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# Mono- and Biphasic Plasma Concentration–time Curves of Mesalazine from a 500 mg Suppository in Healthy Male Volunteers Controlled by the Time of Defecation before Dosing

TOM B. VREE, ERIK DAMMERS*, PETER S. EXLER† AND ROBERT A. A. MAES‡

*Institute for Anaesthesiology, Academic Hospital Nijmegen Sint Radboud, PO Box 9101, 6500 HB Nijmegen, *DADA Consultancy, Dennenstraat 109, 6543 JR Nijmegen, †Disphar International, Hengelo (Gld), and ‡Department of Human Toxicology, University of Utrecht, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands*

**Abstract**

This study was based on data from a bioequivalence study (n = 24) of two different formulations of suppositories containing 500 mg mesalazine (formulation I and II), with a similar dissolution profile in phosphate buffer pH 6·8. There was a large intra- and inter-subject variability in the plasma concentration–time curves of mesalazine from both suppositories.

The aim of the investigation was to identify the parameters that caused the observed large variations in release and absorption of mesalazine in the rectum.

Plasma mesalazine and acetylmesalazine, and urine acetylmesalazine concentrations were determined according to validated methods involving HPLC analysis with coulometric detection. Lower limit of quantitation values were respectively 10·4 and 19·4 ng $mL^{-1}$ in plasma and 0·96 $\mu$g $mL^{-1}$ in urine. The time of defecation before and after insertion was recorded.

There was a clear distinction between subjects who showed monophasic mesalazine release/absorption and those who showed biphasic and more extended release/absorption. With formulation I there was a correlation between time of defecation before dosing and the type of absorption, monophasic and biphasic absorbers showed a significant difference in the time of defecation, e.g. 9·7 ± 5·6 h vs 18·8 ± 11·9 h ($P = 0·0218$). The impact of time of defecation before dosing was non-significant with formulation II, 16·7 ± 7·2 h vs 15·1 ± 4·2 h ($P = 0·67$). The impact of the time elapsed between administration and time of defecation after the insertion of the suppository was not significant for the type of release/absorption.

The plasma concentration–time curves of the metabolite ran parallel to that of the parent drug, the more parent drug was released/absorbed, the more was acetylated ($P = 0·0013$) and excreted into the urine ($P = 0·0004$). After absorption the compound was metabolized into acetylmesalazine, and renally excreted (12–13% of the dose). Monophasic release/absorption resulted in 7·1% metabolite with I and 10·3% with II ($P = 0·0004$), while biphasic release/absorption gave 16·8% metabolite with I and 15·5% with II. The renal clearance of the metabolite acetylmesalazine was independent of the observed defecation patterns (300 mL $min^{-1}$, $P > 0·8$), stool composition, and type of absorption.

Mesalazine (5-aminosalicylic acid, 5ASA) is an anti-inflammatory agent structurally related to the salicylates, which is active in inflammatory bowel disease. The mode of action of mesalazine is uncertain, but may be due, at least in part, to its ability to inhibit local prostaglandin and leukotriene synthesis in the gastrointestinal mucosa (Prakash & Markham 1999). In-vitro studies have indicated that inhibition of eicosanoids, inhibition of cytokines and modulation of their effects and protection against oxygen-derived free radicals are involved (Ahnfelt-Rønne et al 1990).

Mesalazine is given orally (as a prolonged-release formulation or gastroresistant tablet) or

Correspondence: T. B. Vree, Institute for Anaesthesiology, Academic Hospital Nijmegen Sint Radboud, PO Box 9101, 6500 HB Nijmegen, The Netherlands.
E-Mail: T.Vree@anes.azn.nl

rectally in the management of mild to moderate acute ulcerative colitis or the maintenance of remission, particularly for patients with a poor tolerance to sulphasalazine. There are several differently formulated oral formulations of mesalazine available, and dosage recommendations vary (Martindale 1996). Some 20 to 50% of an oral dose was absorbed after oral administration to healthy volunteers (Hardy et al 1987; Meyers et al 1987; Wiltink et al 1990). Absorption from rectal dosage forms also varied widely, and was reported to depend on the dose, the formulation, and the pH, but mean absorption of around 10–20% of the rectal dose has been reported (Brogden & Sorkin 1989; Norlander et al 1989).

The absorbed portion of mesalazine is acetylated in the gut wall and in the liver, and the rate of acetylation, and hence the concentration of parent drug and metabolite in the systemic circulation, is independent of the acetylator status. It has been suggested that the metabolite, acetylmesalazine, may itself have some activity, but this remains in doubt (Fischer et al 1983). The acetylated metabolite is excreted mainly in the urine by filtration and active tubular secretion, together with traces of the parent compound (< 1%) (Brogden & Sorkin 1989; Meyers et al 1987; Wiltink et al 1990). Peak plasma drug levels following rectal administration are very low and highly variable (Norlander et al 1989; Jacobsen et al 1991).

This investigation used the plasma concentration and urinary data of a bioequivalence study of two suppositories (formulation I and II) containing 500 mg mesalazine, with a similar dissolution profile in-vitro. There were large differences in the plasma concentration–time curves of mesalazine released and absorbed from both suppositories.

The aim of this investigation was to identify the parameters that caused the observed large variations in the release plus the subsequent absorption by the rectum.

## Materials and Methods

*Experimental design*

The investigation was a follow-up of an open, randomized, two-treatment, two-period, two-sequence, cross-over phase-I study involving 24 healthy Caucasian male volunteers (age 24·3 ± 3·8 years, body weight 77·1 ± 9·7 kg, body height 185·0 ± 8·0 cm, 13 smokers, 11 non-smokers). Treatments were separated by a one-week washout period.

FarmaResearch (Nijmegen, The Netherlands) conducted the clinical trial in accordance with current GCP (good clinical practice) and GLP (good laboratory practice). The study protocol and written volunteer information were granted approval by the Independent Review Board (IRB), Amsterdam, The Netherlands.

Subjects were not allowed to consume beverages or food containing alcohol from 24 h before dosing until 24 h after dosing. Smoking was allowed, except from 2 h before until 4 h after dosing. Subjects were to refrain from strenuous exercise.

*Trial course*

The subjects were divided randomly into two groups. Group 1 was assigned to treatment sequence I-II; group 2 was assigned to sequence II-I. Formulation I was a single rectal dose of one Salofalk 500-mg suppository, batch number 97C22 (Tramedico BV, The Netherlands). Formulation II was a single rectal dose of one mesalazine suppository 500 mg, batch number 963502 (Disphar International, The Netherlands).

Drugs: mesalazine ($C_7H_7NO_3$; MW 153·4; CAS number 89-57-6; 500 mg = 3·25 mmol); metabolite acetylmesalazine, MW 196·4).

On day 1, between 0800 h and 0855 h, the suppositories were administered rectally by Unit personnel. After 5 min, retainment of suppositories was checked. Before dosing subjects defecated whenever possible. After dosing, subjects postponed defecation for at least 4 h, whenever possible. The respective times of last defecation before dosing, the time of the first defecation after dosing and the exact times of dosing were recorded.

Before drug administration, subjects fasted for at least 10 h. Fasting was continued until 4 h after dosing. Subjects were free to drink water, low-fat milk, apple juice, diluted orange juice, coffee and tea from lunch onwards. All subjects received the same standardized low-fat lunch and dinner.

*Blood sampling*

On the day of dosing a physician inserted an indwelling Venflon 2 IV cannula (Viggo, The Netherlands) into a forearm vein of each subject. The cannula was removed after withdrawal of the 15-h post-dosing sample. The 24-h post-dosing blood sample was drawn by venepuncture.

Blood samples (10 mL) were collected in heparinized glass tubes just before dosing, and at predetermined times after dosing. The blood samples were centrifuged at 4000 rev $min^{-1}$ for 10 min, plasma was separated and stored at −20°C until analysis.

*Urine sampling*
Urine output was collected just before drug administration and at 4-h intervals during 24 h. Samples of approximately 7 mL were taken from each collection interval and stored at −20°C until analysis.

*Bioanalysis*
Plasma mesalazine and acetylmesalazine concentrations were determined using a validated method using HPLC analysis with coulometric detection. Lower limits of quantitation values were 10·4 and 19·4 ng $mL^{-1}$, respectively (Farma-Research protocol 111/97/0436).

In brief, 500 $\mu$L plasma and 500 $\mu$L 1 M perchloric acid were mixed in a 6-mL glass tube, vortexed and centrifuged. Clear supernatant (200 $\mu$L) was transferred to an autosampler vial and 50 $\mu$L was chromatographed using a reversed-phase HPLC system (column C8 15 cm × 2·1 mm) with coulometric detection at 350 mV.

Urine acetylmesalazine concentrations were determined using a validated method with HPLC analysis and electrochemical detection. The lower limit of quantitation value was 0·96 $\mu$g $mL^{-1}$.

In brief, 100 $\mu$L urine was diluted with 900 $\mu$L water. The diluted sample was subjected to a sample-clean up procedure using solid phase extraction columns (quaternary amine) and eluted with 0·4 M HCl. The final extract consisted of 400 $\mu$L 0·4 M HCl. A sample of extract (100 $\mu$L) was diluted with 900 $\mu$L water, and 50 $\mu$L of this diluted extract was chromatographed in a reversed-phase HPLC system using coulometric detection at 350 mV.

*Pharmacokinetic analysis*
Based on the plasma mesalazine and acetylmesalazine concentrations of individual subjects, the following pharmacokinetic parameters were determined by non-compartmental analysis using TOPFIT 2.0 software (Heinzel et al 1993). $C_{max}$, the maximum plasma drug concentration (ng $mL^{-1}$); $t_{max}$, the time to reach the $C_{max}$ (h); $AUC_t$, the area under the plasma concentration–time curve (ng h $mL^{-1}$) calculated (linear trapezoidal method) until the last measurable concentration (Ct); $t_{\frac{1}{2}}$, the elimination half-life associated with the terminal slope of a semilogarithmic concentration–time curve ($\ln 2/\lambda$ [h]), where $\lambda$ = elimination rate constant; $Ae_{(0-t)}$, total amount of acetylmesalazine excreted until the end time of the last collection interval with measurable urine concentrations (0·96 $\mu$g $mL^{-1}$).

*Statistical analysis*
Analysis of variance was used, and significance was defined at $P = 0{\cdot}05$.

## Results

*Pharmacokinetics*
The plasma concentration–time curves of mesalazine for formulation I and II showed a large standard deviation and coefficient of variation (40–90%). The plasma concentrations of parent drug and metabolite acetylmesalazine ran parallel in the mean curve in Figure 1, and also in each individual subject. The mean (± s.d.) values of $t_{max}$ for formulation I and II were respectively 2·57 ± 1·15 and 3·41 ± 2·41 h ($P = 0{\cdot}13$), the $C_{max}$ was 301 ± 98 vs 256 ± 88 ng $mL^{-1}$ ($P = 0{\cdot}27$), the $AUC_t$ was 1876 ± 1002 vs 1635 ± 738 ng h $mL^{-1}$ ($P = 0{\cdot}31$), and $t_{\frac{1}{2}}$ was 2·65 ± 2·37 vs 2·80 ± 3·05 h ($P > 0{\cdot}8$).

The large variation in plasma concentrations and pharmacokinetic data was also seen in the overlay picture of the plasma concentration curves of mesalazine. It was noted that a number of subjects showed a second release/absorption and a relatively long half-life, whereas others showed a single release/absorption and elimination process as shown in Figure 2 for formulation I. A similar observation was made for formulation II.

Tables 1 and 2 show the mean pharmacokinetic parameters and descriptive statistics of mesalazine in formulations I and II, respectively.

Formulation I shows a clear division in the subjects in whom mesalazine was released and absorbed monophasically and those in whom mesalazine showed a biphasic and a more extended release and

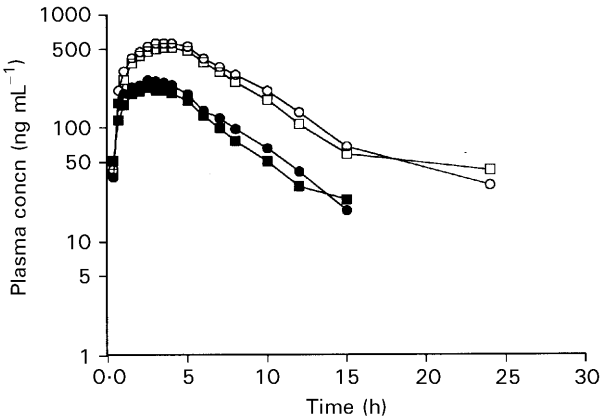


Figure 1. Mean plasma concentration–time curves of mesalazine (●, ■) and metabolite acetylmesalazine (○, □) in 24 male subjects after insertion of 500-mg mesalazine suppository in formulation I (□, ■) and formulation II (○, ●). The concentrations show a coefficient of variation of 40–90%.

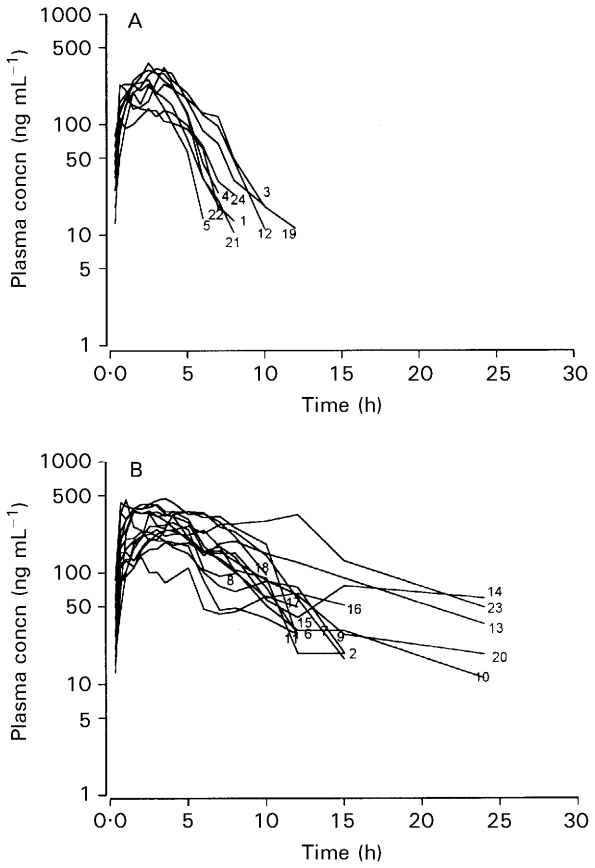


Figure 2. A. Mean plasma concentration–time curves of mesalazine in nine subjects after insertion of 500-mg mesalazine suppository in formulation I, showing a monophasic release and absorption (t = 10 h limit) (numbers are the subject number). B. Mean plasma concentration–time curves of mesalazine in 15 subjects after insertion of 500-mg mesalazine suppository in formulation I, showing a biphasic release and absorption (numbers are the subject number).

absorption. This effect was less pronounced with formulation II and became visible after t = 12 h.

*Exploring the nature of biphasic absorption*

Figures 3 and 4 show the mean plasma concentrations of mesalazine after administration of a 500-mg suppository of formulations I and II, respectively. In both cases a monophasic and a biphasic release/absorption can be distinguished, though the difference between the two types was larger with formulation I.

For formulation I monophasic and biphasic behaviour reached statistical difference for the $AUC_t$ value ($P = 0{\cdot}0009$) and the $t_{\frac{1}{2}}$ value ($P = 0{\cdot}0317$), but not for the $C_{max}$ and $t_{max}$ values (Table 1).

For formulation II monophasic and biphasic behaviour reached statistical difference for the $AUC_t$ value ($P = 0{\cdot}0578$) and the $t_{\frac{1}{2}}$ value ($P = 0{\cdot}0080$), but not for the $C_{max}$ and $t_{max}$ values (Table 2).

*Is the mono-/biphasic release/absorption phenomenon subject dependent?*

Seven subjects released/absorbed both formulations monophasically and six in a biphasic fashion, while 10 subjects released/absorbed formulation I biphasically and formulation II monophasically, and one subject absorbed formulation II biphasically but I monophasically. Thus 13 subjects maintained their mode of release/absorption, while 11 subjects handled mesalazine from the two for-

Table 1. Mean pharmacokinetic parameters and descriptive statistics of mesalazine from suppository formulation I with monophasic (n = 9) and biphasic (n = 15) release/absorption.

| Subjects | Parameter | | | | | | |
|---|---|---|---|---|---|---|---|
| | $C_{max}$ (ng mL$^{-1}$) | $t_{max}$ (h) | $AUC_t$ (ng h mL$^{-1}$) | $t_{\frac{1}{2}}$ (h) | Defecation (h) | | |
| | | | | | Before dosing | After dosing | Δ |
| All | | | | | | | |
| Mean | 301 | 2·57 | 1876 | 2·65 | 15·4 | 10·8 | 25·8 |
| s.d. | 98 | 1·15 | 1002 | 2·37 | 10·8 | 6·2 | 13·6 |
| %CV | 32·6 | 44·7 | 53·4 | 89·4 | 70·1 | 57·4 | 52·7 |
| Monophasic | | | | | | | |
| Mean | 262 | 2·44 | 1053* | 1·18 | 9·77 | 7·33 | 17·1 |
| s.d. | 80·4 | 0·92 | 268 | 0·47 | 5·63 | 2·49 | 5·0 |
| %CV | 30·7 | 37·7 | 25·5 | 39·8 | 57·6 | 34·0 | 29·2 |
| Biphasic | | | | | | | |
| Mean | 324 | 2·64 | 2307** | 2·63** | 18·8** | 12·8 | 31·0** |
| s.d. | 105 | 1·30 | 956 | 0·73 | 11·9 | 6·9 | 14·5 |
| %CV | 32·4 | 49·2 | 40·3 | 27·7 | 63·3 | 53·9 | 46·8 |

*All monophasic, $AUC_t$ $P = 0{\cdot}0141$. **Mono-biphasic: $AUC_t$ $P = 0{\cdot}0009$, $t_{\frac{1}{2}}$ $P = 0{\cdot}0317$, defecation before dosing $P = 0{\cdot}0218$, total defecation time $P = 0{\cdot}0058$. Δ is the total time between two defecations (h). %CV is the coefficient of variation.

Table 2. Mean pharmacokinetic parameters and descriptive statistics of mesalazine from suppository formulation II with monophasic (n = 16) and biphasic (n = 8) release/absorption.

| Subjects | Parameter | | | | | | |
|---|---|---|---|---|---|---|---|
| | $C_{max}$ (ng mL$^{-1}$) | $t_{max}$ (h) | $AUC_t$ (ng h mL$^{-1}$) | $t_{\frac{1}{2}}$ (h) | Defecation (h) | | |
| | | | | | Before dosing | After dosing | Δ |
| All | | | | | | | |
| Mean | 256 | 3·41 | 1635 | 2·80 | 16·5 | 11·8 | 26·7 |
| s.d. | 88 | 2·41 | 738 | 3·06 | 6·33 | 7·29 | 8·15 |
| %CV | 34·4 | 70·7 | 45·1 | 109·3 | 38·4 | 61·8 | 30·5 |
| Monophasic | | | | | | | |
| Mean | 266 | 3·00 | 1401* | 1·46 | 16·7 | 10·2 | 25·7 |
| s.d. | 98·1 | 2·26 | 533 | 0·81 | 7·23 | 4·77 | 7·16 |
| %CV | 36·9 | 75·3 | 38·0 | 55·5 | 43·4 | 46·7 | 27·9 |
| Biphasic | | | | | | | |
| Mean | 235 | 4·25 | 2102** | 5·86** | 15·1 | 14·9 | 28·7 |
| s.d. | 64·0 | 2·63 | 897 | 4·10 | 4·21 | 10·5 | 10·1 |
| %CV | 27·2 | 61·8 | 42·7 | 70·0 | 27·9 | 70·5 | 35·2 |

*All monophasic $AUC_t$ $P = 0{\cdot}3764$; all biphasic $t_{\frac{1}{2}}$ $P = 0{\cdot}0080$. **Monophasic-biphasic $AUC_t$ $P = 0{\cdot}0578$, $t_{\frac{1}{2}}$ $P = 0{\cdot}0008$; Δ is the time between two defecations (h); %CV is the coefficient of variation.

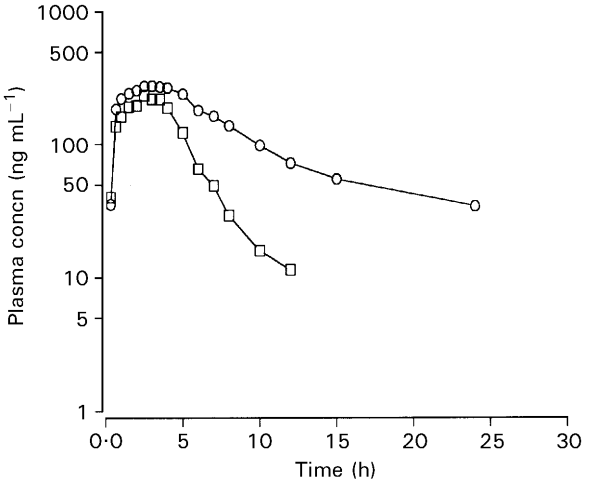


Figure 3. Mean plasma concentration–time curves of mesalazine after insertion of 500-mg mesalazine suppository in formulation I, showing a monophasic release and absorption in nine subjects (□) and in 15 subjects (○) showing a biphasic release and absorption. Plasma concentrations differ from t = 4 h on ($P < 0{\cdot}03$).

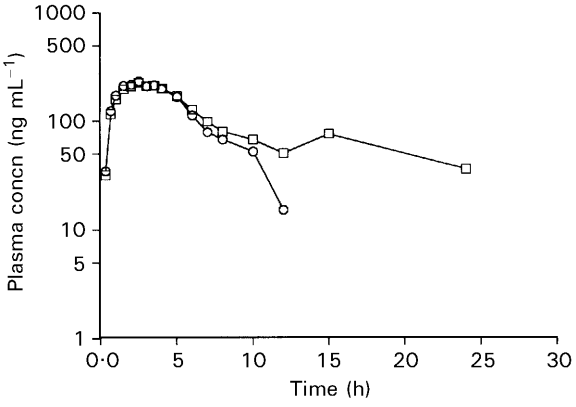


Figure 4. Mean plasma concentration–time curves of mesalazine after insertion of 500-mg mesalazine suppository in formulation II, showing a monophasic release and absorption in 16 subjects (○) and in eight subjects (□) showing a biphasic release and absorption. Plasma concentrations differ from t = 12 h on ($P < 0{\cdot}01$).

mulations in a reversed mode on the two occasions with either formulation I or II (Table 3). This leads to the assumption that a subject-governed-parameter controls the nature of absorption.

*Time of defecation*

The time of defecation before and after insertion of the suppository was recorded (Tables 1 and 2). In the whole group of 24 subjects there was no indication that the time of defecation was related to the type of release/absorption. However, with formulation I there was a correlation between time of defecation before dosing and the type of release/absorption. Monophasic and biphasic absorbers showed a significant difference in the time of defecation e.g. $9{\cdot}7 \pm 5{\cdot}6$ vs $18{\cdot}8 \pm 11{\cdot}9$ h ($P = 0{\cdot}0218$). The impact of time between defecation before dosing and insertion was non-significant with formulation II, $16{\cdot}7 \pm 7{\cdot}2$ vs $15{\cdot}1 \pm 4{\cdot}2$ h ($P = 0{\cdot}67$).

The impact of the time elapsed between administration and time of defecation after the insertion of the suppository was not significant for the type of release/absorption. The total time span between pre- and post-dose defecation influenced the type of absorption only significantly for formulation I, and

Table 3. Individual subjects (numbers) and their type of release/absorption of mesalazine from formulations I and II.

| | | Formulation I | |
|---|---|---|---|
| | | Monophasic | Biphasic |
| Formulation II | Monophasic | 1, 4, 5, 12, 19, 21, 22 | 7, 8, 9, 11, 14, 16, 17, 18, 20, 24 |
| | Biphasic | 3 | 2, 6, 10, 13, 15, 23 |

Non-smokers were subjects number 1, 2, 6, 7, 9, 12, 14, 17, 19, 20, 22. Soft stools were observed by subjects number 9-I, 12-II and 22-II.

was controlled by the time of defecation before dosing (Tables 1–3).

*After absorption of the parent drug*

*Metabolism.* The plasma concentration–time curves of the parent drug and the metabolite acetylmesalazine ran parallel in each subject, independently of the type of absorption. In the 24 subjects there was no difference between $AUC_t$ of both formulations ($P = 0{\cdot}44$). The difference between $AUC_t$ between monophasic and biphasic release/absorption reached significance with formulation I ($2776 \pm 361$ vs $6051 \pm 2597$ ng h mL$^{-1}$; $P = 0{\cdot}0013$) and $P = 0{\cdot}0118$ with formulation II.

*Renal excretion.* The amount of metabolite from formulation I and II in 24 subjects excreted in urine was not significantly different ($83{\cdot}9 \pm 39{\cdot}2$ vs $77{\cdot}0 \pm 38{\cdot}7$ mg; $P = 0{\cdot}50$). However, monophasic release/absorption resulted in less excreted metabolite than biphasic release/absorption after both the reference and the test formulation, i.e. $45{\cdot}2 \pm 13{\cdot}5$ (7·1% of the dose) vs $107{\cdot}2 \pm 29{\cdot}6$ mg (16·8% dose; $P = 0{\cdot}0004$) with formulation I and $66{\cdot}0 \pm 23{\cdot}7$ (10·3%) vs $99{\cdot}2 \pm 53{\cdot}8$ mg (15·5%; $P = 0{\cdot}0411$) with formulation II. No significant difference was found between the amount of excreted metabolite after monophasic ($P = 0{\cdot}17$) or biphasic release/absorption ($P = 0{\cdot}61$).

*Renal clearance.* Renal clearance of the metabolite acetylmesalazine was 300 mL min$^{-1}$ for both formulations. No statistical difference was found in the clearance after mono- or biphasic release/absorption in formulations I and II. The parent drug mesalazine was not present in the urine samples.

## Discussion

Biphasic absorption of mesalazine, as reported in this study, was also shown by Bondesen et al (1991) and Yu et al (1995) after oral administration.

We demonstrated that the time of defecation before the insertion of the suppository was of importance for the discrimination of subjects according to their mode of release/absorption of mesalazine by the rectum wall. The phenomenon was observed in the plasma concentration–time curve, which resulted after release of mesalazine from the suppository and after absorption by the rectum wall. These two processes could not be distinguished in the overall plasma concentration–time curve. The interdefecatory interval of all subjects was $26 \pm 13$ h (Tables 1 and 2) and no significant difference was found between formulations I and II. Formulation I showed the mono-biphasic release/absorption difference more clearly than formulation II, and so despite similar dissolution curves in-vitro, in-vivo the type of formulation also governs the release/absorption process. If release/absorption is hindered by a compact stool, as may be after a long transit time to the rectum, a slow second phase in release and absorption by the gut wall is the result. Formulations I and II showed similar $t_{max}$ and $C_{max}$ values, while with formulation I, 15 of 24 subjects showed the biphasic release/absorption, and eight subjects with formulation II. Thus formulation II in general must release and absorb mesalazine at a slower rate than formulation I.

The discrimination of the subjects was made after close inspection of their individual plasma concentration–time curves, and was confirmed by statistical analysis of the pharmacokinetic parameters. The significant difference between the $AUC_t$ and $t_{\frac{1}{2}}$ values reflects the differences in the concentration–time curves. The difference is made clinically important by association to the physiological circumstances of stool interference and defecation time before insertion of the suppository. Table 3 shows that 13 subjects maintained either mono- or biphasic release/absorption, while 11 changed it.

*Metabolism and renal excretion*

After absorption mesalazine is metabolized into acetylmesalazine and excreted in the urine. The plasma concentration–time curve of parent drug and metabolite ran in parallel in each subject,

independently of the type of absorption. Only 13·1% of formulation I and 12·1% of formulation II was absorbed, metabolized and excreted in the urine (%CV 46·7–50·3%, $P = 0{\cdot}50$). This agrees with data published by Norlander et al (1989). The monophasic release/absorbers showed a lesser $AUC_t$ and amount excreted in the urine than the biphasic ones ($P = 0{\cdot}001$).

Renal clearance of the metabolite showed no differences between monophasic and biphasic release/absorption, because it is a process that proceeds independently after absorption, and even after metabolism. The value of $300\,mL\,min^{-1}$ indicated that the metabolite was excreted by glomerular filtration plus active tubular secretion. A negligible amount of the parent compound was excreted, $< 1\%$ of the dose.

*Tentative mechanism of the difference in release/absorption*

Intuitively it can be understood that the nature of the stool and the time of defecation before insertion of the suppository govern the amount released and absorbed by the gut wall. If the stool mass were only a hindrance for the compound to reach the gut/rectum wall, then a long defecation time before insertion and consequently a more compact stool would result in a lower release/absorption than with fresh and less compact stool. However the situation is just the reverse. Fresh stool limits the release/absorption (7–10% dose) and compact stool makes a second phase in release/absorption possible (15–16% dose), resulting in a 50% difference in amount absorbed, metabolized and excreted.

An explanation might be that 'fresh' stool ($< 10$ h between defecation and insertion) contains more binding places for mesalazine or allows further metabolism into unidentified metabolites (Jensen et al 1993) or more faecal water and more distribution over the stool mass than more compact and older stool ($> 10$ h). With the older and compact stool, the suppository mass with mesalazine may be spread along the rectum wall, enhancing the absorption. Increasing the stool transit time limits the amount to be absorbed (Christensen et al 1987).

Dietary fibre decreases stool pH, increases stool frequency and faecal mass. However, the 24-h faecal and urinary excretion as mesalazine and metabolite was unchanged (Riley et al 1991). Faecal water concentration of mesalazine was higher after suppository treatment compared with enema treatment (Jacobsen et al 1991). Faecal water amount will be different in fresh and old compact stool.

*Clinical implications*

When mesalazine has to act locally as an oxygen scavenger (Ahnfelt-Rønne et al 1990) absorption should be minimal, which is the case when the patient has defecated just before insertion of the suppository. When the place of action is in the wall of the colon/rectum tissue, then a continuous absorption is advantageous, and then a slow defecation process and a long time of stool presence in the rectum at the time of insertion of the suppository is an advantage.

If stool binding of mesalazine is irreversible, then old stool is more advantageous than fresh stool in allowing the compound to reach the gut/rectum wall for local action. In fact, this implication is in contrast to the intuitive impression that insertion just after defecation allows more absorption and penetration of mesalazine.

*Conclusions*

The suppository of both formulations showed a clear distinction between subjects in whom mesalazine was released and absorbed monophasically and in those demonstrating biphasic release and absorption. This difference in release/absorption correlated with the time of defecation before insertion of the suppository, the shorter the stool mass was present before insertion the more monophasic the release/absorption was. Fresh stool was likely to bind or metabolize more drug than older and more compact stool. After absorption the compound was metabolized into acetylmesalazine, and renally excreted. The pharmacokinetic behaviour of the metabolite reflected that of the parent drug, the more parent drug that was released and absorbed, the more metabolite was acetylated and excreted into the urine. The renal clearance of the metabolite acetylmesalazine was independent of the defecation time, stool composition, and type of absorption.

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