International Journal of Pharmaceutics, 25 (1985) 191–197
Elsevier

IJP 00848

The spreading of foam and solution enemas

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(Received February 8th, 1985)
(Accepted February 22nd, 1985)

Key words: enema spreading – gamma-scintigraphy – prednisolone foam

Summary

The spreading of radiolabelled foam and solution enemas administered to normal subjects has been monitored using gamma-scintigraphy. The foam preparation was retained within the rectum and sigmoid colon. Spreading of the solution was highly variable; the preparation reaching the ascending colon in some subjects but not dispersing beyond the sigmoid colon in others. The distributions achieved were unrelated to bowel habit.

Introduction

Drug preparations for intrarectal administration are supplied as solutions, foams and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drugs to the large intestine.

Corticosteroids, such as hydrocortisone and prednisolone, are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to topical action. The concentration of drug reaching the colon will depend on formulation factors, the extent of retrograde spreading and the retention time. Foams (Farthing et al., 1979; Hay et al., 1979) and suppositories (Hay, 1982) have been shown to be retained mainly in the rectum and sigmoid colon. Enema solutions have a greater spreading capacity (Hay, 1982). Swarbrick and colleagues (1974)

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found a wide variation in the distributions of solutions following administration to patients with colitis; the same volume of solution remaining in the rectum and sigmoid colon in one patient, while spreading throughout the large intestine in another. Foams tend to be easier to apply and are more readily retained than solutions (Clark, 1977; Hay, 1982). Due to their limited spreading, however, the use of foam preparations tends to be restricted to the treatment of more distal disease.

The present study has been undertaken to compare the distributions of a foam and a solution as delivery systems for prednisolone metasulphobenzoate. The spreading of the preparations within the large intestine has been considered in relation to the bowel habits of the subjects.

Materials and Methods

Materials

The solution was supplied as placebo 'Predenema' (Pharmax, Bexley) in individual 100 ml doses in plastic bags. Each dose was radiolabelled by the addition of 1 ml [$^{99}Tc^{m}$]-labelled diethylenetriaminepentaacetic acid solution to the bag, via the applicator tube. This tracer is not absorbed from the gastrointestinal tract, and was found to mix uniformly with the enema solution.

Two foam preparations were provided (Pharmax, Bexley), each in an aerosol can fitted with a metering head designed to deliver 1 g doses. One preparation contained prednisolone metasulphobenzoate and the other contained no steroid. The placebo foam was radiolabelled using 30 mg Amberlite CG400 anion exchange resin particles 60–130 μm in diameter (Hopkin and Williams, Chadwell Heath) on to which had been adsorbed [$^{99}Tc^{m}$]pertechnetate (CIS (UK), London). The resin powder was introduced into the empty metering system of the can prior to dispensing the dose. The volume of each dose of foam was approximately 30 ml, and in vitro imaging studies and measurements of radioactivity in samples of foam confirmed uniform radiolabelling. The stability of the radiolabelled placebo foam was compared with that of the two non-radiolabelled foam preparations. All three foams were stable and maintained similar volumes when exposed to the air over a 3-day period at 37°C in glass measuring cylinders.

Subjects

The preparations were administered to 8 male volunteers, aged 21–23 years. All the subjects were healthy and none was taking medication of any kind. The study was approved by the local ethical committee and each subject gave written informed consent prior to participating.

Methods

Each volunteer received the placebo foam and the placebo solution on separate occasions at least 4 weeks apart. During their first studies 4 subjects were given the foam and 4 the solution; and on the second occasion each group was dosed with the alternative preparation. The subjects were all dosed within 1 h of finishing lunch, but

otherwise underwent no special preparation. They all provided information concerning their bowel habits.

Each dose was radiolabelled with 3 MBq technetium-99m, and the solution was warmed to 37°C prior to administration. The 8 cm long applicator tube was lubricated with K-Y Jelly (Johnson and Johnson, Slough) and inserted into the rectum with the subject lying on his side. The solution was administered by squeezing the dose from the bag into the rectum, and the foam was ejected directly from the metering system into the applicator tube in less than 1 s. After withdrawal of the tube a technetium-99m-labelled anatomical reference marker was positioned at the anus. The subject then lay prone and remained in this position for 4 h.

Imaging was carried out using a gamma camera having a 40 cm diameter field of view and the data were recorded by computer. Posterior views of the abdomen each of 60-s duration, were recorded over a 4-h period, at 15-min intervals during the first hour and subsequently at 30-min intervals. At the end of each study an anterior view of the abdomen was recorded with the subject supine. The images were displayed on a television monitor and the extent of spreading assessed in terms of the anatomical

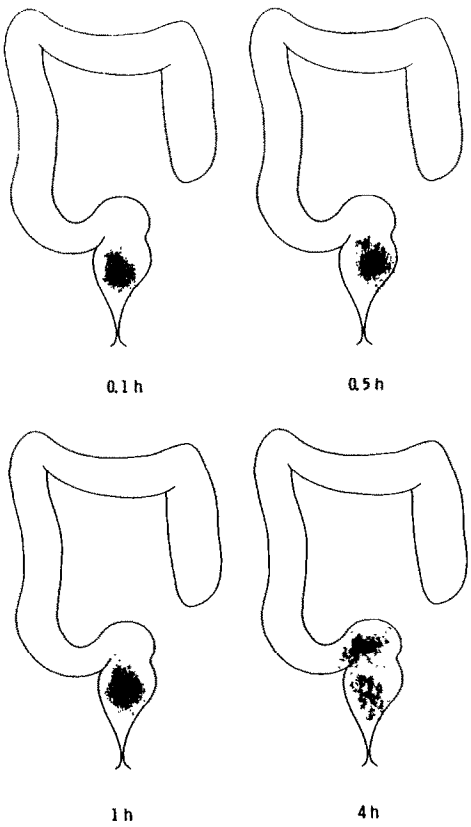

Fig. 1. Distribution of the foam following intrarectal administration (Subject 4).

location of the tracer. The computer was used to define regions of interest within the images, and this allowed the 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 recorded at the end of the study provided a correction for tissue attenuation of the radiation (Hardy and Perkins, 1985). The corrected count rates were expressed as a proportion of the count rate from the whole dose.

Results

The enemas were fully retained by all the subjects for the duration of monitoring.

Immediately following dosing the foam was localized mainly in the rectum in all the subjects. During the 4 h of monitoring there was a gradual retrograde movement of the tracer into the sigmoid colon (Fig. 1). In none of the subjects was the preparation detected in the descending colon.

The extent and rate of spreading of the solution was highly variable. The

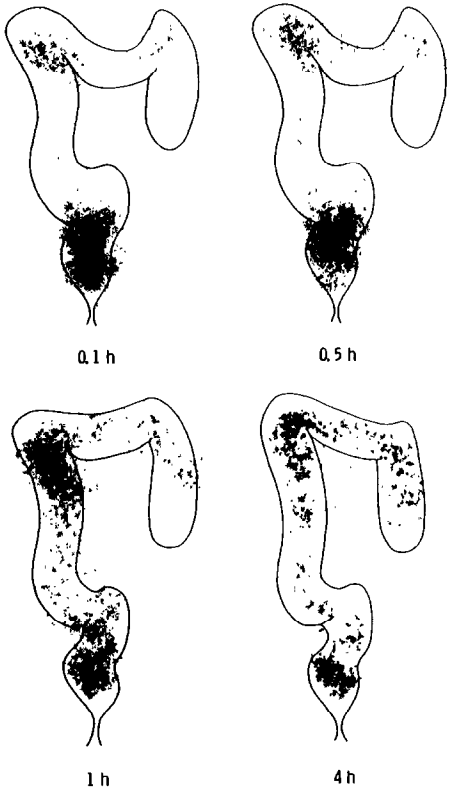

Fig. 2. Distribution of the solution following intrarectal administration (Subject 2).

TABLE 1

DISTRIBUTION OF THE ENEMA SOLUTION 4 h AFTER DOSING

Subject	Distribution within colon (% dose)			
	Rectum/Sigmoid	Descending	Transverse	Ascending
1	35	65		
2	16	38	35	11
3	28	72		
4	28	23	27	22
5	32	68		
6	22	63	15	
7	100			
8	100			

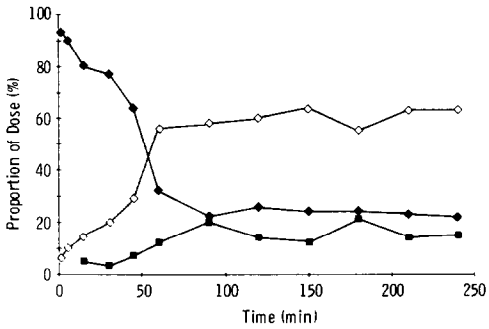

Fig. 3. Spreading of the solution within the large intestine (Subject 6). Preparation in rectum and sigmoid colon (◆), descending colon (◇) and transverse colon (■).

TABLE 2

BOWEL HABITS OF THE VOLUNTEERS

Subjects	Defaecations per day	Time between defaecation and dosing (h)	
		Foam dose	Solution dose
1	2	0.5	1.0
2	2	0.5	1.5
3	1	1.5	4
4	1	12	4
5	1	18	18
6	1	4.5	18
7	0.5	40	1.0
8	1	17	1.0

preparation remained in the rectum and sigmoid colon in two subjects, and spread into the ascending colon (Fig. 2) in two others (Table 1). During 7 of the 8 studies, dispersion of the solution had ceased by 3 h (Fig. 3). The lunches consumed by the volunteers ranged from light snacks to substantial meals, but there was no apparent relationship between the type of meal and the extent of spreading.

All the subjects were regular in their bowel habits (Table 2). The times between defaecation and dosing varied considerably in both the foam and the solution studies. Least spreading of the solution occurred in the 3 volunteers dosed soonest after defaecation. The two volunteers, subjects 2 and 4, in whom greatest spreading occurred had defaecated 1.5 and 4 h, respectively, before the study. There was, however, no clear-cut relationship between defaecation time and extent of spreading.

Discussion

Both foam and solution enemas of corticosteroids provide effective treatments for ulcerative colitis (Matts, 1961; Clark, 1977). The extent and rate of spreading of rectally administered preparations is highly variable, even in normal subjects with regular bowel habits (Table 1). Foams tend to be retained in the rectum and sigmoid colon, while solutions may exhibit more extensive spreading.

The volume of the administered preparation may be an important determinant influencing retrograde movement. When volumes of less than 50 ml are applied either as foams (Farthing et al., 1979; Hay, 1982), solutions (Swarbrick et al., 1974), or suppositories (Hay, 1982), the preparations tend to remain in the rectum and sigmoid colon. In general, increasing the solution volume to 100–200 ml results in greater dispersion (Swarbrick et al., 1974; Hay, 1982). The structure of a foam will inhibit redistribution following administration, and even if it were to breakdown rapidly the resulting solution volume would be insufficient to bring about extensive penetration into the colon. The distributions achieved with larger volumes of solution may be influenced by the normal propulsion of the colon contents. Within the colon, orally dosed tracers have been shown to remain relatively immobile for prolonged periods with occasional bursts of anterograde movement (Hardy and Perkins, 1985). Such movements may prevent spreading of enemas. In the present study, the degree of spreading has been considered in relation to bowel habit. In two subjects the solution was contained entirely within the rectum and sigmoid colon for the duration of the study. These subjects had defaecated only one hour before enema administration. It is possible that the distal colon remained empty at the time of dosing, and was therefore able to accommodate the solution. Subsequent anterograde movement of the colon contents may have inhibited further spreading. Other factors which may be important are the consistency, amounts and location of the colon contents. Additionally, spreading may be more extensive in patients with active colitis (Swarbrick et al., 1974; Farthing et al., 1979), and during a course of treatment there may be a considerable variation in the spreading of doses within the same patient.

In addition to their topical action the corticosteroids may be acting systemically.

Lee et al. (1979) found that the blood concentration following rectal dosing with prednisolone-21-phosphate was 44% of that after oral dosing. Enema containing the poorly absorbed prednisolone metasulphobenzoate, however, has been shown to be equally efficacious (McIntyre et al., 1985). This finding tends to support the view that topical action is the more important.

Acknowledgements

We wish to thank Pharmax Limited for the supply of the enema preparations and for financial assistance with this study.

References

Clark, M.L., A local foam aerosol in ulcerative colitis. Practitioner, 219 (1977) 103–104.

Farthing, M.J.G., Rutland, M.D. and Clark, M.L., Retrograde spread of hydrocortisone containing foam given intrarectally in ulcerative colitis. Br. Med. J., 2 (1979) 822–824.

Hardy, J.G. and Perkins, A.C., Validity of the geometric mean correction in the quantification of whole bowel transit. Nucl. Med. Commun., 6 (1985) 217–224.

Hay, D.J., In Wilson, C.G., Hardy, J.G., Frier, M. and Davis, S.S. (Eds.), Radionuclide Imaging in Drug Research, Croom Helm, London, 1982, pp. 171–180.

Hay, D.J., Sharma, H. and Irving, M.H., Spread of steroid-containing foam after intrarectal administration. Br. Med. J., 1 (1979) 1751–1753.

Lee, D.A.H., Taylor, G.M., James, V.H.T. and Walker, G., Plasma prednisolone levels and adrenocortical responsiveness after administration of prednisolone-21-phosphate as a retention enema. Gut, 20 (1979) 349–355.

Matts, S.G.F., Intrarectal treatment of 100 cases of ulcerative colitis with prednisolone-21-phosphate enemata. Br. Med. J., 1 (1961) 165–168.

McIntyre, P.B., Macrae, F.A., Berghouse, I., English, J. and Lennard-Jones, J.E., Therapeutic benefits from a poorly absorbed prednisolone enema in distal colitis. Gut, in press.

Swarbrick, E.T., Loose, H. and Lennard-Jones, J.E., Enema volume as an important factor in successful topical corticosteroid treatment of colitis. Proc. R. Soc. Med., 67 (1974) 753–754.