 +/- 2203 (121.60%)	22609 +/- 21539 (95.76%)	-

Absorption Rate Constant for Mesalamine & Its Metabolite

1. From the 6 studies selected, two studies were subjected to the Ka analysis to further investigation
2. The criteria for selecting the study for Ka analyses was the study with the high variability
3. The Ka was estimated by WinNonlin

Absorption Rate (ka) for 5-ASA and N-acetyl-5-ASA

PK Parameters (5-ASA)	N	Mean	SD	Min	Max	Median	CV%
Ka	12	0.9925	1.1178	0.0290	3.3621	0.5105	112.62
Ka	16	0.7100	1.7934	0.0686	7.3963	0.2080	252.59

PK Parameters (N-acetyl-5-ASA)	N	Mean	SD	Min	Max	Median	CV%
Ka	12	0.7646	0.7462	0.1332	2.4528	0.3446	97.59
Ka	17	0.3953	0.4447	0.0986	1.9694	0.3147	112.48

Other PK Parameters for 5-ASA

Study	Formulation	T_{max} (hr) Median (Range) (CV%)	$T_{1/2}$ (hr) Mean +/- SD (CV%)	K_{el} (1/hr) Mean +/- SD (CV%)
1	Lialda	4 (3 - 36) (14.24%)	-	-
2	Lialda	12 (5 - 24) (54.91%)	-	-
3	Pentasa	3 (0.5 – 7) (55.91%)	9.28 +/- 5.15 (55.56%)	0.149 +/- 0.21 (140.35%)
4	Pentasa	4 (2 – 9) (31.49%)	9.24 +/- 3.71 (40.12%)	0.087 +/- 0.035 (39.83%)
5	Pentasa	2.5 (0.75 – 6) (54.03%)	9.06 +/- 7.00 (77.24%)	0.20 +/- 0.22 (115.44%)
6	Asacol	13 (4-48) (67.47%)	5.58 +/- 2.32 (41.53%)	0.137 +/- 0.037 (26.99%)

The Variability of 5-ASA PK Parameters

The intra-subject variability (ISV) was calculated by SAS.

Study #	Dosage (mg)	Study Drug	Intra-subject Variability C_{max} (ISV)	Intra-subject Variability AUC (ISV)
1	1200	Lialda	>75%	>50%
2	1200	Lialda	>100%	>100%
3	500	Pentasa	< 50% & >30%	>30%
4	500	Pentasa	>50%	>30%
5	1000	Pentasa	< 50% & >30%	>30%
6	800	Asacol	>100%	>75%

Discussion

Results showed that Mesalamine exhibits different PK profiles and variability from different formulations.

The absorption rate also showed significant variability with high coefficient variation for Lialda.

The inter-subject variability of mesalamine is high for all studies formulations.

The intra-subject variability of mesalamine from randomized crossover studies are high especially for Lialda and Asacol which exhibites different PK from Pentasa.

The Pentasa study 4 (fed) showed the higher CV of the PK parameters than those from study 3 and 5 (fasting). The intra-subject CV was also high for Pentasa under the fed condition.

The metabolite of mesalamine also demonstrated high variability although it seems to be lower than that obtained from the mesalamine parent compound.

Conclusion

Valuable information of the intra-subjects variability was obtained from the crossover randomized studies.

The high intra - subject variability introduces difficulties for comparative bioavailability for determining the appropriate sample size. Food may increase the variability.

The proper steps should be taken to reduce the intra-subject variability for comparative bioavailability of mesalamine.

It was suggested to keep subjects reclined on bed for 12 hours after dosing to reduce any GI track variability.

Further studies may be conducted to assess the method of reducing the variability .

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