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Colonic spread of three rectally administered mesalazine (Pentasa) dosage forms in healthy volunteers as assessed by gamma scintigraphy

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SUMMARY

Background: Rectal administration of enemas, foams and suppositories is the most efficient method of delivering locally-acting drugs to the distal colon, sigmoid colon and rectum. Healthy volunteers provide an effective population to compare different formulations for rectal drug delivery. However, there is still only limited comparative information available on the dispersion of such dosage forms in human subjects. Therefore, the objective of this scintigraphic study was to compare colonic spread of an enema, a rectal foam and a suppository formulation in healthy volunteers.
Methods: This was a randomized, crossover study in eight healthy male volunteers. Each received Pentasa rectal formulations as either a 100 mL suspension enema (1 g mesalazine), one actuation of a non-CFC propellant rectal foam (1 g mesalazine in 5 mL concentrate, expanding to 40 mL on actuation), or one suppository (1 g mesalazine) on three separate occasions. The spread of the radiolabelled formulations was assessed over a 4-h period by gamma scintigraphy.
Results: The formulations were retained by all subjects for the whole of the 4-h imaging period. The enema spread to the splenic flexure in 7 out of 8 subjects, but was retained in the rectum and sigmoid colon in one individual. The foam spread as far as the descending colon in four subjects. In the remaining individuals the foam was retained in the rectum and sigmoid colon. The spread of the suppository was limited and confined to the rectum.
Conclusions: The findings of this study are consistent with previous research and support the intended clinical uses of the enema, foam and suppository formulations to treat distal ulcerative colitis, proctosigmoiditis and proctitis, respectively. The results highlight the potential of gamma scintigraphy in providing *in vivo* 'proof of concept' data to help verify the targeting of pharmaceutical products to their intended site of delivery.

INTRODUCTION

Rectal treatment with enemas, foams and suppositories is the most efficient method of delivering an adequate quantity of locally active anti-inflammatory drugs to the distal colon for the treatment of ulcerative colitis.[1] Several drug formulations available for this purpose contain the active moiety mesalazine, the efficacy of which is considered to be due primarily to its topical action.[2] Rectal administration is also beneficial because a large amount of drug can be delivered to the target site with low systemic absorption and therefore a low incidence of side-effects.[3] Enemas and suppositories have thus become widely accepted in the treatment of patients with distal ulcerative colitis and proctitis, respectively.[4–6]

The spread of rectally administered formulations within the distal colon is dependent on both the type

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and volume of preparation administered.[7, 8] Previous scintigraphic studies have shown that the spread of both suspension enemas and rectal foams is more extensive than that observed for suppository formulations.[8, 9] The spread of suppositories has been shown to be largely confined to the rectum,[10, 11] whilst suspension enemas and rectal foams, depending on volume, spread as far as the transverse colon in colitic patients.[1] Smaller volume suspension enemas and rectal foams[12, 13] are targeted to reach the rectum and sigmoid colon, whereas larger volume preparations are targeted to more proximal areas of the colon.[14]

The spread of rectally administered products can be readily assessed by gamma scintigraphy.[15] Previous rectal scintigraphic studies have shown comparable colonic spread data between healthy volunteers and patients with quiescent ulcerative colitis.[4, 12] In both subject populations, spread of low volume enemas was largely confined to the rectum and sigmoid colon, with only limited dispersion into the more proximal areas, whilst larger volumes spread more extensively within the large bowel. Crossover studies in patients with active colitic disease are intrinsically highly variable because there is no guarantee that the disease state will be similar for each treatment regimen. As a consequence, healthy volunteers provide an effective population to compare different strategies for rectal drug delivery. There is still only limited comparative information available, however, on the dispersion of such formulations in human subjects. Therefore, the objective of this scintigraphic study was to compare colonic spread of a 100 mL enema (1 g mesalazine), a rectal foam (1 g mesalazine in 5 mL concentrate expanding to ≈40 mL on actuation) and a suppository (1 g mesalazine), in a group of eight healthy male volunteers. The preparations were developed to facilitate targeting to the distal colon, sigmoid colon and rectum, respectively, for the treatment of colitic disease. It was envisaged that the results of the scintigraphic study would provide *in vivo* 'proof of concept' data for the different targeting strategies.

MATERIALS AND METHODS

Manufacture of radiolabelled formulations

The products used in the study consisted of: a commercially available Pentasa suspension enema of 100 mL volume containing 1 g mesalazine; a Pentasa non-CFC propellant rectal foam containing 1 g mesalazine per 5 mL concentrate, expanding to ≈40 mL on actuation, and delivered via disposable rectal applicators; and a commercially available Pentasa suppository formulation containing 1 g mesalazine. All formulations were supplied for use in the trial by Ferring Pharmaceuticals A/S (Copenhagen, Denmark).

The suspension and rectal foam were labelled by the direct incorporation of an aqueous solution of ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) into the formulation. Sufficient radionuclide was added to yield ≈4 MBq per actuation at the time of administration. The radiolabel was added to the rectal foam canisters via a syringe following removal of the metering valve. A new valve was then crimped to the canister. A non-CFC propellant and clinical grade nitrogen were then added to the rectal foam canisters through the valve.[9, 15, 16] The radiolabel was added to the suspension enema via a syringe, inserted through the bottom of the container. Following addition of the radiolabel, the hole was then re-sealed.

The suppository formulation was radiolabelled via the technique of neutron activation,[17] a method commonly used to radiolabel oral dosage forms but which, prior to this investigation, has never been applied to rectal products. Each suppository contained 2 mg samarium oxide enriched with the ^{152}Sm isotope. The preparation was irradiated for 6 min, to yield ≈1 MBq of ^{153}Sm per suppository at the time of administration.

Prior to the study, *in vitro* studies were performed on all three formulations. Confirmation of the homogeneity of the radiolabelled enema and foam was assessed by the acquisition of static scintigraphic images of ≈50-cm strips of these formulations. The suppository formulation was irradiated for 6 min and was then analysed to confirm that the neutron activation procedure did not affect the behaviour of the preparations. All suppositories administered to volunteers were irradiated under the same conditions as for the *in vitro* tests, i.e. a maximum of 48 h before dosing. *In vitro* dissolution of mesalazine from the suppository formulation was not affected by the addition of the isotope, nor by the neutron activation technique.

Study design

This was a randomized, crossover study in eight healthy, male volunteers. Prior to entry into the study, the nature of the investigation was explained both verbally and in writing to each subject, and each

volunteer provided written consent. Each subject underwent a medical examination, both prior to entering and on completing the study. Approval to administer rectal preparations labelled with either technetium-99m (^{99m}Tc) or samarium-153 (^{153}Sm), to healthy volunteers, was obtained from the Department of Health, London, and the Clinical Protocol was approved by the Quorn Research Review Committee.

Study procedures

Prior to dosing the subjects were asked to evacuate their bladder and, if possible, their bowel. The formulations were then administered, by a nurse, to subjects lying on their left side. Each volunteer received either the total contents of one enema (100 mL), one actuation of the foam, or one suppository, on each of three separate occasions, separated by a minimum wash-out period of 6 days. For the foam, each actuation of the metering valve delivered ≈1 g mesalazine contained in 5 mL of the formulation, which expanded to ≈40 mL and was delivered via one of the disposable rectal applicators, directly attached to the valve. The weight of foam administered to each subject was calculated by weighing the canister before and after dosing.

Following administration, all subjects remained lying on their left side for 2 h to aid retention of the formulation, and then remained sitting between imaging for the remainder of the study. Dispersion of each formulation was monitored over a 4-h period using a gamma camera (General Electric Maxicamera) with a 40-cm field of view and fitted with a low-energy parallel hole collimator. Scintigraphic images were acquired at 0, 5, 10, 20, 30, 45 and 60 min and every 30 min thereafter for up to 4 h following administration of the formulation. The images were acquired over 60 s for the enema and foam formulations throughout the study and for up to 75 s for the suppository formulation. Anterior images were acquired for the enema and foam formulations, whilst both anterior and lateral images were acquired for the suppository formulation, in order to maximize data collection. A posterior view of the pelvis and lower abdomen was also recorded at 4 h post-dose for all formulations.

Analysis of the scintigraphic data

The images from each subject were displayed on a colour monitor and the extent of spread assessed in terms of the anatomical location of the tracer. The computer was used to define regions of interest within the images for the enema and foam preparations and this allowed count rates to be determined from each section of the intestine. Each count rate was corrected for background counts, and the geometric mean of the anterior and posterior count rates at the end of the study provided a correction for tissue attenuation of the radiation.[9, 18] The corrected count rates for each region of the intestine were expressed as a proportion of the count rate from the whole dose. The data were analysed to determine the percentage of enema and foam present in the rectum, sigmoid colon, descending colon and transverse colon. The spread of the suppository formulation was confined to the rectum and so the lateral images were analysed to show a count rate contour; local tracer spread was expressed in terms of dimensions of the contour.[10]

RESULTS

Gamma scintigraphy is a planar imaging technique, and due to the anatomical orientation of the large bowel, it was not possible to differentiate between activity present in the rectum and sigmoid colon for the suspension enema in subjects 01, 02 and 06, and for the foam in subjects 02, 03, 05, 06 and 08, and therefore the activity in these regions was grouped for these individuals.

For the enema the extent of spread was variable, extending at least as far the splenic flexure in 7 out of 8 subjects with the percentage of the dose, at maximal extent of spread, ranging from 2 to 32%; in four of these volunteers, the enema also spread into the transverse colon. In one individual (subject 03), the preparation was retained in the rectum and sigmoid colon. In no subject in this study did the enema reach the ascending colon. The time to reach maximal extent of spread (Table 1) also varied considerably, ranging from 0.77 h (subject 07) to 4.00 h (subjects 03 and 04). The individual dispersion profile for all eight subjects (Figure 1) shows that at 4 hours post-dose spread into the descending colon of the suspension enema varied from 0% (subject 3) to 42% (subject 5).

The foam was less extensively dispersed in the colon than the enema. Again, the extent of spread was variable and the data could be divided into two discrete groups. In four subjects (01, 06, 07 and 08), 100% of the dose was retained in the rectum and sigmoid colon

Table 1. Maximal extent of spread of the 100 mL enema and foam for each volunteer

	Enema spread			Foam spread		
Subject number	% of dose	Time (h)	Anatomical location	% of dose	Time (h)	Anatomical location
01	9	2.48	Transverse colon	33	2.50	Sigmoid colon
02	25	3.57	Descending colon	66	3.87	Descending colon
03	70	4.00	Sigmoid colon	7	4.03	Descending colon
04	27	4.00	Descending colon	15	3.52	Descending colon
05	5	1.03	Transverse colon	40	3.00	Descending colon
06	32	3.50	Descending colon	100	0.02	Rectum and sigmoid colon
07	22	0.77	Transverse colon	52	3.98	Sigmoid colon
08	2	3.00	Transverse colon	100	0.02	Rectum and sigmoid colon

for the entire imaging period, whilst in the other four volunteers, between 34% and 93% was retained in this region at 4 h post-dose. The foam spread as far as the descending colon in these four individuals. On average, 85% of the foam was retained in the rectum and sigmoid colon at 4 h post-dose and 15% had spread as far as the descending colon. The mean quantity of foam administered per actuation was 4.4 g, corresponding to 1 g of mesalazine.

The spread of the suppository was limited and confined to the rectum. The extent of spread within the rectum was small, but was similar for all subjects, ranging from 5.3 cm (subject 08) to 10.8 cm (subject 03) at 4 h post-dose. The individual spread profiles (Figure 2) show a gradual spread throughout the imaging period, with some fluctuation in the extent of spread occurring, especially during the first hour post-dose. At 4 h post-dose, the mean extent of spread was 7.2 cm.

All three formulations were retained by all volunteers for the duration of the imaging period. Spread of the formulations is illustrated in a series of scintiscans provided for subject 05 (Figure 3).

DISCUSSION

The spread of solution enemas has previously been investigated in healthy volunteers using gamma scintigraphy. Following dosing with 100 mL solution

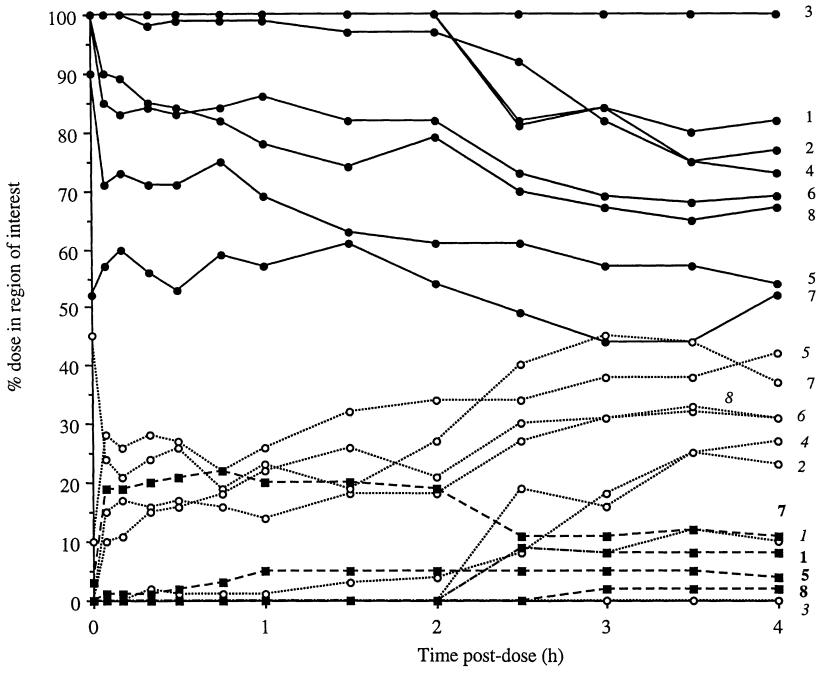

Figure 1. Dispersion profile for 100 mL suspension enema in a group of eight healthy volunteers. (——) Rectum and sigmoid colon, (·····) descending colon, (-----) transverse colon.

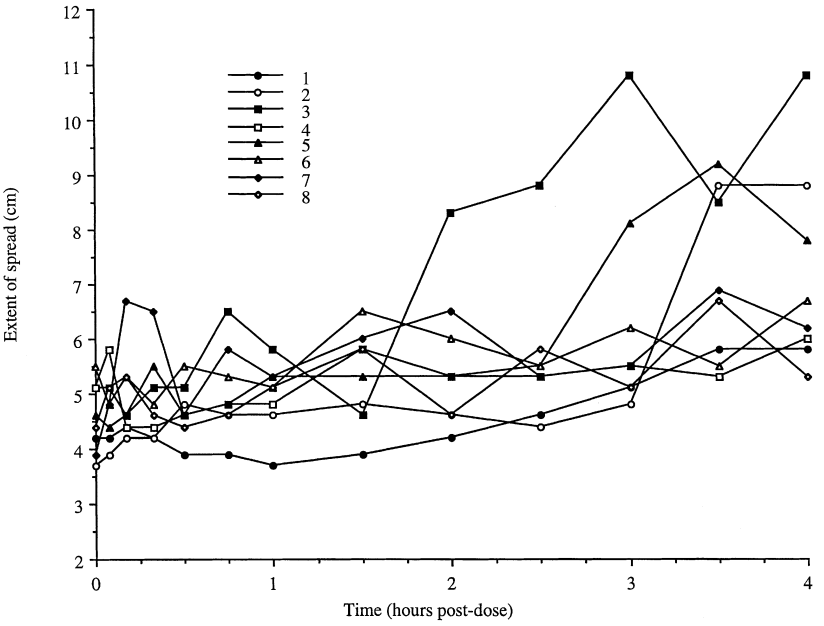

Figure 2. Dispersion of the suppository formulation in eight healthy volunteers.

enemas, dispersion was highly variable, ranging from total retention in the rectum and sigmoid colon to complete coverage of the whole of the large bowel.[9, 14] Only occasionally, however, do such preparations spread into the ascending colon.[8] The results observed in the present study are therefore very similar to other published data. Previous studies have shown that increasing the volume to 200 mL does not necessarily enhance spread into the ascending colon whilst 50 mL doses provide for less spread.[12, 13] A patient study has also shown that volume is an important determinant of colonic spread of mesalazine enemas in ulcerative colitis.[7] Spread patterns were shown to be unrelated to (moderate) disease activity in colitic patients. Suspension enemas can be difficult to self-administer and are also considered to be difficult to retain,[3] however, in this study all eight subjects fully retained the enema for the total duration of the imaging period, albeit under the controlled conditions of a clinical trial.

Foams offer greater convenience to the patient[19] and have been shown to spread more uniformly than suspension enemas.[1] As with solutions, the extent of spread of rectal foams is considered to be dependent on the quantity administered. Studies in healthy volunteers showed that low volume foams (30 mL) are retained within the rectum and sigmoid colon,[9, 13] whereas more bulky preparations (60–120 mL) exhibit comparable spread to that achieved with 100 mL solution enemas.[12, 14] A previous study, conducted by our group, of a rectal mesalazine non-CFC foam (two actuations of 60 mL, 120 mL in total) in patients with quiescent ulcerative colitis[4] showed spread of the foam as far as the descending colon in nine out of the 10 patients studied. The highly variable dispersion profile of the foam compared to the suspension enema is a consequence of the comparatively low expanded volume for the product. In some subjects this provides for delivery of drug to the descending colon whilst in others material is retained in the sigmoid colon. However, rectal foams for use in the treatment of proctosigmoiditis only require dispersion as far as the sigmoid colon, therefore despite the variable spread of the foam, the data from the study strongly supports its use in this indication. Overall spread was comparable to other low volume foams.[9]

The spread behaviour of ^{111}In-labelled suppositories has been examined using gamma scintigraphy on previous occasions;[10] spread of the mesalazine suppository formulation was comparable with findings observed previously. For the suppository formulation in this study, spread was localized in the rectum in all subjects for the entire duration of the imaging period.

CONCLUSIONS

In conclusion, the scintigraphic findings for the enema are consistent with previous research and support its use in the treatment of distal ulcerative colitis. For the

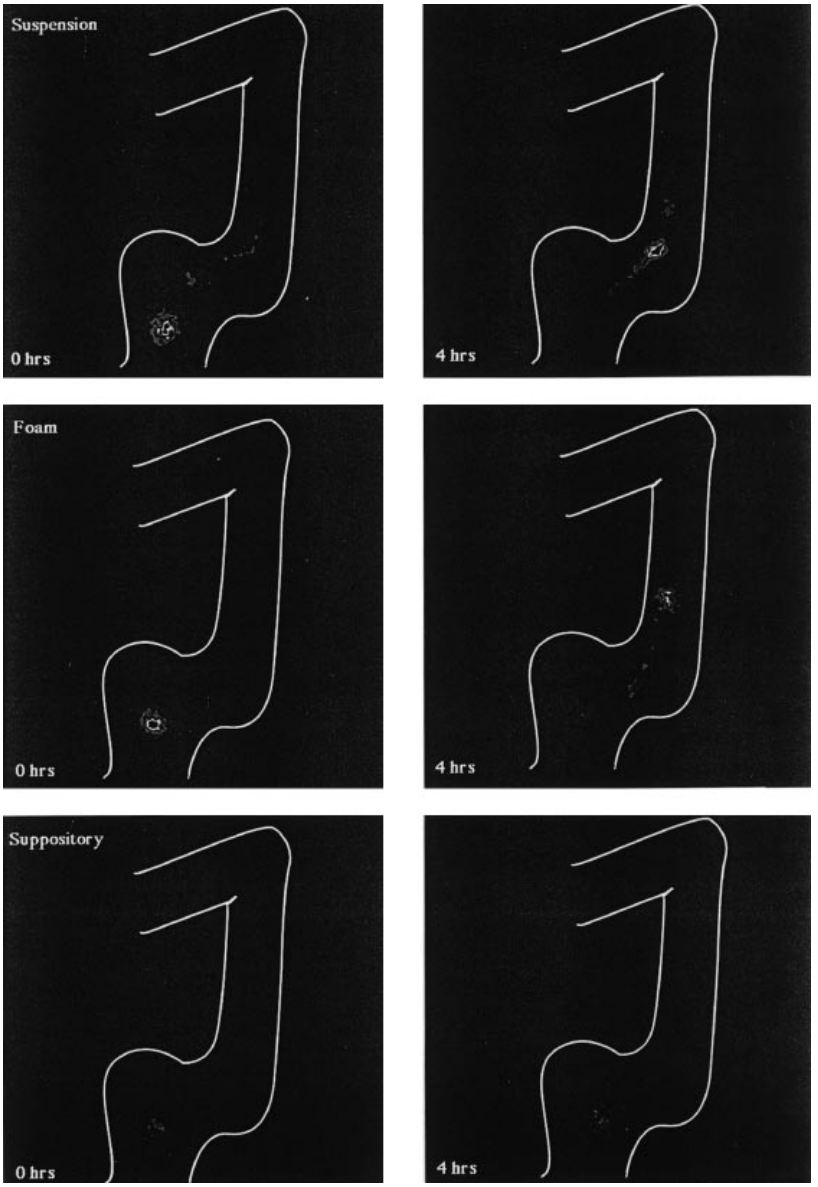

Figure 3. Colonic spreading of suspension enema, foam enema and suppository formulation immediately after dosing and 4 h post-dose in subject 05.

foam, spread was variable and was confined to the recto-sigmoid region in four out of the eight subjects. However, the localized dispersion of the foam was consistent with its intended use in the treatment of proctosigmoiditis. Suppositories are known to have a very limited spread, but the scintigraphic findings support their wide use in patients with proctitis,[3] and are consistent with those previously observed.[10] The results of the study highlight the potential of gamma scintigraphy in providing 'proof of concept' data to help verify the targeting of pharmaceutical products to their intended site of delivery.

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