Original Research Article

Spread of Mesalazine rectal foam after single dose in mild ulcer patients

ABSTRACT

Background: The rectal foam enemas were used for ulcerative colitis of distal regions due to its desired efficacy and less side effects. The spread and persistence of the drug plays a key role in the treatment. Therefore the objective of this present study is to study the spread and persistence of the mesalazine rectal foam in mild ulcerative colitis patients

Methods: This is an open label, uncontrolled study prospective study in ulcerative colitis patients. The patients received 2 g of mesalazine rectal foam (labelled with Tcm99) in two actuations (30 mL). The spread of the radiolabeled formulation was assessed over a period of 4 h by gamma scintigraphy.

Results: The formulation was retained by the patients till 4 h imaging period. The foam spread in rectum, sigmoid colon and descending colon. The percentage radioactive dose exposed is more in sigmoid colon compared to rectum and descending colon in 4 h imaging period. The spread of the foam extended till descending colon for two out of 4 patients.

Conclusion: The study results are consistent with the previous studies and it supports the label indication. The data obtained in the present study provides the in vivo evidence of the spread of formulation in the desired site of action.

Keywords: Mesalazine, ulcerative colitis

1. INTRODUCTION

Rectal treatment with formulations like enemas, foams and suppositories were widely used to administer sufficient quantity of drug to the target site. Mesalazine is delivered rectally to the distal colon for the treatment of ulcerative colitis. Mesalazine administered rectally as enemas and foams act locally to produce the desired action. The large amount of drug administered rectally to the target site reduces the side effects with low systemic exposure(1, 2).

The spread of the drug is determined by the formulation and the delivery mechanism used. The effectiveness depends on the spread of the formulation with appropriate volume towards the target site of action. Rectal foams and enemas spread extensively when compared to the suppositories. The scintigraphic study shows that the spread of suppositories is confined to the rectal region and the spread of foams and enemas is observed till transverse colon in the colitis patients. In practice usually smaller volume of enemas and foams is used to target the distal part of colon and large volumes were used for proximal part of colon (3).

The spread of rectally administered products in both healthy volunteers and patients with signs and symptoms of ulcerative colitis were not different as shown by the previous scintigraphic studies (4). The present scintigraphic study helps in the understanding of spread of formulation in the colon and shall be translated into the clinical practice after diagnosing colitis patients.

2. MATERIAL AND METHODS

PREPARATION OF RADIOLABELED FORMULATION

The objective of the present study is to observe the colonic spread of 30 mL of enema (2 g of mesalazine) following two actuations of commercially available Salofalk (Mesalazine foam Enema), manufactured by Dr. Falk Pharma GmbH. Salofalk consists of a canister, pump dome and the applicator. For each actuation of the mesalazine formulation is delivered through the applicator to produce 30 mL of foam. In the present study 30 mL of the delivered foam is studied after two actuations.

The nuclear medicine technologist placed about 111 MBq (3 mCi) of Tc99m DTPA (Diethylentriaminepentaacetic acid) in the foam generator/cap and fix the same back to the main container. The uniform distribution of the radioactive marker in the foam enema was assessed by the acquisition of static scintigraphic images.

PATIENTS

The study was open label, uncontrolled following single administration of mesalazine foam enema (two actuations containing 2 g of mesalazine in approximately 30 mL of foam) in four male patients with signs and symptoms of mild ulcerative colitis who were recruited by the treating physician. Prior to the entry in to the study the nature of the study procedures were explained to each patient verbally and in writing along with the audio-video recording of the informed consent process as per the local regulatory needs. Each patient underwent a medical examination prior to the entry in to the study and after completing the study, during which the blood samples for haematology, biochemistry and serology were evaluated for normal acceptable levels. ECG recordings were performed for all patients. Patients for whom the motions were normally formed were considered into the study.

Patients having urgency in stool, stool frequency greater than 3 times a day, Presence of macroscopic blood, mucus and pus in the stools, signs and symptoms of systemic disease, Patients with anaemia, patients with fever, elevation of erythrocyte sedimentation rate, patients with tachycardia, patients with stenosis of the rectum, patients with asthma, known hypersensitivity to salicylates or any of the excipients, and patients with severe impairment of hepatic or renal function were excluded.

Approval to conduct the study is obtained from the BIBI Independent Ethics committee Hyderabad, India prior to the study.

STUDY DESIGN

An open label, prospective, single centre, uncontrolled, Observational study. Screening was performed between days -14 to day -1 prior to dose administration. A total of four (04) subjects will be enrolled and housed in the clinic for not less than 1 hour prior to dosing and 04 hours post dose. The eligible patients received the rectal foam and followed by scintigraphic scans at regular intervals to evaluate the spread of foam in the abdomen regions. Patients were asked to refrain from taking any solid food or beverage for 4 hours post dose and only water was permitted until then. Diet which may increase the gastric motility was not allowed.

Prior to drug administration the patients were asked to evacuate both their bowel and bladder.

The study medication was self-administered rectally by the patients after defecation and after shaking the container and discarding the first shot in the presence of the investigational staff. The drug dispensing was done as per the direction of nuclear physician. Patients were instructed not to smoke during the study. Vitals signs (blood pressure and pulse rate) were performed prior to dosing. Foam dispersion was monitored for up to 4 h post dose using a gamma camera. The scintigraphic scans were obtained at 5 min (Time zero), 15 minutes, 30 minutes, 1 hr, 2 hr, 3 hr and 4 hr post dose. The patients were asked to remain seated after each scan. Adverse events were monitored by the physician during the study. A follow up visit was performed after 4 days of dosing to ensure safety.

SCINTIGRAPHIC DATA

The images from each patient were displayed on a colour monitor and the extent of spreading assesses in terms of the anatomical location of the tracer. The computer was used to define regions of interest within the images, and this allowed count rates to be determined from each section of the intestine. The counts were corrected for background counts. The system itself corrects for the decay time of the Tc99m. The radioactivity counts in different regions of the intestine were expressed as a proportion of the count rate from the whole dose.

3. RESULTS AND DISCUSSION

RESULTS

The scintigraphic data were analyzed to determine the percentage of foam present in the rectum, sigmoid colon, descending colon and transverse colon (Table 1). The distribution of the radioactivity was observed in rectum, sigmoid colon and descending colon in 2 out of 4 patients; however the spread was observed in 2 out of 4 patients in descending colon.

Predominantly the foam containing radioactivity was observed in the rectum and sigmoid colon. The total dose administered was evident in the rectum and sigmoid colon at 0 time. Following the rectal administration the radioactivity remaining in the rectal applicator was quantified and only the dose delivered is considered as 100% during the calculation. The mean residual activity detected in the rectal foam applicator was 13%; which suggest that about 87% percent of intended radioactivity (3 mCi/ 111 mBq) was administered to each patient.

The rectal foam enema was detected in rectum and sigmoid colon at 0 min in all the patients. On an average about 83 % of the administered dose was detected in the sigmoid colon at 30 minutes post dose and approximately the same levels were observed till 240 minutes (Table 1 and Figure 1). The inter subject variability for the detected radioactivity is less across the time points (Figure 1).

DISCUSSION

Several studies were conducted before using mesalazine rectal formulations in ulcerative colitis patients. There are advantages in using rectal delivery system for mesalazine which includes the direct delivery to the site of inflammation, reduced systemic adverse events and improved efficacy. The spread of the drug in the site of action is always a question because it varies based on the dose, volume, the type of formulation and delivery mechanism used to administer the drug.

In the present study the mesalazine rectal foam enema was studies for its spread following rectal administration in mild ulcerative colitis patients. This study suggests that mesalamine containing foam spreads till descending colon and in two patients where it reached only till sigmoid colon. The results were in consistent with the reported literature which suggest that the exposure of drug following suppositories, foam, and liquid/gel administration was till rectum, sigmoid colon and descending colon, respectively5.

The persistence of the mesalazine rectal foam is important for its action on the target site. The commercially available mesalazine foam is intended to treat the mild ulcerative colitis of rectum and sigmoid colon. The data in the present study supports the indication proposed in the package insert and the formulation stays for minimum of up to 4 hr post dose in rectum and the sigmoid colon; which is expected to produce clinically desirable effect.

In the present study no adverse events were reported and there were no acceptance issues with respect to the mesalazine rectal foam by the patients.

Table 1: Percentage of radiolabeled foam enema present in different regions of colon during 20 hr imaging period.

Time (min)	Percentage radioactivity (Mean ± SD)		
	Rectum	SC	DC
0	36 ± 17	65 ± 17	-
30	17 ± 8	83 ± 8	-
60	10 ± 13	90 ± 13	-
120	7 ± 14	89 ± 14	5 ± 10
240	7 ± 14	79 ± 5	14 ± 10

SC: sigmoid colon; DC: distal colon

Figure 1a: Dispersion profile of rectally administered Mesalazine foam enema in ulcer patients

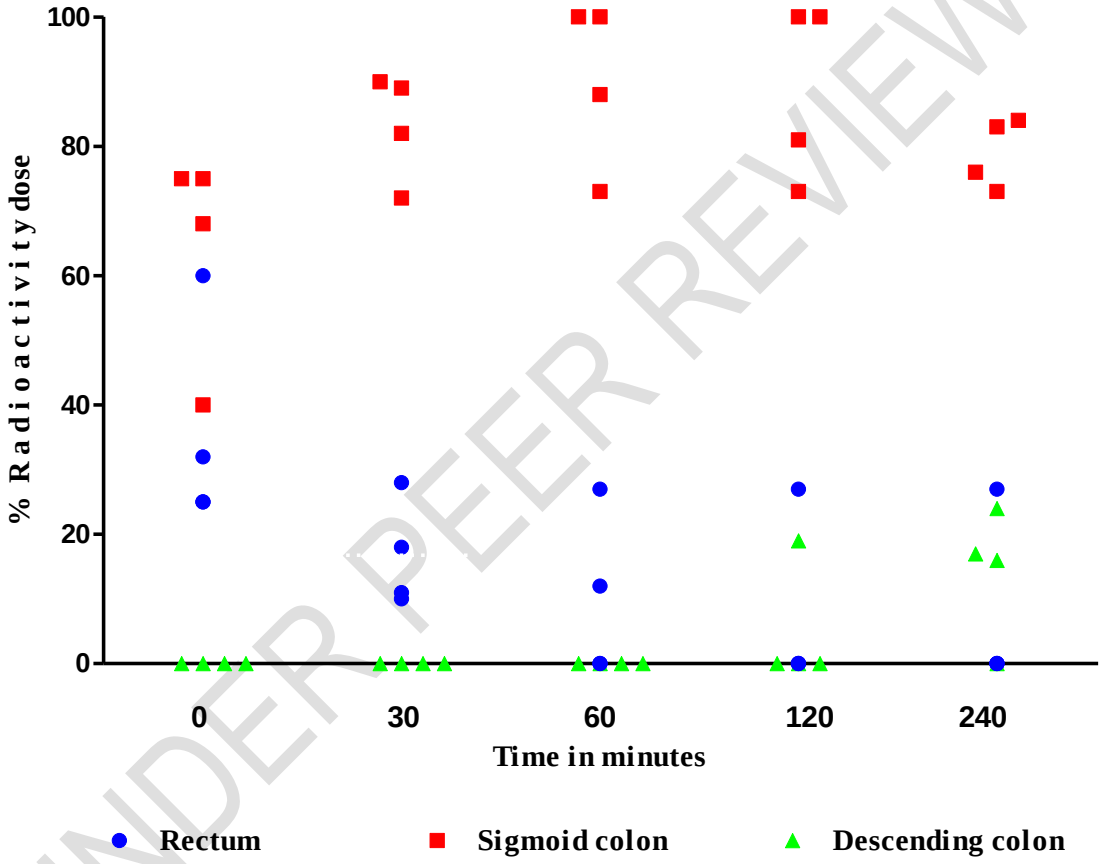


Figure 1b: Mean profile of rectally administered Mesalazine foam enema in ulcer patients

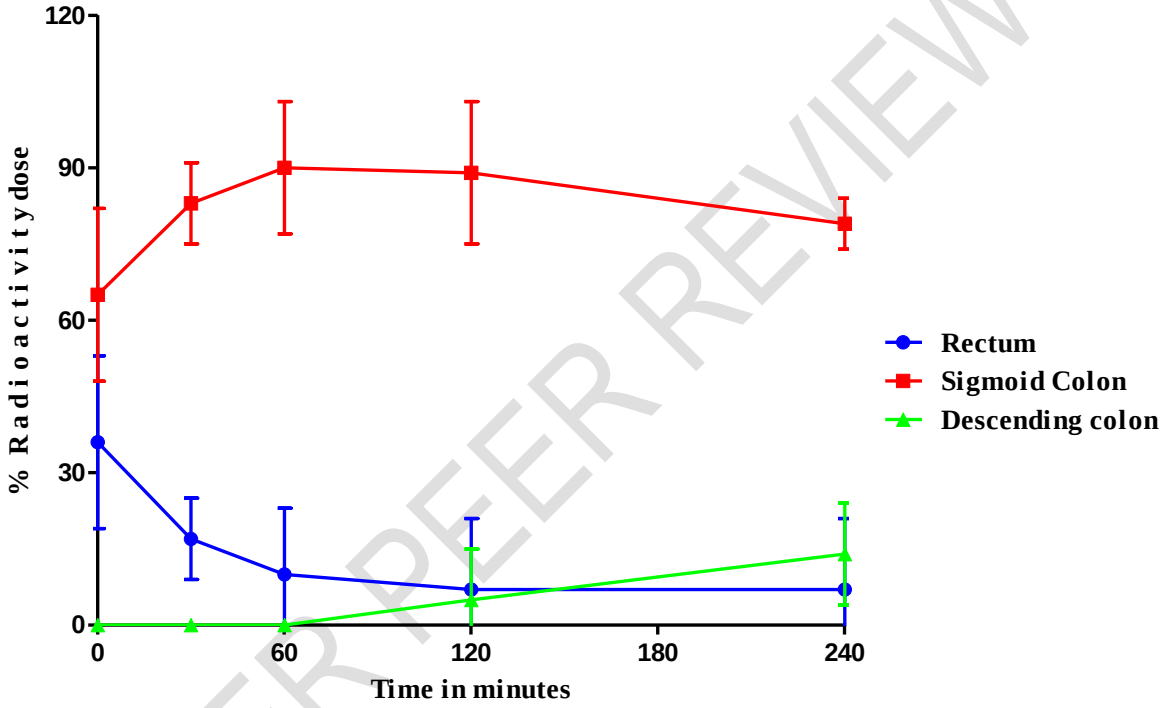


Figure 2: Scintiscans (lateral view) showing spreading of the foam enema in rectum and sigmoid colon.

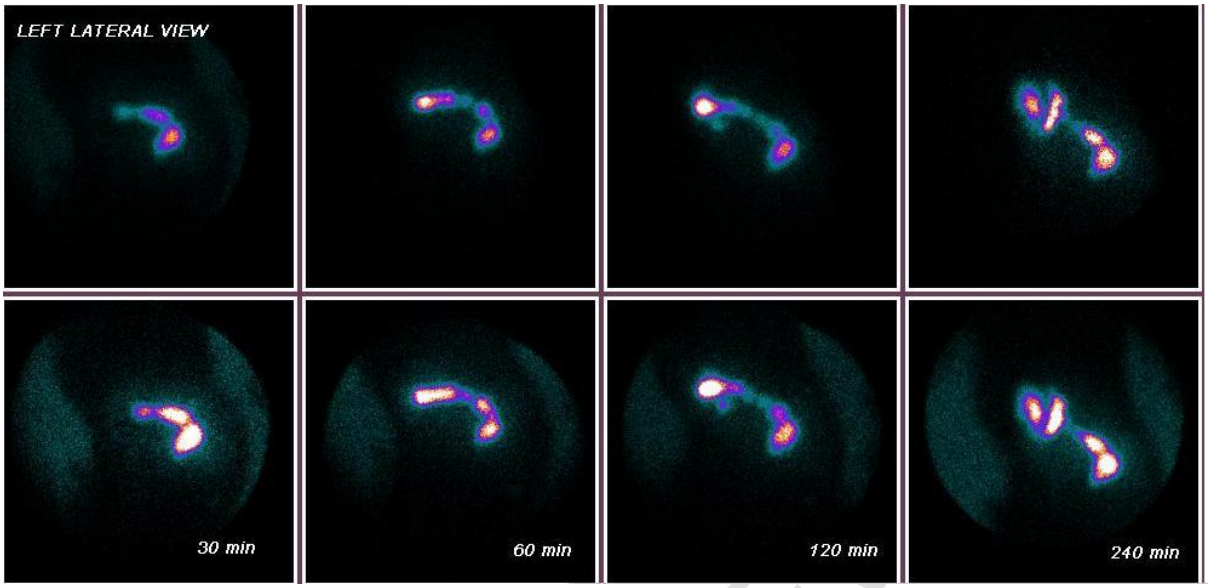
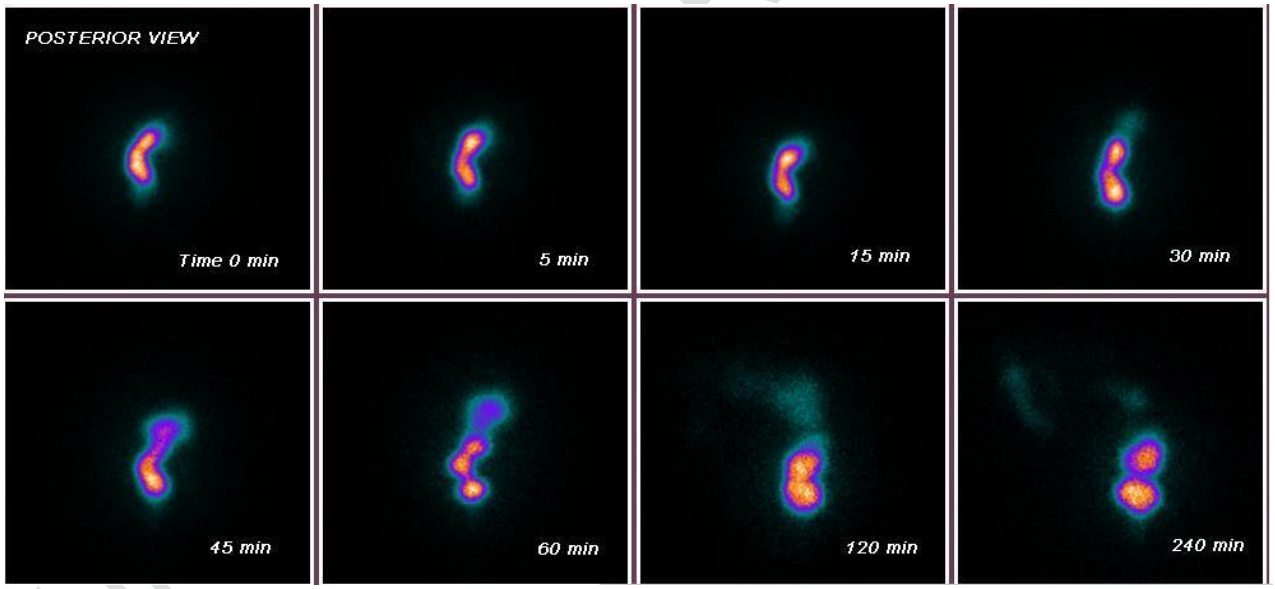


Figure 3: Scintiscans (Posterior view) showing spreading of the foam enema in rectum and sigmoid colon.



4. CONCLUSION

In conclusion, the mesalazine foam rectal formulation was well tolerated in the patients. In all the four patients the foam enema was observed to reach the rectum, sigmoid colon and

descending colon, which supports the use of this formulation in patients with mild ulcerative colitis of rectum and sigmoid colon.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

“All authors hereby declare that "EC approval was obtained and followed GCP was followed , as well as specific national laws where applicable.

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Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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