Release profile of Salofalk 750 mg tablets

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V HO, JE BLAIR, Z COHEN, RS MCLEOD. Release profile of Salofalk 750 mg tablets. *Can J Gastroenterol* 1995;9(5):247-250. This study determined the release profile of Salofalk 750 mg tablets (Axcen Pharma), an enteric-coated 5-aminosalicylic acid (5-ASA) preparation. Twenty-one ileostomates were divided into two groups and studied. Group 1 consisted of 10 subjects (five males, five females, mean age 39 years) who had a mean length of 65 cm of small bowel resected or out of circuit. Group 2 consisted of 11 subjects (eight males, three females, mean age 59 years) whose small bowel was intact. Following an overnight fast and collection of baseline samples, one Salofalk tablet was ingested. Ileostomy effluent and urine were collected for 24 h. Plasma samples were collected hourly for 6 h, then at 8, 12 and 24 h. All subjects ate standardized meals. All samples were stored at -10°C and 5-ASA and N-ac-5-ASA (a metabolite of 5-ASA) were measured by high performance liquid chromatography. The mean intestinal transit time was not statistically different between the groups but the mean ileostomy effluent output was higher in group 1 versus group 2 (10.9 versus 13.1 h, $P=0.4$; 918 versus 606 mL, $P=0.05$). The mean peak plasma concentrations of 5-ASA and N-ac-5-ASA were not significantly different (6.12 and 5.42 $\mu\text{g/mL}$, $P=0.8$, respectively, in group 1 versus 6.75 and 6.66 $\mu\text{g/mL}$, $P=0.8$ in group 2). On average, 33.1% of the ingested dose was recovered in the ileostomy effluent in group 1 versus 21.2% in group 2 ($P=0.06$) whereas the mean recovery in urine was 40.9% in group 1 but 62.9% in group 2 ($P=0.001$). These results suggest that 5-ASA is released in the small bowel. There was decreased absorption of 5-ASA and increased recovery of 5-ASA in the ileostomy effluent of subjects who had a small bowel resection.

Key Words: 5-Aminosalicylic acid, Mesalamine

Mode de libération des comprimés de Salofalk de 750 mg

RÉSUMÉ : Cette étude a déterminé le mode de libération des comprimés de Salofalk de 750 mg (Axcen Pharma), une préparation d'acide 5-aminosalicylique (5-ASA) à enrobage entérique. Vingt-et-un iléostomisés ont été divisés en deux groupes et étudiés. Le groupe 1 comportait 10 sujets (5 hommes, 5 femmes dont l'âge moyen était de 39 ans) chez qui une longueur moyenne de 65 cm d'intestin grêle avait été réséquée ou mise hors fonction. Le groupe 2 comportait 11 sujets (8 hommes, 3 femmes dont l'âge moyen était de 59 ans) chez qui l'intestin grêle était

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OVER THE PAST 10 YEARS, VARIOUS preparations of mesalamine (5-aminosalicylic acid [5-ASA]) have become available to treat Crohn's disease and ulcerative colitis. They have the advantage over sulfasalazine of having fewer side effects. In addition, some are formulated to release 5-ASA in the small bowel; hence, they may be effective in small bowel disease treatment (1).

Recently a new mesalamine preparation, Salofalk 750 mg tablets (Axcen Pharma), was developed that has a water-based, pH sensitive Eudragit LD 30 coating, different from the solvent-based, pH-sensitive coating on the 250 mg Salofalk preparations. These tablets offer two potential benefits over other mesalamine preparations. First, they contain a larger dose of medication so fewer tablets must be ingested, which may lead to increased patient compliance. Second, in vitro studies show that Salofalk 750 mg is released in the more proximal bowel (2). They may, therefore, be more effective in treating patients with Crohn's disease involving the more proximal small bowel and patients who have had previous surgical resections.

The objective of this study was to determine the in vivo release profile of Salofalk 750 mg tablets and to determine the urinary and fecal excretion of both 5-ASA and its metabolite, N-ac-5-ASA.

METHODS AND MATERIALS

Subject population: Two groups of ileostomy subjects were studied. Group 1

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Received for publication March 3, 1994. Accepted March 10, 1995

intact. Après un jeûne d'une nuit et une cueillette d'échantillons de départ, un comprimé Salofalk a été administré. L'effluent d'iléostomie et l'urine ont été recueillis sur une période de 24 heures. Des échantillons plasmatiques ont été prélevés aux heures, six heures durant, puis après 8, 12 et 24 heures. Tous les sujets ont pris des repas standardisés. Tous les spécimens ont été conservés à -10°C et le 5-AAS et le N-ac-5-AAS (un métabolite du 5-AAS) ont été mesurés à l'aide d'une chromatographie liquide de haut rendement. Le transit intestinal moyen n'a pas été statistiquement différent d'un groupe à l'autre, mais le débit d'effluent d'iléostomie moyen était plus élevé dans le groupe 1 que dans le groupe 2 (10,9, contre 13,1 h, $P=0,4$; 918, contre 606 mL, $P=0,05$). Les concentrations plasmatiques de pointe moyennes de 5-AAS et de N-ac-5-AAS n'ont pas été significativement différentes (6,12 et 5,42 $\mu\text{g/mL}$, $P=0,8$ respectivement dans le groupe 1, contre 6,75 et 6,66 $\mu\text{g/mL}$, $P=0,8$ dans le groupe 2). En moyenne, 33,1 % de la dose ingérée ont été récupérés dans l'effluent d'iléostomie du groupe 1, contre 21,2 % dans le groupe 2 ($P=0,06$), alors que la récupération moyenne d'urine a été de 40,9 % dans le groupe 1 contre 62,9 % dans le groupe 2 ($P=0,001$). Ces résultats suggèrent que le 5-AAS est libéré dans l'intestin grêle. Une absorption réduite de 5-AAS et une récupération accrue de 5-AAS dans l'effluent d'iléostomie chez les sujets qui avaient subi une résection de l'intestin grêle ont été notées.

comprised 10 subjects who had had a proctocolectomy plus either a small bowel resection (seven subjects) or loop ileostomy, constructed at least 35 cm proximal to the ileocecal junction (three subjects). Group 2 comprised 11 subjects who had had a proctocolectomy without a small bowel resection or exclusion. All subjects had ulcerative colitis. Subjects were excluded if they had a history of renal disease, were known to be allergic to sulfasalazine or mesalamine, or were pregnant or nursing.

Experimental design: Baseline samples of plasma, urine and ileostomy effluent were taken at 08:00, following an overnight fast. Subjects then ingested one tablet of Salofalk 750 mg and four plastic markers. The latter were used to determine the small bowel transit time. At 09:00, 12:00 and 18:00 subjects ate standardized meals. Throughout the 24 h period they were allowed water ad libitum. All medications, other than acetylsalicylic acid, sulfasalazine and

mesalamine, were continued, including antidiarrheal medications. The subjects remained at the Clinical Investigation Unit at the Toronto Hospital, General Division, Toronto, Ontario from 08:00 to 20:00. The following morning at 08:00 subjects returned for the final collection of samples. Activity was unrestricted throughout the duration of the study.

Ethics approval was obtained from the Toronto Hospital Committee for Research on Human Subjects and each subject gave informed consent.

Laboratory methods – Plasma samples: Five millilitre samples of blood were drawn into heparinized vacutainers at baseline and at hourly intervals for 6 h, then at 8, 12 and 24 h. Each sample was centrifuged at 10°C and the plasma was stored at -10°C until 5-ASA and N-ac-5-ASA (a metabolite of 5-ASA) were assayed. Additionally, serum creatinine was measured at baseline and at 24 h.

Urine samples: A baseline urine sam-

ple was collected at 08:00. Then urine was collected every 4 h for 12 h, and for 12 h until 08:00 the next morning. The volume of each sample was recorded and a 20 mL aliquot saved and stored at -10°C for 5-ASA and N-ac-5-ASA assays. The urine recovery of 5-ASA and N-ac-5-ASA was calculated by multiplying the respective urine concentration by the total volume of the urine excreted. Then, the total urine recovery of 5-ASA was calculated by adding the urine recovery of 5-ASA and N-ac-5-ASA, the latter expressed as equivalent milligrams of 5-ASA.

Ileostomy effluent: A sample of ileostomy effluent was collected at 08:00 for the baseline sample. Subsequently, the effluent was collected every 2 h for 8 h, then at 12 and 24 h. Each sample was strained, and any undissolved tablet and intestinal transit markers were looked for. If present, they were removed and the time at which they passed was recorded. The small bowel transit time for each subject was determined by calculating the mean time of passage of the four markers.

Each effluent sample was homogenized and the total volume was recorded before a 20 mL aliquot was saved and stored at -10°C until assays were performed. 5-ASA and N-ac-5-ASA recovery and the total amount of 5-ASA recovered in the ileostomy effluent were determined as described above.

MEASUREMENTS: ASSAYS FOR 5-ASA and N-ac-5-ASA were performed by Biopharm Laboratories, Laval, Quebec, using a method similar to that described by Hansen (3).

ANALYSIS: Means and standard deviations of all relevant data were calculated. Differences were tested using Student's *t* test for continuous data or the χ^2 test for proportions.

TABLE 1
Characteristics of the two study groups

	Mean age (years)	Mean height (cm)	Mean weight (kg)	Sex M:F	Mean duration of ileostomy (years)	Mean small bowel transit time (h)	Mean length small bowel resected (cm)	Range (cm)
Group 1	38.5 $\pm$ 9.2	172 $\pm$ 10	76.6 $\pm$ 16.5	5:5	3.4 $\pm$ 2.1	10.9 $\pm$ 5.0	65.0 $\pm$ 22.4	35 to 110
Group 2	59.0 $\pm$ 14.0*	171 $\pm$ 7	75.9 $\pm$ 13.1	8:3	5.9 $\pm$ 7.2	13.1 $\pm$ 5.9	NA	NA

Group 1 (n=10) comprised small bowel resection patients; Group 2 (n=11) comprised patients without small bowel resection. NA Not applicable. * $P<0.01$; †Mean of nine subjects; ‡Mean of 10 subjects

Figure 1) Mean plasma concentration of 5-aminosalicylic acid (5-ASA) in group 1 and 2 subjects

Figure 2) Mean plasma concentrations of N-ac-5-aminosalicylic acid (N-ac-5-ASA) in group 1 and 2 subjects

RESULTS

Subjects: The characteristics of the subjects are given in Table 1. The subjects were similar with the exception of age: subjects in group 1 were significantly older than those in group 2 ($P < 0.01$). In group 1, the mean length of small bowel resected or out of circuit was 65 ± 22 cm (range 35 to 110 cm). Two subjects (one from each group) did not pass all four small bowel transit markers and were not included in the small bowel transit time calculations. Although the mean small bowel transit time was shorter in group 1, the difference was not significant.

Four subjects complained of symptoms possibly related to the medication: gas (one subject), headache (one) and watery ileostomy effluent (two).

Plasma: The mean plasma concentrations of N-ac-5-ASA and 5-ASA are shown in Figures 1 and 2, respectively. Both substances were first detected in the plasma at 1 h. Mean times of the peak concentration of N-ac-5-ASA and 5-ASA were similar in both groups (N-ac-5-ASA: 3.40 ± 1.78 h in group 1 and 3.45 ± 2.16 h in group 2; 5-ASA: 3.10 ± 1.91 h and 3.27 ± 2.28 h, respectively). Additionally, there were no significant differences in the mean peak concentrations of either N-ac-5-ASA (5.42 ± 3.71 µg/mL in group 1 versus 6.75 ± 5.06 µg/mL in group 2) or 5-ASA (6.12 ± 5.16 µg/mL versus 6.66 ± 4.86 µg/mL, respectively).

Ileostomy and urine excretion: Urine and ileostomy effluent recovery data

TABLE 2

Recovery of 5-aminosalicylic acid (5-ASA) and N-ac-5-ASA in each group of subjects

Group	Mean V of urine (mL)	URINE EXCRETION			
		Mean 5-ASA (mg)	Mean N-ac-5-ASA (mg)	Mean T as 5-ASA (mg)	Mean T dose (%)
1	1045 ± 576	76.5 ± 44.3	317.9 ± 117.9	307.0 ± 96.3	40.9 ± 12.8
2	1346 ± 650	134.0 ± 53.1	465.5 ± 77.9	471.6 ± 77.6	62.9 ± 10.3

Group	Mean V of effluent (mL)	ILEOSTOMY EXCRETION			
		Mean 5-ASA (mg)	Mean N-ac-5-ASA (mg)	Mean T as 5-ASA (mg)	Mean T recovery (%)
1	918 ± 336	172.8 ± 90.2	104.1 ± 112.9	248.3 ± 126.8	74.0 ± 21.2
2	606 ± 215	68.5 ± 40.4	124.8 ± 84.9	159.0 ± 73.6	84.0 ± 14.2

T Total; V Volume

are given in Table 2. There was no significant difference in the mean urine volume passed by the two groups whereas the mean total volume of ileostomy effluent was significantly greater in group 1 versus in group 2 ($P < 0.05$).

The mean recovery of both 5-ASA and N-ac-5-ASA in urine was significantly less in group 1 compared with group 2 ($40.9 \pm 12.8\%$ versus $62.9 \pm 10.3\%$, $P = 0.001$). Approximately one-quarter of the amount recovered in the urine in all subjects was excreted as 5-ASA.

Conversely, the mean recovery of both 5-ASA and N-ac-5-ASA in the ileostomy effluent of group 1 was greater than in group 2 although this difference did not reach statistical significance ($33.1 \pm 16.9\%$ versus $21.2 \pm 9.8\%$, $P = 0.06$). Of the mean total amount recovered in the ileostomy effluent, 69.6% was recovered as 5-ASA

in group 1 subjects and 43.1% as 5-ASA in group 2 subjects. The mean total recovery of both substances in both ileostomy effluent and urine was $74.0 \pm 21.2\%$ in group 1 compared with $84.0 \pm 14.2\%$ in group 2 ($P > 0.20$).

DISCUSSION

The effectiveness of mesalamine in the treatment of inflammatory bowel disease is attributed mainly to its topical action on the intestinal mucosa. Mesalamine is readily absorbed from the small intestine so various polymeric coatings allowing delayed release of the medication have been developed to prevent release of mesalamine until the drug reaches the target site in the small bowel or colon. Most of these coatings are pH-dependent. Thus, release characteristics of the different tablets vary depending on the coating and are important in predicting the site of drug activity. The Salofalk 750 mg tablets

TABLE 3
Abbreviated Rowasa I* recovery results

	Mean total dose in urine	Mean total volume of ileostomy effluent	Mean total dose of ileostomy effluent	Mean total re- covery
Group 1	8.5±12.9%	1321±299 mL	53.0±25.0%	61.5±27.5%
Group 2	35.6±18.1%	604±216 mL	45.3±23.3%	80.7±23.2%

*Available only in the United States (Solvay Pharmaceuticals, Georgia)

have an enteric coating composed of a water-based, pH-sensitive polymer, Eudragit LD 30. In previous in vitro studies, maximal dissolution occurred between pH 6 and 7.5. In simulated intestinal pH 6.8, there was evidence of dissolution at 2 h and these tablets were completely dissolved by 3.5 h (2).

In the present study, ileostomates were chosen as models to study the release profile of Salofalk 750 mg tablets in the small bowel. Group 1 subjects were chosen to simulate patients who had a small resection and group 2 subjects to simulate those with normal intestinal anatomy. In both groups there was evidence that the tablets disintegrated (based on plasma levels and urine excretion) yet the medication was incompletely absorbed and present in the distal small bowel. Thus, these results suggest that the Salofalk 750 mg tablets should be effective in the treatment of small bowel disease.

As one would predict, because of the shorter intestinal surface area, group 1 subjects had a shorter mean small bowel transit time and an increased mean ileostomy effluent output, although only the latter was statistically significant compared with group 2 subjects. The mean plasma concentrations

of 5-ASA and N-ac-5-ASA in group 1 was not significantly smaller than in group 2. However, urinary excretion of mesalamine was significantly decreased in group 1, suggesting that there was decreased total absorption of mesalamine in subjects in whom there was less small bowel surface area. On the other hand, a higher proportion of mesalamine was recovered in the ileostomy effluent of group 1 than in group 2. Again, these results are predictable in group 1 because of the previous small bowel resection in these subjects.

The abbreviated results from a similar study with Rowasa I tablets (a 250 mg preparation of mesalamine available only in the United States (Solvay Pharmaceuticals, Georgia) are given in Table 3 (3). The two groups of subjects in that study were similar to those in the present study: group 1 comprised ileostomates who had had a small bowel resection while group 2 comprised ileostomates with an intact small bowel. The mean peak plasma concentrations of N-ac-5-ASA (5-ASA was not detected in any subjects receiving Rowasa I tablets) were significantly higher in both groups ingesting Salofalk compared with those receiving Rowasa I. In addition, a greater proportion of the mesalamine was recovered

in the urine and a smaller proportion in the ileostomy effluent of both groups of subjects taking Salofalk. These differences can be explained, only in part, by differences in the subject groups. In the present study, group 1 subjects had a shorter mean small bowel resection (65.0±22.4 cm versus 95±25 cm), longer mean intestinal transit time (10.9±5.0 h versus 7.1±3.6 h) and lower mean volume of ileostomy effluent (918±336 mL versus 1321±299 mL) than the group 1 subjects receiving Rowasa I. However, group 2 subjects in both studies had similar characteristics. Thus, the differences seem to be due, at least in part, to differences in the release characteristics of the medications. Salofalk 750 mg has a water-based, pH-sensitive, Eudragit enteric coating, whereas the Rowasa I coating is based on a matrix erosion system that is also pH-dependent.

CONCLUSIONS

These data suggest that Salofalk tablets disintegrate in the more proximal part of the small intestine compared with Rowasa I, resulting in greater absorption and less active 5-ASA available in the terminal ileum. Further investigation by gamma scintigraphy to confirm the exact release site of Salofalk 750 mg tablets in the small bowel would be useful. If it is indeed a more proximal release, Salofalk 750 mg may have greater efficacy in the treatment of Crohn's disease present in the proximal small bowel or in patients who have had a significant small bowel resection.

ACKNOWLEDGEMENTS: This study was supported by Axcan Pharma.

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