Mesalazine pharmacokinetics and NAT2 phenotype

Lück, H; Kinzig, M; Jetter, A; Fuhr, U; Sörgel, F
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Abstract

BACKGROUND: Mesalazine undergoes extensive metabolism by N-acetylation. While there is some evidence for an involvement of N-acetyltransferase (NAT) type 1, a potential role of NAT type 2 (NAT2) in vivo has not been tested. METHODS: In two studies in healthy young Caucasians, NAT2 phenotyping was carried out using a caffeine metabolic ratio in urine 4-6 h postdose. In study A, 1,000 mg mesalazine doses were given thrice daily for 5 days, and urine and blood samples were drawn during the last dosing interval. In study B, a 1,000 mg single dose was given, and samples were taken for 48 h postdose. Pharmacokinetics of mesalazine and N-acetylmesalazine (LC-MS/MS) were calculated by noncompartmental methods. RESULTS: NAT2 phenotype could be allocated unequivocally in 21 slow and 5 rapid acetylators in study A, and in 9 slow and 8 rapid acetylators in study B. Geometric mean (CV%) values in study A for slow [rapid] acetylators were as follows: mesalazine AUC 11.1 [12.0] microg/mL.h (51%) [52%], N-acetylmesalazine AUC 27.7 [30.5] microg/mL.h (32%) [27%], mesalazine Ae 8.53% [9.03%] (89%) [52%], N-acetylmesalazine Ae 31.4% [32.2] (46%) [41%]. Values in study B were as follows: mesalazine AUC 3.45 [2.36] microg/mL.h (113%) [87%], N-acetylmesalazine AUC 21.3 [18.0] microg/mL.h (29%) [39%], mesalazine Ae 0.2% [0.1%] (256%) [359%], N-acetylmesalazine Ae 30.9% [18.1%] (44%) [84%]. Higher AUC and Ae values for mesalazine in steady state study indicate saturation of mesalazine metabolism. Statistics provided no evidence for a true difference in mesalazine pharmacokinetics between slow and rapid acetylators, and no significant correlation between NAT2 activity and any mesalazine pharmacokinetic parameter was found. CONCLUSION: NAT2 has no major role in human metabolism of mesalazine in vivo.
Mesalazine Pharmacokinetics and NAT2 Phenotype

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ABSTRACT

Background: Mesalazine undergoes extensive metabolism by N-acetylation. While there is some evidence for an involvement of N-acetyltransferase (NAT) type 1, a potential role of NAT type 2 (NAT2) in vivo has not been tested.

Methods: In two studies in healthy young Caucasians, NAT2 phenotyping was carried out using a caffeine metabolic ratio in urine 4-6 hours postdose. In study A, 1000 mg mesalazine dosis was given thrice daily for 5 days, and urine and blood samples were drawn in the last dosing interval. In study B, a 1000 mg single dose was given, and samples were taken until 48 hours postdose. Pharmacokinetics of mesalazine and N-acetylmesalazine (LC-MS/MS) were calculated by noncompartmental methods.

Results: NAT2 phenotype could be allocated unequivocally in 21 slow and 5 rapid acetylators in study A and in 9 slow/8 rapid acetylators in study B. Geometric mean [CV%] values in study A for slow (rapid) acetylators were: mesalazine AUC 11.1 [51 %] (12.0 [52 %]) µg/mL*h; N-acetylmesalazine AUC 27.7 [32 %] (30.5 [27 %]) µg/mL*h; mesalazine Ae 8.53 [89 %] (9.03 [52 %]) %; N-acetylmesalazine Ae 31.4 [46 %] (32.2 [41 %]) %. Values in study B were: mesalazine AUC 3.45 [113 %] (2.36 [87 %]) µg/mL*h; N-acetylmesalazine AUC 21.3 [29 %] (18.0 [39 %]) µg/mL*h; mesalazine Ae 0.2 [256 %] (0.1 [359 %]) %; N-acetylmesalazine Ae 30.9 [44 %] (18.1 [84 %]) %. Higher AUC and Ae values for mesalazine in steady state study indicate saturation of mesalazine metabolism. Statistics provided no evidence for a true difference in mesalazine pharmacokinetics between slow and rapid acetylators, and no significant correlation between NAT2 activity and any mesalazine pharmacokinetic parameter was found.

Conclusion: NAT2 has no major role in human metabolism of mesalazine in vivo.
INTRODUCTION

Mesalazine is an anti-inflammatory drug mainly used in the treatment of ulcerative colitis but also with some value in Crohn’s disease. It undergoes extensive metabolism by N-acetylation [1]. On an average, concentrations of N-acetylmesalazine in plasma and N-acetylmesalazine amounts excreted in urine exceed those of the parent compound more than twofold. Two enzymes are known to primarily mediate N-acetylation in humans, i.e. N-acetyltransferase type 1 (NAT1) and type 2 (NAT2). However, currently it is not clear which enzyme plays the key role in N-acetylation of mesalazine. In the mouse (which has 3 NATs), all NATs were able to metabolize mesalazine in vitro, while murine NAT2 had the highest activity [2]. In an in vitro study with human enzymes, both NAT1 and NAT2 were able to mediate 4-aminosalicylic acid N-acetylation (mesalazine is 5-aminosalicylic acid), with NAT1 having a 131-fold higher intrinsic clearance than NAT2 [3].

Both human enzymes are expressed at high levels in the human intestine and in the liver [4]. N-acetylation of mesalazine is highly variable [5]. As both human NATs have genetic polymorphisms, this finding provides no information on the identity of the enzyme. In one study, pharmacokinetics of mesalazine and sulfapyridine, the two bacterial metabolites of sulfasalazine formed by reductive cleavage of the azo bond linking these two components, were determined. While acetylation of sulfapyridine, a known NAT2 substrate, was polymorphic, this could not be shown for mesalazine [6]. Mesalazine pharmacokinetics did also not co-segregate with NAT2 activity as assessed by sulfadimidine, but the respective study was conducted in 6 subjects only [7]. Furthermore, under saturation conditions for mesalazine, no relationship of ex vivo mucosal N-acetylation of mesalazine to systemic N-acetylation of sulfapyridine following systemic administration of sulfasalazine was found [8]. On the other hand, in two studies there was also no difference with regard to mesalazine tolerability and therapeutic response between NAT1 genotypes [9, 10].
In summary, current evidence for a major role of NAT1 in acetylation of mesalazine \emph{in vivo} is partially contradictory, and the evidence suggesting that NAT2 has no major role originates from studies with relevant methodological limitations. Thus, the objective of the present evaluation is to assess the role of NAT2 in the \textit{N}-acetylation of mesalazine in humans \emph{in vivo} by comparison of mesalazine pharmacokinetics to NAT2 phenotype based on a validated caffeine-based NAT2 metric.
Volunteers and Methods

A total number of 28 and 18 young female and male Caucasian volunteers were included in two separate studies A and B, respectively (Table 1). The studies were approved by the Ethics Committee of the University of Cologne. Each study participant provided written informed consent prior to inclusion in the study. Participants were considered to be healthy based on a screening examination including physical examination, medical history, vital signs, ECG recording, clinical chemistry tests, urinalysis, and test on drugs of abuse and alcohol. Smokers could be included if smoking not more than 10 cigarettes per day.

In both studies, NAT2 phenotyping was carried out using a urine sample collected 4-6 hours after a 150 mg caffeine test. Caffeine metabolites were quantified by LC-MS/MS, and the molar ratio of caffeine metabolites (AFMU + AAMU)/(AFMU+AAMU+ 1X+1U) (for abbreviations, see legend to Fig. 1) was used as a validated NAT2 metric [11]. Based on maximum log likelihood analysis, individuals with a ratio below 0.23 were classified as slow acetylators, those with values above 0.26 were considered as rapid acetylators (Fig. 1). Those with intermediate values were rated as “unclassified”.

Individuals were studied under standardized conditions. Alcohol and grapefruit products were prohibited before and during the study. The volunteers had to remain in the Clinical Pharmacology ward from the evening prior to dosing at the profiling days until withdrawal of the last sample.

In study A, no food intake was allowed from 8 hours before until 2 hours after each morning administration, from 2 hours before until 2 hours after each afternoon administration and from 3.5 hours before until 8 hours after each late evening administration, with the exception of a snack given 10 min prior to each administration of the study medication. Standardized meals were given 12 hours prior to and 2 and 5 hours after the last mesalazine dose on the profiling day. In study B, subjects were fasting from 10 hours prior to mesalazine administration until 6
hours thereafter, and they adhered to supine position for 6 hours postdose. Meals were given 6, 9, 12 and 16 hours after mesalazine administration. The generally allowed fluid intake was 1.8 to 2.0 liters daily. In both studies, no fluid intake additional to that provided for drug intake (180 ml) was allowed from 2 hours before to 2 hours after drug intake. Thereafter, 120 mg of water was administered every hour.

Mesalazine doses were 1000 mg given as two 500 mg commercial prolonged release tablets (Pentasa®). In the multiple dose study A, this 1000 mg dose was given thrice daily for 5 days, and urine (0-4 and 4-8 hours postdose) and 17 blood samples were drawn in the last dosing interval. In the 1000 mg single dose study B, 21 blood samples were taken until 48 hours postdose, and urine was collected 0-4, 4-8, 8-12, 12-24, and 24-48 hours postdose.

Plasma and urine samples of mesalazine and N-acetylmesalazine were analyzed by validated LC-MS/MS assays. For mesalazine, plasma samples (0.1 mL) were precipitated by addition of 200 µL of acetonitrile containing the internal standard. After thorough mixing, the samples were centrifuged for 10 minutes at 3,280 g at approximately +4 °C, and the supernatant was diluted (1:4) with ammonium acetate buffer. 60 µL of each sample were chromatographed on a reversed-phase column (Nucleosil 100-5 Protect 1), eluted with an isocratic solvent system consisting of ammonium acetate (pH 3.5) buffer and acetonitrile (75/25,v/v) and monitored by LC-MS/MS with a SRM method as follows: Precursor → product ion for mesalazine m/z 152 → m/z 108 and m/z 266 → m/z 223 for internal standard, all analyses were in negative mode. Under these conditions mesalazine and the internal standard were eluted after approximately 1.5 and 1.6 minutes, respectively. The MacQuan software (version 1.6, PE Sciex, Thornhill, Ontario, Canada, 1991 - 1998) was used for evaluation of chromatograms. Urine samples were thawed, and stored for 20 minutes at 37 °C. 0.02 mL of each sample were diluted using 1.98 mL of mobile phase containing the internal standard. After thorough mixing, the samples were stored for 10 minutes at 37 °C. 25 µL of each sample were chromatographed as described above. There was no interference observed in plasma or urine for mesalazine or the internal standard. Weighted linear regression (1/concentration) was performed for calibration in human plasma and urine. Linearity of the calibration could be proven in human plasma between 0.0493 µg/mL and 4.89 µg/mL (Study A and B) and in human urine between 0.953 and 97.9 µg/mL for Study A and between 0.251 to 60.1 µg/mL for Study B. Lower limit of
quantification were identical with the lowest calibration levels. The inter-day precision of mesalazine in human plasma ranged from 6.0 to 8.3 % with an analytical recovery between 99.3 % and 102.2 %. The inter-day precision of the spiked quality control standards of mesalazine in human urine ranged from 6.4 to 14.3 % with an analytical recovery between 97.6 and 107.5 % for Study B. For N-acetyl mesalazine preparation of the human plasma and urine samples see mesalazine. Thereafter, human plasma (35 µL) and urine (25 µL) samples were chromatographed on a reversed-phase column (Waters Symmetry Shield C-8), eluted with an isocratic solvent system consisting of ammonium acetate (pH 3.5) buffer and acetonitrile (70/30,v/v) and monitored by LC-MS/MS with a SRM method as follows: Precursor → product ion for N-acetyl mesalazine m/z 194 → m/z 150 and m/z 266 → m/z 223 for internal standard, all analyses were in negative mode. Under these conditions N-acetyl mesalazine and the internal standard were eluted after approximately 1.4 and 0.9 minutes, respectively. The MacQuan software (version 1.6, PE Scix, Thornhill, Ontario, Canada, 1991 - 1998) was used for evaluation of chromatograms. There was no interference observed in plasma or urine, for N-acetyl mesalazine or the internal standard. Weighted linear regression (1/concentration) was performed for calibration. Linearity of the calibration could be proven in human plasma between 0.0497 µg/mL and 4.94 µg/mL (Study A and B) and in human urine between 0.956 and 98.2 µg/mL for Study A and between 2.00 and 100 µg/mL for Study B. Lower limit of quantification were identical with the lowest calibration levels. The inter-day precision of N-acetyl mesalazine in human plasma ranged from 6.3 to 9.1 % with an analytical recovery between 98.3 and 103.4 %. The inter-day precision of the spiked quality control standards of N-acetyl mesalazine in human urine ranged from 2.4 to 10.4 % with an analytical recovery between 95.3 and 111.0 %.

Pharmacokinetic parameters were calculated by noncompartmental methods (WinNonlin 2.0, Pharsight Corporation, Palo Alto, U.S.A.). Statistical evaluations are considered as descriptive. Mesalazine pharmacokinetics were compared between acetylator groups by the t-test for independent samples. The relationship of mesalazine kinetics vs. NAT2 activity was further examined by linear regression (SPSS 15.0 for Windows, SPSS Inc., Chicago, U.S.A.). For metabolic ratios, AUC, Cmax and Ae, a multiplicative model was assumed, and geometric instead of arithmetic means and ratios instead of differences were calculated by ln transformation of the data prior to analysis and respective back-transformation thereafter.
RESULTS
The frequency distribution of NAT2 activities is shown in Fig. 1. Overall, 30 rapid and 13 slow acetylators were identified. Concentration vs. time profiles for both mesalazine and N-acetylmesalazine are depicted in Fig. 2 and 3. Irregular profiles and persisting low concentrations of mesalazine at the final part of some profiles precluded a reliable calculation of apparent elimination half lives; thus, these are not reported, and extrapolation of AUC was not done.

Concentration vs. time plots are presented separately for slow and rapid acetylators of the multiple dose study (Fig. 2) and the single dose study (Fig. 3), main pharmacokinetic parameters with relevance for the rate and extent of metabolism are presented in Table 1. There is pronounced interindividual variability in the profiles and the respective parameters, which is even higher in the single dose study. Considerably higher AUC values for mesalazine at steady state study indicate saturation of mesalazine metabolism. This is also reflected by less than 0.3 % of a mesalazine dose being excreted unchanged in the single dose study while roughly 9 % of the doses were excreted unchanged in the multiple dose study (Table 1).

There is no evidence for a true difference in mesalazine pharmacokinetics between slow and rapid acetylators. The plots do not show clear differences between NAT2 phenotypes (Fig. 2, 3). Only for one parameter out of 25, a statistically significant difference (p<0.05) was observed, and this one does not support a more rapid metabolism of mesalazine in NAT2 rapid acetylators. There was no overlapping of 95 % CIs for the comparison between acetylator phenotypes between the NAT2 metric and any mesalazine parameter in the multiple dose study, and only marginal overlapping for a few parameters in the single dose study (Tab. 1). Also, there was no significant correlation between NAT2 phenotype and any of the mesalazine pharmacokinetic parameters (for AUC values, see Fig. 4).
DISCUSSION

In this evaluation, pharmacokinetics of mesalazine were compared between slow and rapid acetylators for NAT2 both in a single dose and a multiple dose study as acetylation is saturated during chronic administration. Our results do not provide evidence for a major role for NAT2 in the metabolism of mesalazine in vivo.

Traditionally, NAT2 phenotypes were described as “slow” or “rapid” acetylators; however, depending on the number of NAT2 alleles coding for a highly active enzyme variant (i.e. 0, 1 or 2, respectively), three groups of individuals with respect to acetylation rate of individual NAT2 substrates may be discerned [12], although statistical analysis usually fails to identify more than two groups based on pharmacokinetic parameters. In the present study, 30 % of classifiable individuals were allocated to the slow acetylator phenotype, which is lower than the 50 % of Caucasians reported to have two low-activity alleles [13]. Thus, the allocation to “slow” and “rapid” acetylator phenotype may represent some ambiguity with regard to NAT2 genotype. However, the caffeine metabolic ratio used here as the NAT2 metric has been validated extensively [11 and references therein]. From 4 hours after dosing on, this ratio remains unchanged for at least another 12 hours and thus is robust against deviations in urine sampling [14]. Therefore, the results of NAT2 phenotyping are considered as reliable from both a scientific and technical point of view and, as for any valid phenotyping procedure, may provide information beyond genotyping [15]. It should be mentioned that the metabolic caffeine ratio has been shown to reflect the activity of hepatic NAT2 [16], but activity differences between NAT2 genotypes most probably also apply to intestinal tissue [17].

Pharmacokinetic parameters of mesalazine observed here are similar to those reported, including saturation of acetylation for chronic administration [1, 18]. Because of the short elimination half-life of mesalazine of clearly less than 3 hours [1, 7], a prolonged release preparation is needed for maintaining plasma concentrations during a dosing interval, but also for direct delivery to any intestinal site of action. Mesalazine release from this formulation
has been reported to occur throughout the gastrointestinal tract [19]. It has a bioavailability of approximately 30% [18] which is lower than that of gastroresistant tablets and may be in part be caused by a more extensive intestinal first pass metabolism which is saturable [7] (see also Table 1). Indeed, in vitro studies showed that homogenates of colonic mucosa [8] and more specifically the cytosol of human colonic epithelial cells are able to mediate mesalazine N-acetylation [20].

The current evaluation was done within the framework of bioequivalence studies, which had not been powered explicitly to assess the role of NAT2 phenotype in mesalazine pharmacokinetics. Because the limited number of individuals and the pronounced interindividual variation in mesalazine pharmacokinetics, we are not able to exclude an effect of NAT2 genotype on mesalazine acetylation in vivo. However, the 95% CIs for the comparison between phenotypes clearly show that if there were any differences in mesalazine kinetics between acetylator phenotypes, they would be much smaller than differences in enzyme activity. In contrast, for isoniazid as a known NAT2 substrate, pharmacokinetic differences fully reflect differences in enzyme activity [12]. Thus, our data show that NAT2 has no major – if any – role in human metabolism of mesalazine in vivo. As NAT2 (and NAT1) polymorphisms have also no influence on inflammatory bowel disease by itself [21], there is no rationale to consider NAT2 activity in the treatment with mesalazine.

It is still desirable to identify sources for variability in mesalazine pharmacokinetics other than NAT2 polymorphism. Obviously, intestinal liberation rate of the drug from the preparation may contribute. Furthermore, there is clear role of bacterial NAT in overall N-acetylation of mesalazine, albeit its magnitude is controversial [22, 23]. Also, the reported lack of differences in mesalazine response and tolerability between NAT1 genotypes [9, 10] does not exclude differences in mesalazine pharmacokinetics, because differences in activity in NAT1 variants are limited [24, 25] and pharmacodynamic parameters are less sensitive than pharmacokinetic parameters. Finally, in patients the degree of intestinal inflammation affects mesalazine pharmacokinetics [26]. Further research is needed to improve our
understanding of the fate of mesalazine in the human body in order to assess a rationale for individual dose optimisation, with the chance to improve the risk/benefit ratio of this drug and maybe also to reduce the risk for rare adverse effects such as interstitial nephritis [27].
### Table 1: Pharmacokinetic parameters of mesalazine (arithmetic means ± SD or geometric means [% CV]) and the respective comparison for rapid acetylators relative to slow acetylators (difference or ratio [95% CI]) following oral administration of 1000 mg doses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study A (multiple dose)</th>
<th>Study B (single dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point estimates and metric of variability</td>
<td>Comparison rapid vs. slow acetylators</td>
</tr>
<tr>
<td></td>
<td>slow</td>
<td>rapid</td>
</tr>
<tr>
<td>acetylator phenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>number classifiable</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>NAT2 metric*</td>
<td>0.086 [58 %]</td>
<td>0.299 [13 %]**</td>
</tr>
<tr>
<td>sex (n male / female)</td>
<td>16 m / 5 f</td>
<td>3 m / 2 f</td>
</tr>
<tr>
<td>age (years)</td>
<td>26.0 ± 4.3</td>
<td>27.8 ± 2.0</td>
</tr>
<tr>
<td>body weight (kg)</td>
<td>73.0 ± 10.8</td>
<td>72.4 ± 10.1</td>
</tr>
<tr>
<td>body height (cm)</td>
<td>179 ± 8</td>
<td>175 ± 10</td>
</tr>
<tr>
<td>mesalazine AUC$_{τ}$ (0-8h) (µg/mL*h)</td>
<td>11.1 [51 %]</td>
<td>12.0 [52 %]</td>
</tr>
<tr>
<td>N-acetylmesalazine AUC$_{τ}$ (0-8h) (µg/mL*h)</td>
<td>27.7 [32 %]</td>
<td>30.5 [27 %]</td>
</tr>
<tr>
<td>AUC$_{τ}$ (0-8h) ratio N-acetylmesalazine / mesalazine</td>
<td>2.49 [28 %]</td>
<td>2.54 [38 %]</td>
</tr>
<tr>
<td>mesalazine C$_{max}$ (µg/mL)</td>
<td>3.00 [57 %]</td>
<td>3.48 [60 %]</td>
</tr>
<tr>
<td>N-acetylmesalazine C$_{max}$ (µg/mL)</td>
<td>5.71 [51 %]</td>
<td>7.13 [47 %]</td>
</tr>
<tr>
<td>C$_{max}$ ratio N-acetylmesalazine / mesalazine</td>
<td>3.68 [74 %]</td>
<td>3.57 [32 %]</td>
</tr>
<tr>
<td>mesalazine Ae$_{0-8h}$ (% of dose)</td>
<td>8.53 [89 %]</td>
<td>9.03 [52 %]</td>
</tr>
<tr>
<td>N-acetylmesalazine Ae$_{0-8h}$ (% of dose)</td>
<td>31.4 [46 %]</td>
<td>32.2 [41 %]</td>
</tr>
<tr>
<td>Ae$_{0-8h}$ ratio N-acetylmesalazine / mesalazine</td>
<td>3.68 [74 %]</td>
<td>3.57 [32 %]</td>
</tr>
<tr>
<td>mesalazine t$_{max}$ (h)</td>
<td>2.15 ± 0.75</td>
<td>2.70 ± 0.45</td>
</tr>
<tr>
<td>N-acetylmesalazine t$_{max}$ (h)</td>
<td>2.49 ± 0.75</td>
<td>2.70 ± 0.45</td>
</tr>
<tr>
<td>mesalazine half value duration (h)</td>
<td>2.15 ± 0.75</td>
<td>2.70 ± 0.45</td>
</tr>
<tr>
<td>N-acetylmesalazine half value duration (h)</td>
<td>2.49 ± 0.75</td>
<td>2.70 ± 0.45</td>
</tr>
</tbody>
</table>

*urinary caffeine metabolic ratio (AFMU+AAMU)/ (AFMU+AAMU+1X+1U); **p<0.05; ***p<0.0001< n.a., not applicable
FIGURES

Figure 1: Relative Frequency Distribution of NAT2 activities

Individuals with a caffeine metabolic ratio below 0.23 were classified as slow acetylators, those with a ratio above 0.26 were considered as rapid acetylators. 1X, 1-methylxanthine; 1U, 1-methyluric acid; AFMU, 5-acetylamino-6-formylamino-3-methyluracil; AAMU, 5-acetylamino-6-amino-3-methyluracil.
**Figure 2:** Individual and mean ± SD mesalazine (upper part) and N-acetylmesalazine (lower part) concentration vs. time profiles in the last dosage interval following multiple dose administration of 1000 mg mesalazine thrice daily for 5 days (study A).
Figure 3: Individual and mean ± SD mesalazine (upper part) and N-acetylmesalazine (lower part) concentration vs. time profiles following administration of a 1000 mg mesalazine single dose (study B)
Figure 4: Relationship of mesalazine and N-acetylmesalazine AUC to NAT2 activity
There was no significant correlation of AUC values calculated separately for studies A and B, respectively, and the caffeine NAT2 metabolic ratio. 1X, 1-methylxanthine; 1U, 1-methyluric acid; AFMU, 5-acetylamino-6-formylamino-3-methyluracil; AAMU, 5-acetylamino-6-amino-3-methyluracil.
REFERENCES


