Journal of Pharmaceutical Research International

34(40B): 39-44, 2022; Article no.JPRI.88064
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Spread of Mesalazine Rectal Foam after Single Dose in Mild Ulcer Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Authors KR and KK did the nuclear imaging. Authors SP, MS, SK and SVSA did the clinical study and manuscript preparation. Author RS helped in medical statistics. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i40B36265

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/88064

Original Research Article

Received 23 March 2022
Accepted 06 June 2022
Published 07 June 2022

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 the present study is to study the spread and persistence of Salofalk (Mesalazine foam Enema), manufactured by Dr. Falk Pharma GmbH (mesalazine) rectal foam in mild ulcerative colitis patients.
Methods: This is an open label, uncontrolled 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 obtained data of the present study provides in vivo evidence of the spread of formulation in the desired site of action.

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Keywords: Mesalazine; ulcerative colitis.

1. INTRODUCTION

Rectal treatment with formulations like enemas, foams and suppositories has been widely used to ensure sufficient drug administration 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 acts locally, in order to induce the desired action. The large amount of drug administered rectally to the target site reduces the side effects because of the 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. MATERIALS AND METHODS

2.1 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.

2.2 Patients

This is an open label, uncontrolled study searching the 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 their recruitment, study procedures were explained to each study participant verbally and in writing format, along with an audio-video recording of the informed consent process, as per local regulatory requirements. Each patient underwent a physical examination prior to his entry into the study and after completing the study, during which blood samples for hematology, biochemistry and serology were evaluated for normal acceptable levels. Electrocardiogram recordings were performed for all patients. Those with normal findings were considered for the study.

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

2.3 Study Design

This is an open label, prospective, single centre, uncontrolled, observational study. The medical screening was performed between days -14 and day -1 prior to the study medication administration. A total of four (04) subjects were 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 scintigraphic scans were conducted at regular intervals in order to evaluate the spread of foam in the large bowel regions. Patients were asked

to avoid any solid food or beverage for 4 hours post dose and only oral water intake was permitted until then. Any diet that 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 4 days after dosing to ensure the safety of the study.

2.4 Scintigraphic Data

The images from each patient were displayed on a color 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

3.1 Results

The scintigraphic data was 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 suggests that about 87% percent of the 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 Fig. 1). The inter subject variability for the detected radioactivity is less across the time points (Fig. 1).

3.2 Discussion

Several studies have been conducted so far, using mesalazine rectal formulations in ulcerative colitis patients [4,5,6,7,8,9,10,11]. There are advantages in using rectal delivery system for mesalazine which includes the direct delivery to the site of inflammation, with 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 evaluated for its spread following rectal administration in mild ulcerative colitis patients. According to the study results, mesalazine containing foam spreads till descending colon in the half of the participants and in the half reaches only sigmoid colon. Our results were consistent with other literature reports which suggest that the exposure of drug following suppositories, foam, and liquid/gel administration may reach rectum, sigmoid colon and descending colon, respectively.

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

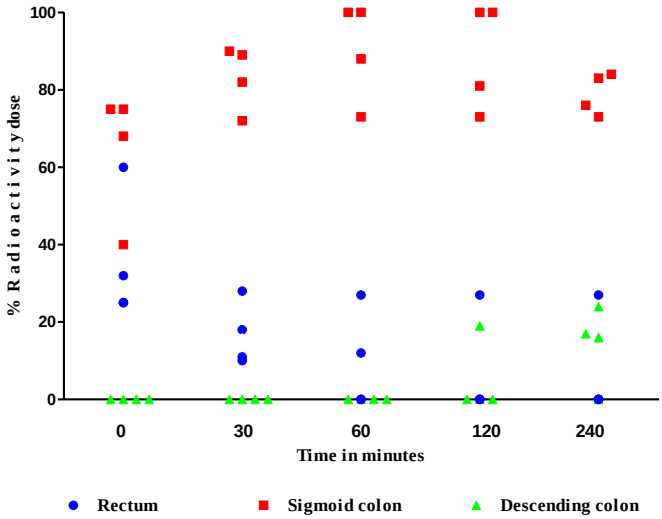

Fig. 1a. Dispersion profile of rectally administered Mesalazine foam enema in ulcer patients

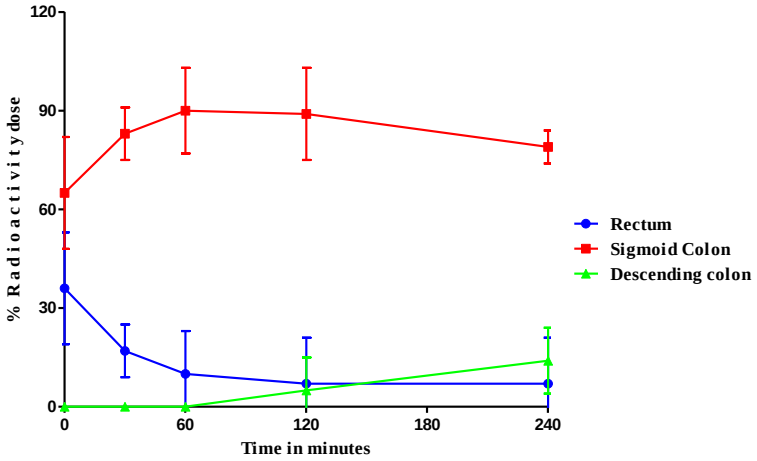

Fig. 1b. Mean profile of rectally administered Mesalazine foam enema in ulcer patients

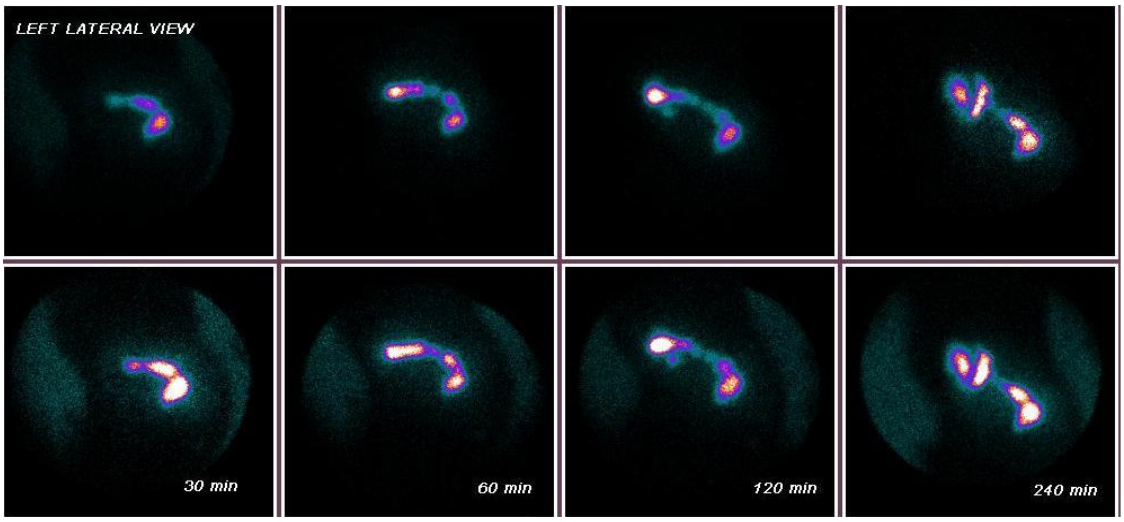

Fig. 2. Scintiscans (lateral view) showing spreading of the foam enema in rectum and sigmoid colon

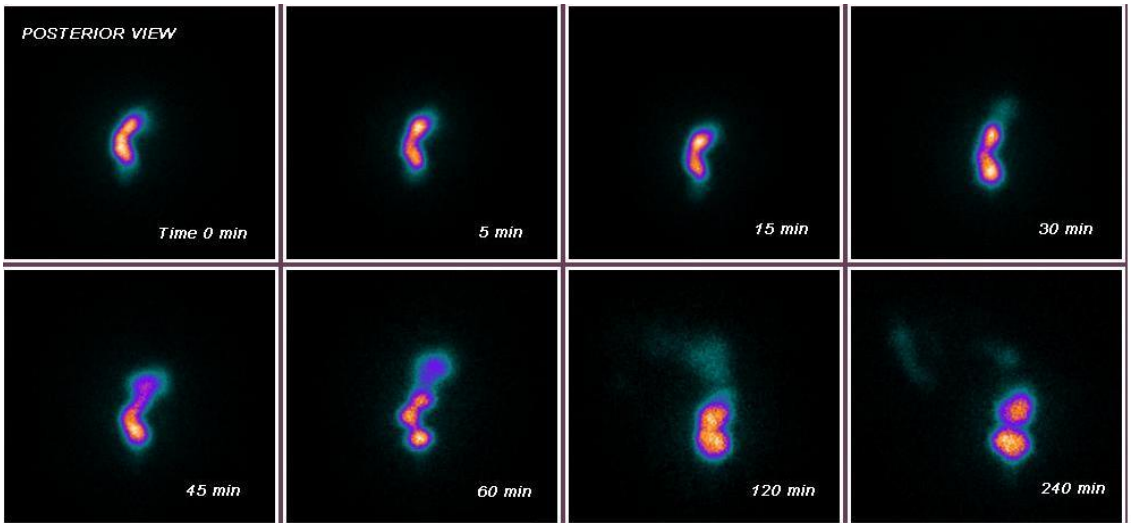

Fig. 3. Scintiscans (Posterior view) showing spreading of the foam enema in rectum and sigmoid colon

4. CONCLUSION

In conclusion, the mesalazine foam rectal formulation was well tolerated from the study participants. 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.

DISCLAIMER

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.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

An ethical approval to conduct this study was obtained from the BIBI Independent Ethics committee Hyderabad, India.

ACKNOWLEDGEMENTS

We thankfully acknowledge the sponsors and participants of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/88064