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Disposition of radiolabelled suppositories in humans

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The disposition of Witepsol H 15 suppositories radiolabelled with [^{99m}Tc] technetium hydroxymethyldiphosphonate was studied after rectal administration in volunteers. The migration of the radiolabel was monitored continuously by external scintigraphy. The resulting scintiphotos were superimposed on lower GI radiographs to determine the extent of spreading of the dosage form in the rectum. The dosage form migrated approximately 5–7 cm into the rectum in nearly all of the studies and was, in general, confined to the lower and middle regions of the rectum. Since the venous supply to the lower rectum leads primarily to the inferior vena cava, the data presented here indicate that the metabolism of drugs sensitive to the 'first-pass' effect may be partially avoided by their rectal administration.

Some controversy exists concerning the degree to which the 'first-pass' effect can be avoided by administering a drug as a rectal dosage form such as suppositories (Jonkman et al 1979). The avoidance of first-pass metabolism appears to be related to the area of spread of the suppository base within the rectum (de Boer et al 1979). Since the venous supply to the lower rectum (caudal and medial rectal veins) leads primarily to the inferior vena cava whereas blood supply to the proximal rectum (superior rectal vein) leads to the portal vein, it has been suggested that less presystemic metabolism is likely to occur if the contents of the suppository were confined to the distal rectum (Rutten-Kingma et al 1979). This was confirmed by Kamiya et al (1982) in rats given glyceryl trinitrate suppositories. The first-pass metabolism of propranolol was recently shown to be significantly decreased when the drug was absorbed from the most distal regions of the rectum (de Leede et al 1984). However, the biopharmaceutics of rectally administered suppositories in man has not been fully elucidated. The use of suppositories labelled with radioactive markers can provide information as to the fate of these dosage forms in-vivo.

A steroid foam-enema labelled with [^{99m}Tc]-pertechnetate bound to an ion exchange resin has been used to study the spread of the foam after rectal administration (Hay et al 1979) and a similar study has been made with a foam-enema labelled with ^{99m}Tc-sulphur colloid (Farthing et al 1979). In the present study, the degree of spreading of suppository bases after rectal administration was studied in volunteers using the external scintigraphic technique (Casey et al 1976). Witepsol H 15 suppositories labelled with [^{99m}Tc]technetium hydroxymethyldiphosphonate ([^{99m}Tc]HDP; Proctor and Gamble, Cincinnati, Ohio) were used to obtain serial images for the evaluation of the disposition of the dosage form.

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Methods

Preparation of suppositories. Witepsol H 15 suppositories (2 g) were prepared containing 50 μCi (0·01 ml) of [^{99m}Tc]HDP. Before administration, a suppository made from the same batch was tested for uniformity of distribution of the radiolabel by being divided into five segments of approximately equal size; the segments were weighed, placed in vials, and counted in a gamma scintillation counter (Packard Instrument Co., Downers Grove, Illinois), and the counts min^{-1} per unit weight were calculated for each segment. Variation from one segment to another never exceeded 5%.

Subjects. Four healthy male volunteers ranging from 25–44 years participated in the study according to a protocol approved by the institutional review board (12/14/81). The subjects were asked to maintain a record of their diet and bowel movements for the duration of the study. The subjects self-administered a ^{99m}Tc-labelled suppository each day for three consecutive days. The radiation exposure for each study was as follows: whole body = $9{\cdot}90 \times 10^{-4}$ rads; lower large intestinal wall = $8{\cdot}18 \times 10^{-2}$ rads.

External scintigraphic studies. After the self-administration of the labelled suppositories, the subjects lay prone while a gamma scintillation camera (General Electric, Cincinnati, Ohio) fitted with a pinhole collimator was positioned posterior to the sacral region. The camera, which allowed continuous observation of the suppository behaviour was interfaced with a computer thereby permitting data to be accumulated every 30 s for 1·5 h. To obtain qualitative information on the position of the radioactivity relative to anatomical features, an external marker was placed on the right iliac crest of each subject. Quantitative data on the spreading behaviour of the suppository in the rectum was obtained by a screening and optimization technique to choose two computer regions of interest (see Fig. 1). One region was chosen directly over the suppository immediately after it was administered (region A) while another region (region B) which surrounded region A was chosen to quantify the rate and degree of spreading. Activity versus time data generated by the computer for these areas of interest were obtained and are illustrated in Fig. 2.

To determine more precisely the extent of spreading of the dosage form in the rectum and understand the anatomical landmarks, a lower GI radiograph was obtained for two of the subjects. The radiographs were superimposed on the scintiphotos to permit the linear measurement of distance of spreading of the suppository base in the rectum (Fig. 3).

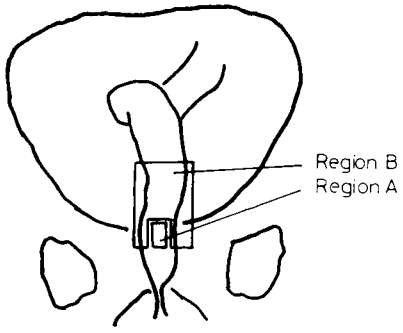

FIG. 1. Computer regions of interest for the measurement of a [^{99m}Tc]HDP labelled suppository. Region A detected radioactivity in the area of the rectum initially occupied by the suppository shortly after administration while the spreading of the suppository was detected in Region B.

Results

The in-vitro uniformity tests revealed that the distribution of the radiolabel [^{99m}Tc]HDP was effectively uniform throughout the Witepsol H 15 suppository base. In 11 of the 12 scintigraphic procedures, the suppository base migrated 5–7 cm into the rectum as determined by the radiographs superimposed on the scintiphotos. In others, little or no movement was observed, the dosage form apparently remaining in the anal canal. There was a negative slope for diminution of activity from the original insertion site (see curve A, Fig. 2) for all subjects. The loss of activity from region A was biphasic. The onset of melting or collapse of the suppository can be seen to be about 25 min (Fig. 2). Conversely, all subjects showed an increase in activity in the areas surrounding the dosage form after an initial plateau (curve B, Fig. 2).

The composite radiograph/scintiphotos (Fig. 3) demonstrate that the dosage form was confined to the middle or lower rectum for the 1·5 h of observation. It has been suggested that the spreading of rectal dosage forms may be less extensive in man when prone than when erect and moving due to the pressure exerted on the rectum by internal organs (Moolenaar & Schoolen 1980). However, a radiographic study employing cocoa butter suppositories containing barium sulphate revealed no difference in spreading between subjects in the upright and horizontal positions (Quevauviller & Jund 1951). The limited spreading of the suppository base observed in the present study supports the contention that the first-pass metabolism of many drugs may indeed be avoided by rectal administration.

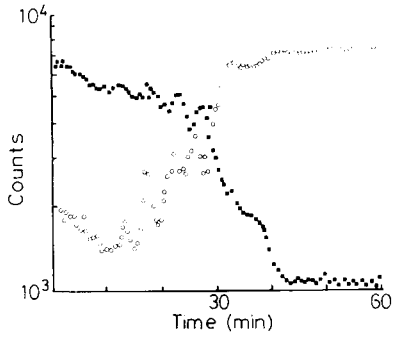

FIG. 2. Activity vs time curves for a radiolabelled suppository in regions A and B as defined in Fig. 1 in one of the subjects.

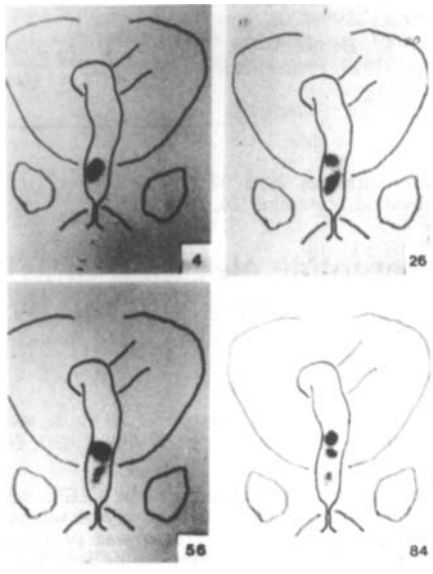

FIG. 3. Serial scintiphotos superimposed on a lower GI radiograph for a radiolabelled suppository in one of the subjects. The suppository is shown to spread upward in the rectum from the 4th to the 84th min after administration.

Discussion

In this communication, qualitative and quantitative information is presented on the disposition of Witepsol H 15 suppositories labelled with [^{99m}Tc]HDP using external scintigraphic techniques in combination with lower GI radiographs. Although a significant inter- and intra-subject variability was apparent, several generalities were observed. In particular, the insertion depth and extent of spreading of the suppository base was effectively uniform and, in no case, did the dosage form enter the colon.

Previous literature reports have provided conflicting information on the spreading of suppositories and

suppository bases after rectal administration even suggesting spreading into intestinal regions (Rutten-Kingma et al 1979). However, in three reports, suppositories were mistaken for renal calculi on abdominal radiographs (Spitzer et al 1976; Lesher & Scott 1979; Brown & Gould 1982). In all of the reports, the radiopacity was confined to the rectum of the patient for extended periods of time after the administration of the suppository, as much as 5 h in one case.

In summary, the data obtained supports the conclusion that the absorption of drugs administered in suppository dosage forms is confined to the lower rectum. Therefore, the metabolism of drugs sensitive to the first-pass effect may be partially avoided by their rectal administration.

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Pergolide elevation of MHPG sulphate concentration in rat hypothalamus blocked by spiperone and mimicked by other dopamine agonists

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Pergolide increased the concentration of MHPG sulphate (3-methoxy-4-hydroxy-phenylethylene glycol sulphate) in rat hypothalamus, and the increase was prevented by pretreatment with spiperone, a dopamine antagonist. An increase in hypothalamic MHPG sulphate concentration similar to that caused by pergolide was found after injection of quinpirole, a 'partial ergoline' that is a selective D_2 agonist not affecting α-adrenoceptors, and by (−)-*N*-propylnorapomorphine, a dopamine agonist not related to the ergolines. Although the increase in MHPG sulphate concentration produced by pergolide had earlier been assumed to result from blockage of α-adrenoceptors, the present data indicate that it is an effect produced by dopamine D_2 receptor stimulation.

Pergolide and lergotrile, two ergolines that are dopamine agonists, have been reported to increase brain concentrations of MHPG sulphate (3-methoxy-4-hydroxy-phenylethyleneglycol sulphate), the metabolite of noradrenaline (Fuller et al 1979; Fuller & Perry 1983). The ergolines, like many other ergot-related drugs, have relatively high affinities for α-adrenoceptors (McPherson & Beart 1983). Since α-adrenoceptor antagonists increase noradrenaline turnover and MHPG sulphate concentration in brain (Braestrup & Nielsen, 1976; Fuller et al 1978; Baumann & Waldmeier 1978), we had supposed that the increase in MHPG sulphate caused by pergolide and lergotrile might be due to blockage of central α-receptors by those drugs. In fact, an increase in MHPG sulphate concentration or other measures of noradrenaline turnover by bromocriptine, lisuride and other ergot drugs that are dopamine agonists, has been interpreted as due to block of α-adrenoceptors (Kehr 1977; Burki et al 1978). We describe here evidence that the increase in MHPG sulphate produced by pergolide is instead a result of its activation of dopamine receptors. The evidence consists of the findings that spiperone, a dopamine antagonist, blocks the effect of pergolide completely and that quinpirole, a 'partial ergoline' much less potent than pergolide in interacting with α-adrenoceptors (McPherson & Beart 1983), as well as (−)-*N*-n-propylnorapomorphine (NPA), a potent dopamine agonist unrelated chemically to the ergolines (Neumeyer et al 1973), mimics the effect of pergolide in elevating brain levels of MHPG sulphate.

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