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# The in vivo behaviour of a colonic delivery system: a pilot study in man

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**Abstract**

Eight healthy male volunteers were recruited for a study to determine the in vivo behaviour of an enteric coated, modified release beclomethasone dipropionate formulation. The non-invasive technique of gamma scintigraphy was used to relate position and integrity of the tablet formulation within the gastrointestinal tract to blood levels of beclomethasone dipropionate and its metabolites. Following fasted administration, tablet integrity was maintained in the stomach, and onset of disintegration occurred in the small intestine, leaving a sustained release core which eroded gradually. Complete tablet disintegration occurred in the small bowel in three volunteers and in the proximal colon in the remaining subjects. Low plasma concentrations of beclomethasone monopropionate were detectable in seven volunteers. In only one subject were both beclomethasone monopropionate and beclomethasone alcohol detected in the urine. Transit, disintegration and absorption were consistent with a formulation designed for topical treatment of inflammatory disease in the distal small bowel and proximal colon.

*Keywords:* Beclomethasone dipropionate; Enteric coating; Colonic delivery; Gamma scintigraphy; Gastrointestinal transit

## 1. Introduction

Beclomethasone dipropionate (BDP), in the form of low dosage (0.5–2.0 mg) topically acting retention enemas, has been successfully used in the treatment of patients with distal idiopathic ulcerative colitis, proctitis, and rectal Crohn's disease (Levine and Rubin, 1985). Topical use of BDP has the advantage of reducing systemic side effects, such as Cushing's Syndrome and suppression of the hypothalamic-pituitary-adrenal axis (Kumana et al., 1982), which are evident with conventional corticosteroid treatment (Singleton, 1982; Levine and Rubin, 1985). The reduction in side effects following topical delivery of BDP is largely due to the high degree of first-pass metabolism, in both circulating erythrocytes and in the liver, following absorption from the lower gastrointestinal tract (Brogden et al., 1984; Harting, 1992). The metabolites of BDP have little or no biological activity (Brogden et al., 1984).

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In patients with Crohn's disease, or ulcerative colitis of the proximal regions of the colon, it is not feasible to effect topical drug delivery via the rectal route; the treatable area following rectal administration being confined to the descending colon, sigmoid colon and rectum (Hardy et al., 1986). Topical BDP treatment of the distal small bowel and the proximal colon in patients with Crohn's disease and ulcerative colitis must therefore make use of the oral route. Modified release formulations have already been developed to target drugs, such as 5-ASA, to the colon for the treatment of inflammatory bowel disease (Hardy et al., 1987; Levine et al., 1987).

To date there has been little or no published work on the development and evaluation of oral delivery systems containing topically acting corticosteriods targeted to the colon. Levine and colleagues (1987), however, have shown an increase in BDP, and its metabolites, in the ileostomy effluent of patients dosed with enteric coated BDP capsules, compared with those dosed with uncoated capsules.

The objectives of this pilot study were to determine the gastrointestinal transit and in vivo disintegration characteristics of an enteric coated, modified release BDP formulation, using gamma scintigraphy. This non-invasive technique enables a visual evaluation of the in vivo position and integrity of the delivery system to be made which can then be related to drug absorption (pharmacoscintigraphy) (Hardy et al., 1987; Wilson et al., 1989; Davis et al., 1990; Wilding et al., 1991). Corticosteroid absorption from the gastrointestinal tract was assessed by determination of the appearance of BDP and its metabolites, beclomethasone monopropionate (BMP) and beclomethasone alcohol (BOH), in the systemic circulation from the assay of both blood and urine samples collected during the 24 h study period.

## 2. Materials and methods

### 2.1. Materials

The modified release core of the tablet consisted of approx. 25% w/w hydroxypropylmethylcellulose (Methocel K4M) and the enteric coating was provided by Eudragit L100/55. BDP (5 mg) enteric coated modified release tablets were manufactured containing 2 mg of samarium oxide, enriched with the $^{152}Sm$ isotope. Prior to the study, tablets were irradiated for 4 min in a flux of $10^{12}$ neutrons $cm^{-2}$ $s^{-1}$. In vitro studies were then performed to determine the disintegration and release characteristics of the formulation. These studies confirmed that the neutron activation procedure did not affect either the release behaviour of the formulation or the stability of the drug. All tablets used for administration to volunteers were irradiated under the same conditions, 23 h before dosing, to give a specific activity of 1 MBq $^{153}Sm$ per tablet at the time of administration.

### 2.2. Subjects

Eight healthy male volunteers aged 19–23 years, and all non-smokers of at least 12 months duration, were recruited for the study. Volunteers were not taking any medication at the time of the study, and all abstained from alcohol for 24 h prior to dosing and throughout the study period.

The study protocol was approved by the Quorn Research Review Committee, and the administration of radioactive tracers was authorised by the Department of Health, London. The total effective radiation dose equivalent to each subject from participation in the study was 0.8 mSv. Prior to recruitment, the nature of the study was explained both verbally and in writing to the volunteers, and each volunteer provided written informed consent.

### 2.3. Procedure

After fasting from midnight, a radiolabelled enteric coated modified release BDP tablet was administered to each volunteer with 150 ml water. An anterior anatomical marker containing 0.1 MBq $^{153}Sm$ was taped to the skin on the right-hand side of the body at the level of the pylorus. Anterior scintigraphic images of 60 s duration were recorded at frequent intervals using a gam-

ma camera (General Electric Maxicamera) with a 40 cm field of view and fitted with a low-energy parallel hole collimator. During the first 4 h after dosing, images were recorded at approx. 20 min intervals, and thereafter at 30 min intervals until 12 h post-dose. A final image was recorded at 24 h post-dose. During the study, volunteers remained moderately active, and all images were acquired with volunteers standing in front of the gamma camera. The images were recorded using a Bartec computer system, and were stored on magnetic tape for subsequent analysis.

On each study day all volunteers consumed a standard diet, which consisted of 200 ml water 2 h post-dose, a light lunch (two filled rolls, one packet of crisps, tea or coffee) at 4 h post-dose, and dinner (10 inch pizza with a selection of toppings, orange juice, tea or coffee) at 9 h post-dose. Fluids were allowed ad libitum after lunch. Immediately prior to dinner, each subject received 150 ml of water containing 1 MBq $^{99}Tc^{m}$ diethylenetriaminepentaacetic acid (DTPA) to enable an outline of the stomach anatomy to be acquired.

Blood samples (10 ml) were obtained at frequent intervals during the first 12 h of the study via an indwelling cannula irrigated with heparinised saline. A 24 h blood sample was obtained by direct venepuncture. The blood was centrifuged and the plasma transferred to polypropylene tubes prior to freezing at −20°C. The concentration of BDP and its metabolites (BMP and BOH) in each sample was determined using a combined high-performance liquid chromatography/negative ion chemical ionisation mass spectrometric technique.

A baseline urine sample was collected prior to dosing. Urine was then collected quantitatively by timed fractions during the 24 h study period. After recording the total volume of each fraction, aliquots (10 ml) were frozen at −20°C. Analysis for BDP and its metabolites was carried out using an analogous technique to that used for analysis of the plasma samples.

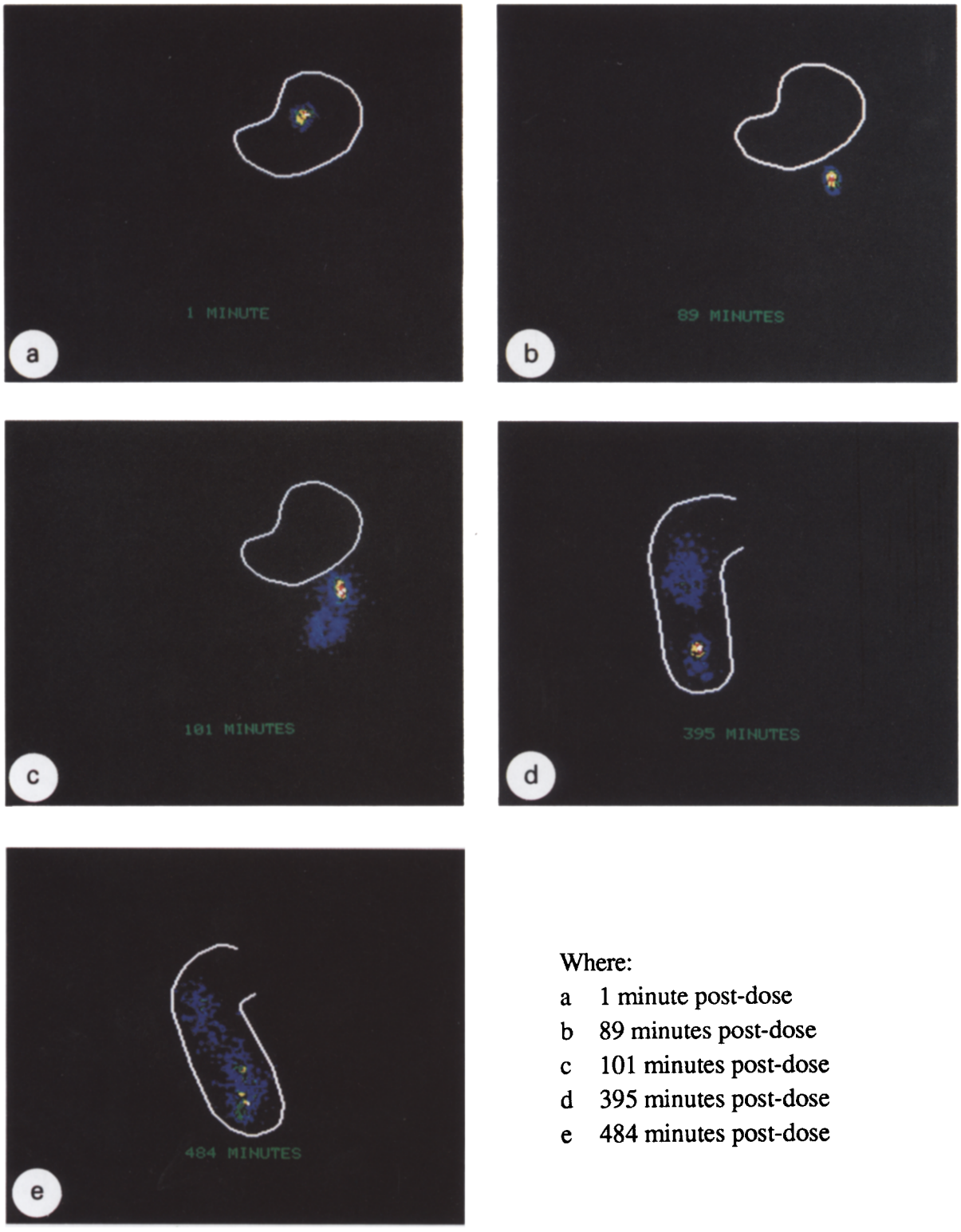
Table 1
Gastrointestinal transit profile for an enteric coated modified release beclomethasone dipropionate delivery system

| Subject no. | Gastric emptying time (min) | Small intestinal transit time (min) | Colon arrival time (min) |
|---|---|---|---|
| 1 | 76 | 197 | 273 |
| 2 | 20 | 179 | 199 |
| 3 | 45 | – | – |
| 4 | 20 | – | – |
| 5 | 17 | – | – |
| 6 | 20 | 256 | 276 |
| 7 | 7 | 269 | 276 |
| 8 | 19 | 224 | 243 |
| Mean | 28 | 225 | 253 |
| SD | 22 | 38 | 33 |
| Median | 20 | 224 | 273 |
| Sample size | 8 | 5 | 5 |

## 3. Results

The recorded time for movement of the tablet from the stomach to the small intestine was taken as the mid-time between the times recorded for the two images about the transition. The time for onset of tablet disintegration and the time for complete tablet disintegration were determined in a similar manner. The gastrointestinal transit and tablet disintegration data are shown in Tables 1 and 2, respectively.

In all volunteers, tablet integrity was maintained whilst the preparation resided within the stomach. The mean gastric emptying time for the formulation was $28 \pm 22$ min post-dose (range 7–76 min) (Table 1). Once in the small intestine, the tablets remained intact for a considerable period of time, range 57–118 min (Table 2), before showing initial signs of disintegration. In all cases, following onset of disintegration, a sustained release tablet core remained, which was observed to erode gradually over an extended period of time, the time between onset and complete tablet disintegration ranging between 103 and $> 614$ min (Table 2). In five subjects, small intestinal transit time for the tablet ranged between 179 and 269 min (Table 1), and in these volunteers complete tablet disintegration occurred in the proximal colon (Table 2). In the three remaining volunteers complete tablet disintegration occurred within the small intestine.




Where:

a 1 minute post-dose
b 89 minutes post-dose
c 101 minutes post-dose
d 395 minutes post-dose
e 484 minutes post-dose

Table 2
In vivo disintegration data for an enteric coated modified release beclomethasone dipropionate delivery system

| Subject no. | Initial tablet disintegration (min) | | | Complete tablet disintegration (min) | | |
|---|---|---|---|---|---|---|
| | Time post-dose | Time post-GE | Position | Time post-dose | Time post-ITD | Position |
| 1 | 156 | 80 | SI | 502 | 346 | AC |
| 2 | 138 | 118 | SI | 434 | 296 | HF |
| 3 | 156 | 111 | SI | 274 | 118 | ICJ |
| 4 | 77 | 57 | SI | 240 | 163 | SI |
| 5 | 96 | 79 | SI | 199 | 103 | ICJ |
| 6 | 110 | 90 | SI | 568 | 458 | HF |
| 7 | 96 | 89 | SI | 433 | 337 | AC |
| 8 | 110 | 91 | SI | > 724 [a] | > 614 [a] | Caecum |
| Mean | 117 | 89 | | 379 | 260 | |
| SD | 29 | 19 | | 141 | 134 | |
| Median | 110 | 90 | | 433 | 296 | |
| Sample size | 8 | 8 | | 7 | 7 | |

[a] Not included in mean data.
GE, gastric emptying; ITD, initial tablet disintegration; SI, small intestine; ICJ, ileocaecal junction; AC, ascending colon; HF, hepatic flexure.

Table 3
Plasma concentration (ng/ml) of beclomethasone monopropionate in subjects dosed with an enteric coated modified release beclomethasone dipropionate formulation

| Time (h) post-dose | Subject | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 0.00 | < LOQ | 0.00 | < LOQ | < LOQ | < LOQ | 0.00 | 0.00 |
| 4 | 0.00 | 1.27 | < LOQ | < LOQ | < LOQ | 1.12 | 0.00 | 0.00 |
| 6 | 0.00 | < LOQ | < LOQ | < LOQ | < LOQ | < LOQ | 0.00 | 0.00 |
| 8 | < LOQ | < LOQ | 3.56 | < LOQ | < LOQ | < LOQ | 0.00 | 0.00 |
| 12 | < LOQ | < LOQ | 1.64 | < LOQ | < LOQ | < LOQ | 0.00 | < LOQ |
| 24 | < LOQ | 0.00 | < LOQ | 0.00 | < LOQ | < LOQ | 0.00 | 0.00 |

< LOQ, less than the limit of quantification.

A series of representative scintigraphic images to highlight the gastrointestinal transit and disintegration of the formulation are provided in Fig. 1. In views (c) and (d) the presence of the sustained release tablet core can be clearly seen.

Analysis of the biological samples showed no evidence of BDP in either the plasma or urine of any of the volunteers. In seven of the eight volunteers BMP was detected in the plasma (Table 3), and in subject 2 traces of both BMP and BOH were found in the urine. However, in most instances, although BDP metabolites were detectable, the concentrations were typically below the minimum quantifiable amount (1 ng/ml).

## 4. Discussion

As a relatively large, indigestible object in a fasted stomach, it is likely that gastric emptying

Fig. 1. Scintigraphic images of subject 7 at (a) 1, (b) 89, (c) 101, (d) 395, (e) 484 min after ingestion of a $^{153}$Sm-labelled, enteric coated, modified release beclomethasone dipropionate tablet.

of the tablet was largely controlled by phase III (housekeeper wave) of the physiological process known as the migrating myoelectric complex (MMC) (Coupe et al., 1991). This serves to empty the stomach of large indigestible particles at approx. 2 h intervals in fasted individuals. The inter-individual variation in time for gastric emptying observed in these subjects is therefore likely to have been determined by the phase of the MMC at which the formulation was administered (Park et al., 1984). The observed range of gastric emptying times (7–76 min) is in keeping with previous studies on non-disintegrating pharmaceutical dosage forms administered to fasted individuals (Kaus et al., 1984; Wilson et al., 1984; Davis et al., 1986; Parker et al., 1988).

In all volunteers a lag time between entry of the tablets into the small intestine and signs of initial tablet disintegration (range 57–118 min) was observed. This delay in onset of tablet disintegration was in keeping with both the thickness of the enteric coating on the tablets, and the pH threshold of the coating used. This lag time prior to disintegration is in good accord with that observed in previous studies on enteric coated dosage forms (Latini et al., 1986; Wilding et al., 1992). Enteric coating of the formulation ensured that no loss of integrity occurred within the acid milieu of the stomach. The normal pH range of the fasting stomach (0.8–2.0) is considered to be below the point at which pH-sensitive enteric coating polymers begin to dissolve (Healey, 1989). After an initial delay, the onset of tablet disintegration was observed in the small intestine, leaving a sustained release core which eroded gradually over an extended period of time.

Although initial disintegration occurred in the small intestine, in five out of the eight subjects complete disintegration did not occur until the tablet core had reached the proximal colon. It is therefore likely that, although drug release will have started in the small intestine, a proportion of the dose will have been delivered to the proximal colon in these individuals. The extended time period during which the tablet core is still viable as a sustained release entity suggests that this formulation provides a means for the delivery of topically acting drug to the distal small bowel and, in some individuals, the proximal colon. Such a formulation could therefore provide an efficient and acceptable means for topical treatment of patients with inflammatory bowel disease.

In one subject the tablet core remained intact for over 12 h, and as a result, complete disintegration occurred during the night, after the volunteer had left the clinical unit. It is interesting that in this subject the tablet core remained within the caecum for many hours after arrival in the colon, and it is possible that the poor mixing of intestinal contents in this part of the large bowel may have contributed to the slow erosion of the tablet matrix.

BDP was not detected in any of the plasma or urine samples provided by the volunteers. However, in seven of the eight volunteers BMP was detected in the plasma, although concentrations of this metabolite were extremely low. In four of the volunteers where BMP was detected, plasma levels, though detectable, were below the quantification limit of the method at all times. In only one subject were metabolites of BDP detected in the urine. The low levels of BDP metabolites detected in either plasma or urine samples in this study suggest that BDP is poorly absorbed from the distal small bowel and colon; the inference being that the major part of the dose remains within the intestinal lumen, and is therefore available for topical treatment of the gut wall.

Comparison of the scintigraphic tablet disintegration data and the appearance of BMP in the blood shows that, in all but one volunteer with detectable plasma BMP concentrations, scintigraphic evidence of tablet disintegration occurred prior to detection of metabolite in the blood. This serves to illustrate the value of pharmacoscintigraphic studies in relating the anatomical position and integrity of a formulation within the gastrointestinal tract, to subsequent effects on drug absorption.

In conclusion, the design of this formulation allows for drug delivery to the distal small bowel and proximal colon over an extended period of time. In a number of volunteers, total tablet disintegration occurred prior to entry into the colon which suggests that this formulation may be useful for topical treatment of inflammatory dis-

ease in the distal small bowel. However, it must not be forgotten that this study was carried out in healthy volunteers, and that a different picture may well emerge when the performance of this formulation is evaluated in patients suffering from Crohn's disease or ulcerative colitis. Many such patients show evidence of altered motility patterns and altered regional transit rates (Hardy et al., 1988; Davis et al., 1991) when compared with healthy individuals (Watts et al., 1992).

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