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A pharmacoscintigraphic evaluation of oral budesonide given as controlled-release (Entocort) capsules

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SUMMARY

Aims: To investigate the gastrointestinal pharmacokinetics of controlled-release (Entocort) and standard budesonide capsules.

Methods: Six Crohn's disease patients and eight healthy controls were given controlled-release capsules containing budesonide and an inert ¹¹¹In label, following breakfast. In the patients, a standard capsule containing deuterium-labelled budesonide was given simultaneously. In the controls, on a separate occasion, the controlled-release capsules were given in the fasting state. Gastrointestinal transit was recorded by a gamma camera. Plasma budesonide and deuterium-labelled budesonide were used to estimate drug release, and urine cortisol was used to assess systemic effects.

Results: Budesonide delivery to the ileo-colonic region was significantly greater after the intake of the controlled-release capsules [69%; 95% confidence interval (CI), 54–84] than after the standard capsules (30%; 95% CI, 15–45) ($P = 0.005$). Fasting had little impact on uptake. The transit and pharmacokinetics of budesonide were similar in both subject groups, although systemic availability was higher in patients (21%; 95% CI, 13–33) than in controls (12%; 95% CI, 10–14) ($P = 0.009$). Urinary cortisol was, however, similar in both groups.

Conclusions: A major fraction of budesonide is released in the ileum and throughout the colon, the intended target for the controlled-release formulation. The prandial state has little effect on budesonide uptake.

INTRODUCTION

Crohn's disease is an inflammatory bowel disease of unknown aetiology, which can affect any part of the gastrointestinal tract, but lesions occur mainly in the ileum and/or ascending colon. During acute symptomatic relapses, systemic glucocorticosteroids are used as primary therapy. Budesonide is a glucocorticosteroid that has been used for many years in the treatment of asthma and rhinitis. It possesses a high local anti-

inflammatory effect and, in comparison with prednisolone, has the advantage of low systemic effects due to an extensive (85–90%) biotransformation to metabolites with minimal or no biological activity.¹

Budesonide, given as oral controlled-release capsules, has been shown to be effective and safe for the acute treatment of active Crohn's disease,² and long term to prolong remission in Crohn's disease localized to the ileum and/or the ascending colon.³ The drug appears to be more effective and at least as well tolerated as mesalamine,⁴ the current first-line treatment option in mild to moderate Crohn's disease.

Budesonide is rapidly absorbed from the gastrointestinal tract.⁵ The controlled-release formulation tested in

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this study consists of a gelatine capsule containing pellets, which are designed to release budesonide during passage through the intestine.⁶ The primary target sites for the budesonide controlled-release formulation, Entocort, are the ileum and colon.

The release of a drug in different parts of the gastrointestinal tract can be estimated by relating systemic uptake to nuclear image registrations showing the transit of labelled drug in the gastrointestinal tract. Previous studies have demonstrated the usefulness of pharmacoscintigraphic monitoring for investigating the absorption behaviour of a drug in a particular dosage form along the gastrointestinal tract,^{7–11} and it is currently perceived as the method of choice for gastrointestinal transit measurements.¹²

This investigation, previously only presented as abstracts or summarized in reviews, is the first to delineate the pharmacokinetics, intestinal transport and release of budesonide after administration in patients with Crohn's disease. It compares the ileo-colonic uptake of Entocort controlled-release capsules with that of standard capsules, using intravenous drug as a reference. Indium-labelled pellets were used to measure gastrointestinal transit. Finally, using this technique in a group of healthy controls, the effect of the prandial state on ileo-colonic uptake was studied.

SUBJECTS AND METHODS

Study design

This study was of an open design. Controlled-release capsules containing pellets of budesonide mixed with ¹¹¹In-labelled pellets were administered immediately after breakfast or in the fasting state 1 h before breakfast (controls only). Gastric emptying could be followed as the outline of the stomach was visualized by co-administration of ^{99m}Tc colloid. The transit of the formulation through the gastrointestinal tract was recorded by a gamma camera. Blood samples were taken for at least 24 h to assess the rate and extent of budesonide availability in the systemic circulation.

On the treatment day, the subjects had fasted (food and beverages) since 22.00 h on the previous evening. Alcoholic beverages were not allowed for 24 h before drug administration or during the study. Medication, apart from the study drug and medicines deemed to be necessary for the subjects' well-being, was not allowed for 72 h before to 120 h after drug administration. All

intake of food or fluid was noted from 72 h before to 96 h after drug administration. Food and beverages were standardized during the first 24 h after drug administration. Breakfast (two slices of white bread with butter, two fried eggs, two slices of bacon, 60 g hash-browned potatoes and 250 mL whole milk) was eaten just before drug administration. When budesonide was administered in the fasting state, a light breakfast (two slices of white bread with cheese and marmalade, 500 mL coffee, tea or water) was served 60 min after budesonide intake. Lunch was consumed immediately after the 4-h gamma camera image. Coffee or tea was consumed 7 h after budesonide administration. The evening meal was served 10 h after drug administration.

Anatomical reference markers, radio-labelled with ⁵⁷Co, were taped onto the skin over the xiphoid and iliac spines before each scintigraphic image. At about 09.00 h (08.30 h for controls), the subjects swallowed the following units in the referred order: (i) 50 mL of ^{99m}Tc-albumin colloid solution; (ii) the investigated product with 2 × 100 mL of water. Nuclear image registration started 5 min after drug administration.

Faeces and urine were collected for radioactivity investigation of ¹¹¹In content by a well counter.

Subjects and drug administration plan

Part 1. Six patients (three females) were included in the study (Table 1). Patients P1, P3, P4 and P5 were smokers, and all were moderate consumers of alcohol. All had X-ray or endoscopically verified, but non-operated, Crohn's disease in the ileum and/or colon. Patients P3 and P4 were in an active state, and patient P5 had a low grade of continuous activity. The others had quiescent disease.

Each patient was given 5 MBq ^{99m}Tc colloid, together with a single 18-mg dose of budesonide (Entocort), 4 mg deuterium-labelled (²H₈)-budesonide in a standard capsule and 3 MBq ¹¹¹In-labelled pellets. At least 12 weeks later, each patient was given a single intravenous dose of budesonide (0.25 mg) and (²H₈)-budesonide (0.25 mg).

Part 2. Eight male controls, healthy as judged by physical examination, haematology and clinical chemistry tests, were included in the study (Table 1). Two (H3 and H5) were current smokers. All had normal bowel and defecation habits (1–2 defecations/day). Concurrent medication, smoking and the regular use of snuff were not allowed.

Table 1. Demographic data of Crohn's disease patients (P1–P6) and healthy subjects (H1–H8)

	Sex	Age (years)	Height (cm)	Weight (kg)	Time since diagnosis (years)	Disease activity and localization
P1	Male	63	163	78	18	In remission; ileum + colon
P2	Female	46	162	62	3	In remission; ileum + ascending colon
P3	Female	36	160	63	3	Active; ileum
P4	Male	21	182	72	0	Active; ileum
P5	Female	42	161	55	21	Low-grade active; ileum, caecum and ascending colon
P6	Male	24	181	69	6	In remission; ileum
Patients (mean \pm s.d.)		39 \pm 15	168 \pm 10	67 \pm 8		
H1	Male	41	190	90		Healthy
H2	Male	46	178	80		Healthy
H3	Male	53	178	77		Healthy
H4	Male	46	182	94		Healthy
H5	Male	46	178	76		Healthy
H6	Male	40	182	80		Healthy
H7	Male	46	176	85		Healthy
H8	Male	52	193	89		Healthy
Healthy subjects (mean \pm s.d.)		46 \pm 5	182 \pm 6	84 \pm 7		

Each control was given 5 MBq ^{99m}Tc colloid, together with a single 18-mg dose of budesonide (Entocort) and 3 MBq ^{111}In -labelled pellets, just after breakfast or 1 h before breakfast. On another occasion, each patient was given a single intravenous dose of budesonide (0.5 mg). Each dose of study drug was separated by at least 10 weeks.

Study drugs

Budesonide controlled-release pellets had a diameter of 1–1.4 mm and a density of about 1.3 g/mL. The ^{111}In pellets (about 0.5 g), 1–1.4 mm in diameter and with a density of about 1.3 g/mL, contained ion exchange resin onto which approximately 3.0 MBq $^{111}\text{In}^{3+}$ ($t_{1/2} = 67$ h) was adsorbed. ^{111}In was delivered by Amersham UK to the Pharmaceutical Laboratory at AstraZeneca R&D, Lund, where the labelled formulations were prepared. The labelled pellets were mixed with budesonide controlled-release pellets (budesonide content, 18 mg) in gelatine capsules. The radioactivity of the capsules was measured immediately before administration.

For intravenous administration in Crohn's disease patients, 0.25 mg of budesonide and 0.25 mg of ($^2\text{H}_8$)-budesonide were dissolved in 20 mL of sterile

isotonic saline containing 10% ethanol, and administered over 10 min into an arm vein not used for blood sampling. Individual doses, estimated by weighing the syringe used for administration before and after dosing, ranged from 0.268 to 0.271 mg of budesonide and 0.246 to 0.249 mg of ($^2\text{H}_8$)-budesonide. Similarly, in healthy controls, the individual dose of budesonide [($^2\text{H}_8$)-budesonide was not given to controls] was 0.517 mg (0.505–0.531 mg).

The ^{99m}Tc colloid formulation (50 mL, 5 MBq, $t_{1/2} = 6.02$ h) was prepared and administered according to standard hospital practice. The formulation was dispensed by the Hospital Pharmacy at the University Hospital, Lund.

Nuclear imaging and radioactivity measurements

The nuclear imaging and radioactivity measurements were performed at the Department of Clinical Physiology, University Hospital, Lund. Scintigraphic imaging was performed with the subject standing (anterior and posterior, each with a duration of 2 min) using a gamma camera (General Electric 400T) with a collimator (diameter of field of view, 40 cm). The scintigraphic data were collected in a computer for subsequent analysis. Five minutes after administration of the pellets,

the first scintigraphic images were recorded. Subsequent images were recorded every 30 min during the first 4 h, every hour between 4 and 8 h, and then at 10, 12, 16, 20, 24, 30, 36, 48, 60 and 72 h after administration. In healthy controls, an identical scheme was followed, except that the 16 and 20 h images were replaced with one image at 18 h. Blood sampling always preceded image registration when these coincided.

Faeces and urine were collected in pre-weighed containers for 120 h following oral treatment. Defecation times were noted. The content of ^{111}In in urine and faeces was measured in a sodium iodide detector connected to a single-channel analyser. The measurements of radioactivity in urine and faeces were adjusted for radioactive decay and corrected to the time for the administration of the dose. The total amount of ^{111}In excreted in urine and faeces was calculated as a percentage of the given dose.

Pharmacokinetic assessments

Blood samples for pharmacokinetic assessments were taken on all treatment occasions. Venous blood samples (20 mL/sample) were obtained from an indwelling catheter inserted into an arm vein or by venepuncture. In the case of intravenous treatment, blood samples were taken from the arm not used for infusion. The samples were stored frozen at $-20\text{ }^{\circ}\text{C}$ until analysis.

Plasma budesonide assay

The budesonide assay, based on a combination of liquid chromatography and mass spectrometry,¹³ was able to measure budesonide in human plasma down to 0.1 nmol/L (0.043 $\mu\text{g/L}$). The inter-assay variation at 0.1 nmol/L was found to be about 10%. For one of the subjects (H1), after intravenous administration, plasma was analysed with a combined high performance liquid chromatography radioimmunoassay method.¹⁴

Urine cortisol assay

Urine was collected in pre-weighed polyethylene bottles in $6 \times 24\text{-h}$ fractions: one before treatment (baseline), and then during 0–120 h (5 days) after oral treatment. The total urine weight was measured and volumes were calculated assuming a density of 1.02 g/mL. Two

portions of each fraction were stored at $-20\text{ }^{\circ}\text{C}$ until analysis by gas chromatography-mass spectrometry.¹⁵ The reference range for normal urinary cortisol was 45–190 nmol/L per 24 h (AstraZeneca, data on file).

Nuclear image evaluation

Indium pellets were assumed to have the same transit time through the gastrointestinal tract as budesonide controlled-release pellets. The radioactivity present in the ventricle at different times could be estimated, as the outline of the stomach was visualized by co-administration of 50 mL $^{99\text{m}}\text{Tc}$ colloid. The maximum measured radioactivity of indium in the ventricle (MR) was used as a basis for the calculation of both the time of gastric emptying (radioactivity in the ventricle decreased to 50% of MR) and the time for caecum arrival (radioactivity in the caecal region increased to 50% of MR). The small intestinal transit time (SITT) was defined as the difference between these two times. The ileal transit time was calculated as 60% of SITT (assuming that there is a constant rate of transit through the small intestine and that the ileum constitutes 60% of the small intestine). The arrival of 50% of the radioactivity to the transverse colon was also estimated. The determination was based on both visual assessment of scintigraphic images and radioactivity counts in the regions of interest.

Pharmacokinetic evaluation

Values at scheduled sampling times were estimated from those at actual sampling times using linear interpolation. For intravenous administration, the area under the plasma concentration vs. time $[C(t)]$ curve (AUC) was calculated using the trapezoidal rule up to the last measured point above the limit of quantification (LOQ) plus the extrapolated part (AUC_{ext}), calculated using the last measurable concentration above LOQ and the terminal elimination rate. The mean residence time (MRT) was calculated by first integrating the function $t \times C(t)$ in a similar manner as for AUC . This area under the first moment curve ($AUMC$) was used for the calculation of MRT by the equation: $(AUMC/AUC) - (\text{infusion time}/2)$.

For oral administration, AUC was calculated in the same way as for intravenous administration, using the terminal elimination rate from intravenous administration. The mean absorption time (MAT) was calculated by first integrating the function $t \times C(t)$, in a similar

manner as for *AUC*, in order to obtain *AUMC*. The formula for *MAT* was $AUMC/AUC - MRT$, where *MRT* is the mean residence time after intravenous administration. The systemic availability (*F*) was calculated as the ratio of the dose-adjusted *AUC* values after oral and intravenous administration. The cumulative absorption of budesonide was estimated using deconvolution.

When the amounts of budesonide absorbed in different regions of the gastrointestinal tract were calculated, prompt trans-mucosal diffusion was assumed. Cumulative absorption curves were estimated using deconvolution (Proost's method¹⁶), and gastrointestinal transit times were used to estimate the fractions absorbed in different regions.

In a preliminary attempt to quantify any influence of the trans-mucosal penetration lag time (which was assumed to be negligible in this study) on the uptake estimates, the data were also adjusted for the systemic uptake time. The adjustments were based on findings from another small study, in which budesonide was released in different segments of the gut using a telemetric, remote-release capsule.¹⁷ Median trans-mucosal penetration lag times, defined as the time at which half the systemically available dose had been absorbed, were found to be 0.48 h for the ileum and 1.24 h for the proximal colon. The median rather than the mean absorption time was used for this estimate, as gastrointestinal transit times derived from scintigraphic data are based on median times. As the method has obvious shortcomings with regard to inter-subject variability (adjustments are based on data from three separate healthy subjects in a different laboratory setting), the data should be regarded as preliminary, and are therefore not presented in any detail in the 'Results' section.

The means, variances and confidence limits for the means were estimated for pharmacokinetic parameters and urine cortisol suppression.

Ethics

The study was performed in accordance with the principles stated in the Declaration of Helsinki and was approved by the Ethics Committee at Lund University, Lund, Sweden.

RESULTS

Participating subjects complied well with the study protocol and there were no treatment discontinuations.

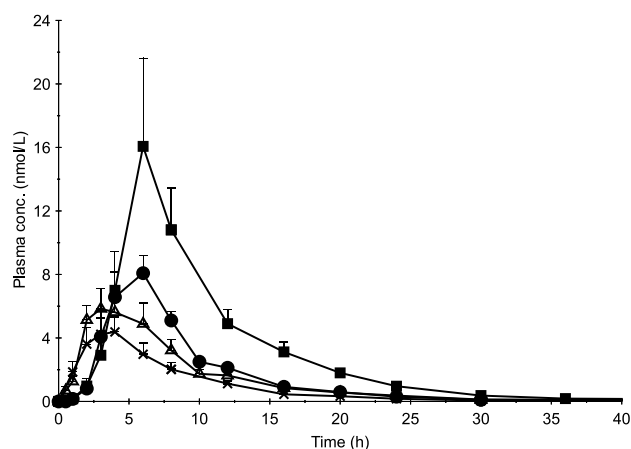


Figure 1. Mean (S.E.M.) plasma concentrations of budesonide after Entocort controlled-release capsules (■, 18 mg single dose in fed patients; ●, 18 mg single dose in fed healthy subjects; △, 18 mg single dose in fasted healthy subjects) and standard immediate-release (²H₈)-budesonide capsules (×, 4 mg single dose in fed patients).

Pharmacokinetic evaluation

The mean plasma concentrations of budesonide after oral doses of the controlled-release capsules (18 mg) and the standard capsules (4 mg) are illustrated in Figure 1, with kinetic parameters listed in Table 2. In 21 of the 22 plasma concentration vs. time curves obtained following the controlled-release formulation of budesonide, plasma concentrations were above LOQ for at least 24 h. After the standard formulation, all six patients had concentrations above LOQ after 20 h and four out of six at 24 h.

When budesonide was given as controlled-release Entocort capsules, the time to peak concentration (*T*_{max}) was slightly longer (6.0 h vs. 4.0 h) and *MAT* was significantly longer (9.0 h vs. 5.5 h; *P* = 0.018) than when it was given as standard capsules. Systemic exposure, measured as the dose-normalized *AUC* or as the systemic availability, was similar for the two formulations: the mean systemic availabilities were 20.5% and 21.5% for Entocort and the standard formulation, respectively.

Pharmacokinetic parameters after intravenous administration were similar for the two groups of subjects (Table 3). In addition, when intravenous budesonide and (²H₈)-budesonide were given simultaneously, there was no apparent isotope effect in any of the estimated parameters (Table 3).

Table 2. Pharmacokinetic parameters of oral budesonide [mean (95% confidence intervals)]

	Standard capsules CD patients fed	Controlled-release capsules		
		CD patients fed	Healthy subjects fed	Healthy subjects fasting
Dose (mg)	4.12 (4.10, 4.14)	18.0 (17.9, 18.1)	17.9 (17.9, 18.0)	18.3 (18.1, 18.5)
$AUC_{0-\infty}$ (nmol \times h/L)	33.5 (24.4, 46.0)	114.0 (81.4, 159.5)	60.4 (45.1, 80.8)	48.5 (39.1, 60.2)
$C_{\max(0-\infty)}$ (nmol/L)	4.1 (3.0, 5.8)	14.3 (8.9, 22.9)	9.1 (6.0, 13.7)†	5.9 (4.3, 7.9)
T_{\max} (h)*	4.0 (2.0, 4.0)	6.0 (6.0, 16.0)	6.0 (3.0, 8.0)	3.0 (2.0, 6.0)
MAT (h)	5.5 (4.5, 6.4)	9.0 (7.4, 10.5)‡	6.4 (5.6, 7.2)	5.8 (5.1, 6.6)
Systemic availability (%)	21.5 (16.5, 27.8)	20.5 (15.1, 27.8)‡	11.5 (8.8, 15.0)	9.1 (7.3, 11.3)

AUC , area under the concentration–time curve; CD, Crohn's disease; MAT, mean absorption time; C_{\max} , maximum concentration; T_{\max} , time to C_{\max} .

* Median and range.

† Statistically significant vs. fasting ($P < 0.05$).

‡ Statistically significant vs. healthy subjects ($P < 0.05$).

Table 3. Pharmacokinetic parameters of intravenous budesonide [mean (95% confidence intervals)]

	Crohn's disease patients		Healthy subjects
Dose (mg)	0.269 (0.269, 0.269)	0.248 (0.247, 0.248)*	0.517 (0.512, 0.522)
$AUC_{0-\infty}$ (nmol \times h/L)	8.31 (8.18, 8.44)	7.98 (7.86, 8.11)*	15.1 (12.5, 18.4)
$T_{1/2}$ (h)	2.4 (2.1, 2.6)	2.6 (2.3, 3.0)*	2.2 (2.0, 2.3)
CL (L/min)	1.3 (1.2, 1.3)	1.2 (1.2, 1.2)*	1.3 (1.1, 1.6)
V_{ss} (L)	151 (124, 183)	142 (135, 150)*	173 (146, 205)

AUC , area under the concentration–time curve; CL, clearance; $T_{1/2}$, plasma half-life; V_{ss} , steady state volume of distribution.

* (2H_8)-Budesonide.

When comparing the pharmacokinetics of Entocort capsules in the two groups of subjects, C_{\max} and AUC were greater in patients than in healthy controls. As the intravenous data were similar in the two groups (Table 3), the higher systemic exposure in patients could be translated into a significantly greater systemic availability in patients than in healthy controls (20.5% vs. 11.5%; $P = 0.009$) given the same regimen.

In healthy controls given the controlled-release formulation of budesonide after food, C_{\max} was significantly higher (9.1 nmol/L vs. 5.9 nmol/L; $P = 0.044$) and T_{\max} was longer (6.0 h vs. 3.0 h; N.S.) compared with administration in the fasting state. In accordance with the higher C_{\max} , the mean systemic availability was higher after food (11.5% vs. 9.1%), but this difference was not statistically significant. MAT was similar, approximately 6 h, irrespective of food intake.

Gastrointestinal transit

After gastric emptying, the ^{111}In -labelled pellets spread along the small intestine. Later, the radioactivity became concentrated in the caecal region and ascending colon,

after which it again became scattered in the more distal parts of the colon (Figure 2). Data for gastric emptying, ascending colon arrival and transverse colon arrival are

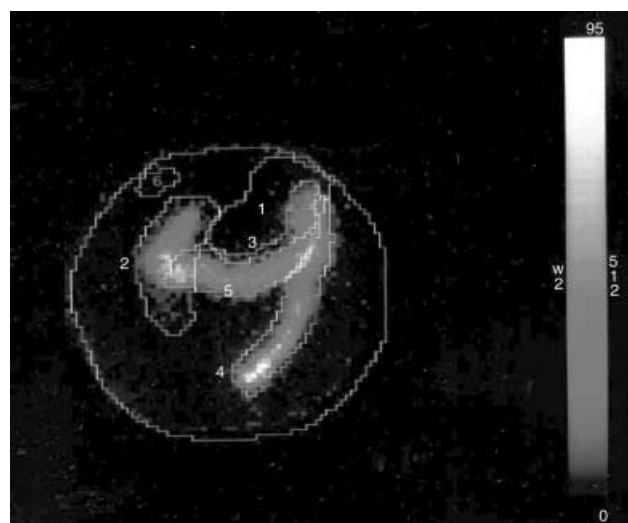


Figure 2. Scintigraphic image from one healthy subject at 36 h after administration of Entocort capsules. This image shows the presence of the budesonide formulation with the highest intensity in the transverse colon and descending colon.

Table 4. Gastrointestinal transit data [mean (95% confidence intervals)]

	Crohn's disease patients fed (h)	Healthy subjects fed (h)	Healthy subjects fasting (h)
Gastric emptying	4.0 (3.3, 4.7)†	2.7 (2.1, 3.2)*	0.8 (0.3, 1.3)
Ascending colon arrival	6.4 (5.1, 7.8)	5.6 (4.5, 6.8)*	3.8 (3.2, 4.4)
Transverse colon arrival	14.5 (7.7, 21.3)	21.1 (15.2, 27.0)	18.1 (14.2, 22.0)
Time to 90% absorbed	13.0 (9.8, 16.1)	9.7 (7.0, 12.4)	11.2 (9.8, 12.6)

* Statistically significant vs. fasting ($P < 0.05$).† Statistically significant vs. healthy subjects ($P < 0.05$).

given in Table 4. Post-prandial gastric emptying was longer in Crohn's disease patients [4.0 h; 95% confidence interval (CI), 3.3–4.7] than in healthy controls (2.7 h; 95% CI, 2.1–3.2) ($P = 0.006$). The difference in SITT between Crohn's disease patients (2.4 h; 95% CI, 0.9–3.9) and controls (3.0 h; 95% CI, 1.7–4.3) did not reach statistical significance. Transit through the ascending colon varied, but tended to be shorter in patients (8.1 h; 95% CI, 1.4–14.8) than in healthy controls (15.5 h; 95% CI, 9.7–21.3). The difference was not statistically significant ($P = 0.09$). The three patients who had active disease (P3, P4 and P5) had the shortest ascending colon transit times (1, 7 and 1 h, respectively).

Gastric emptying was considerably delayed by break-fast: the mean times to a 50% reduction of the maximum radioactivity in the ventricle were 0.8 h and 2.7 h in the fasting state and after food, respectively ($P < 0.001$) (Table 4). The mean times for transit through the small intestine (approximately 3 h) and through the caecum and ascending colon (mean data ranging from 14 to 16 h) were not significantly influenced by food.

Most of the active drug following administration of the controlled-release capsules appeared to be absorbed within 10–15 h in both groups of subjects, and was

little affected by the prandial state. The mean times to absorption of 90% of the totally absorbed dose were 13.0 h (95% CI, 9.8–12.6), 9.7 h (95% CI, 7.0–12.4) and 11.2 h (95% CI, 9.8–12.6) in fed Crohn's disease patients, fed healthy controls and fasting healthy controls, respectively (Table 4).

Site of absorption

The absorption of budesonide from controlled-release capsules in different parts of the gastrointestinal tract was primarily estimated by relating the accumulated systemic uptake to the gastrointestinal transit time, derived from nuclear image registrations. For this estimation, the time of absorption was assumed to be identical to the time of systemic appearance, i.e. the systemic uptake from the gastrointestinal tract was assumed to be momentary. The estimated absorption of budesonide in different regions of the gastrointestinal tract is shown in Table 5 for patients with Crohn's disease and in Table 6 for healthy controls. Regional absorption is illustrated in Figures 3 and 4.

A significantly larger fraction of the totally absorbed steroid dose was absorbed in the ileo-colonic region following the controlled-release capsules (68.7%; 95% CI, 53.8–83.6) vs. the standard capsules (30%; 95%

Table 5. Uptake of budesonide in Crohn's disease patients in different regions of the gastrointestinal tract following a standard capsule and Entocort controlled-release capsule. Individual data (patients P1–P6) and means (95% confidence intervals)

		P1	P2	P3	P4	P5	P6	Mean (95% CI)
Upper small intestine	Standard	64	80	54	78	68	80	70.7 (56.1, 85.2)
	Controlled-release	18	24	21	63	5	61	32.0 (17.4, 46.6)*
Ileum	Standard	4	9	4	8	3	12	6.7 (0.5, 12.8)
	Controlled-release	14	30	12	15	1	30	17.0 (10.9, 23.1)*
Ascending colon	Standard	30	11	7	11	5	4	11.3 (–1.8, 24.5)
	Controlled-release	70	42	20	14	2	4	25.3 (12.2, 38.5)
Transverse + descending colon	Standard	2	1	36	4	25	5	12.2 (–7.4, –31.8)
	Controlled-release	0	4	48	8	92	5	26.2 (6.6, 45.8)

* Statistically significant vs. standard capsule ($P < 0.05$).

Table 6. Uptake of budesonide in healthy subjects in different regions of the gastrointestinal tract (% of absorbed dose). Individual data (healthy subjects H1–H8) and means (95% confidence intervals)

		H1	H2	H3	H4	H5	H6	H7	H8	Mean (95% CI)
Upper small intestine	Fasted	23	30	21	44	35	22	18	2	24.4 (11.8, 37.0)
	Fed	33	53	27	34	49	8	15	51	28.8 (16.2, 41.3)
Ileum	Fasted	32	25	38	26	46	22	15	9	26.6 (19.6, 33.6)
	Fed	44	36	52	47	40	6	21	12	32.3 (25.2, 39.3)
Ascending colon	Fasted	41	45	42	26	19	50	65	48	42.0 (30.8, 52.7)
	Fed	20	51	21	20	7	85	60	31	36.9 (25.9, 47.8)
Transverse + descending colon	Fasted	3	0	0	4	0	6	2	40	6.9 (– 0.5, 14.3)
	Fed	2	0	0	0	4	0	4	5	1.9 (– 5.5, 9.3)

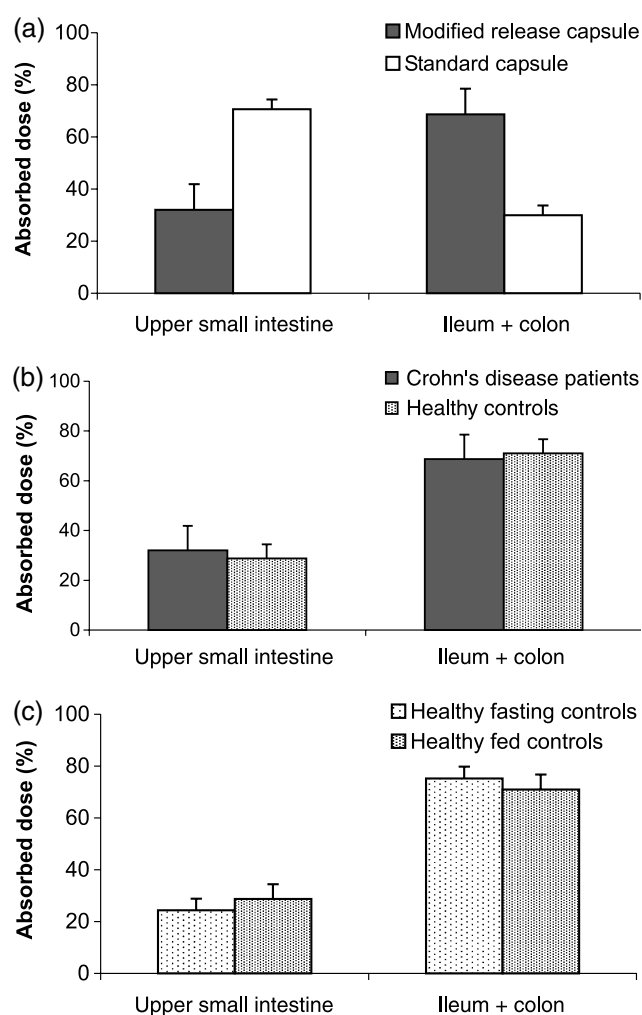


Figure 3. Dose absorbed in the upper small intestine vs. ileum + colon, expressed as a percentage of the total absorbed dose (mean values and S.E.M.): (a) controlled-release vs. standard capsules; (b) Crohn's disease patients vs. healthy controls; (c) healthy fasting controls vs. healthy fed controls.

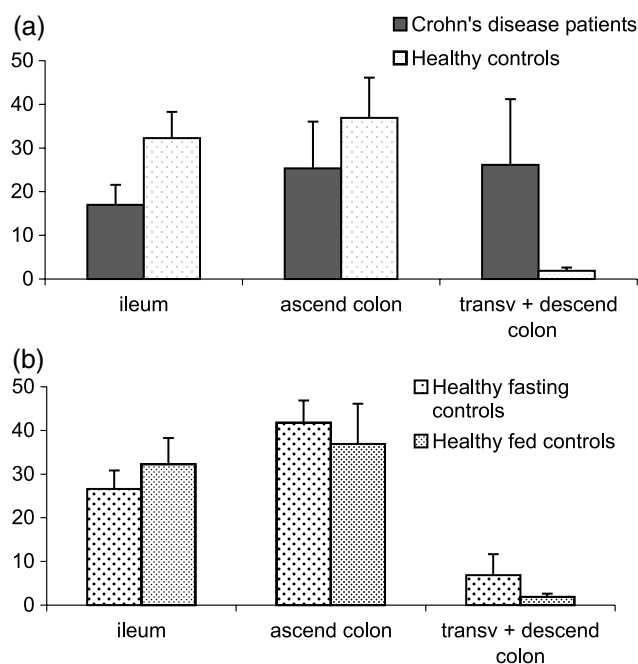


Figure 4. Dose absorbed in different gastrointestinal regions, expressed as a percentage of the total absorbed dose (mean values and S.E.M.): (a) Crohn's disease patients vs. healthy controls; (b) healthy fed controls vs. healthy fasting controls.

CI, 15.1–44.9) ($P = 0.005$) (Figure 3a). Although the net uptake in the ileo-colonic region was much greater for the controlled-release formulation, the relative absorption in the three regions of interest (ileum, ascending colon and rest of the colon) was roughly equal for the two formulations (Table 5), with about 20–25% of the overall ileo-colonic uptake occurring in the ileum, 40% in the ascending colon and 40% in the rest of the colon.

There was no major difference in the overall budesonide uptake in the ileo-colonic region following the controlled-release capsules in Crohn's disease patients (68.7%; 95% CI, 53.8–83.6) vs. healthy controls (71.0%; 95% CI, 55.7–86.3) (Figure 3b). However, whereas Crohn's disease patients showed similar relative absorption in each of the three regions of interest, in healthy controls, less budesonide was absorbed in the distal parts of the colon (1.9% in healthy controls vs. 26.2% in patients; $P = 0.08$) (Figure 4a). The overall absorption in the ileo-colonic region was little affected by food (Figure 3c), and was 75.3% (95% CI, 62.5–88.0) in healthy fasting controls vs. 71.0% (95% CI, 55.7–86.3) in fed controls. In fasting controls, however, slightly more was absorbed more distally, although the differences were not significant (Figure 4b).

In a small study using a telemetric remote-release capsule filled with a budesonide solution, the transmucosal absorption lag times were estimated to be 0.48 h in the ileum and 1.24 h in the colon.¹⁷ When these lag times were introduced into the pharmacoscintigraphic estimates of budesonide uptake, similar results were obtained as when no lag time adjustment was made: the adjusted estimates of budesonide uptake in the ileum and colon were 61% (95% CI, 46–77) after Entocort capsules and 27% (95% CI, 11–43) after the standard formulation in fed patients. Similar to when the adjustment factor was not used, this difference in uptake was statistically significant ($P = 0.011$). Similarly, when the uptake in different segments (upper small intestine, ileum and colon) was separately compared between Entocort capsules and the standard formulation, all comparisons showed a statistically significant difference (P values of 0.011, 0.025 and 0.049 were obtained for the difference in upper small intestine, ileal and colonic uptake, respectively). Finally, when Entocort capsule data were compared between fed and fasting healthy controls, budesonide uptake in the ileum and colon was estimated to be 61% (95% CI, 47–75) and 67% (95% CI, 53–80), respectively (N.S.).

Radioactivity in faeces and urine

The mean total recovery of radioactivity in faeces was 79% (range, 61–95%) in Crohn's disease patients and 84% (range, 66–104%) and 90% (range, 61–111%) in healthy controls following administration in the fasting state and after a heavy breakfast, respectively. Less than 0.1% of the total radioactivity was found in the urine

samples, which indicates that there was virtually no systemic absorption of the marker.

Urine cortisol

Urine cortisol excretion was highly variable and did not correlate with any pharmacokinetic parameter of budesonide exposure. In patients, the mean urine excretion decreased by 41% (95% CI, –22–71) vs. baseline values during the 24 h following the administration of 22 mg of steroid [18 mg budesonide and 4 mg ($^2\text{H}_8$)-budesonide]. Values then gradually returned to pre-treatment levels. In healthy controls, the mean urine cortisol excretion decreased by 49% (95% CI, 34–61) (fasting state) and 37% (95% CI, 20–51) (after a heavy breakfast) during the first 24 h after the administration of 18 mg budesonide. Again, after the first day, the values gradually returned to pre-treatment levels. Although the mean cortisol excretion tended to be lower in fasted than in fed subjects during the first 48 h, the difference was not statistically significant.

Adverse events

Adverse events were mild and included dizziness (four occasions in three control subjects and one patient), malaise (two controls), headache (three patients), face oedema (one patient), nausea (one control) and slight hypertension (one patient). At follow-up, the reported adverse events had disappeared.

DISCUSSION

This study aimed to elucidate whether the controlled-release formulation of budesonide (Entocort capsules) differed in its rate, site and extent of uptake vs. a standard budesonide formulation. It was clearly shown that a delayed and more distal delivery and uptake are achieved with the controlled-release formulation. In addition, food has little influence on the site and extent of budesonide uptake from the controlled-release formulation.

The ability of the controlled-release formulation of budesonide to provide targeted deposition in the ileum and throughout the colon was tested under different conditions: in fed Crohn's disease patients also given a standard immediate-release budesonide formulation and in healthy controls with and without food. The tested dose of the controlled-release formulation was

twice that clinically recommended for active disease. This allowed for accurate plasma concentration–time measurements over a wide time interval. Previous studies have shown that the pharmacokinetics of budesonide are proportional to the dose after inhalation of up to 3.2 mg/day (Pulmicort),¹⁸ as well as after oral administration of 3–15 mg of the controlled-release capsules.¹⁹ Any saturation of absorption, metabolism or distribution within the target tissue or systemic circulation thus appears unlikely with the doses used in the current study.

A technique of plasma concentration measurements combined with transit estimates using ¹¹¹In-labelled granules was utilized to quantify the uptake in different regions of the gastrointestinal tract. The ¹¹¹In granules consisted of an inert ion exchange resin onto which up to 3.0 MBq ¹¹¹In ($t_{1/2} = 67$ h) was absorbed. They were developed to achieve the same diameter (1–1.4 mm) and buoyant density (1.3 g/mL) as the Entocort capsule granules. This should ensure that the ¹¹¹In granules have similar gastric emptying and intestinal transit times as the Entocort granules. The ¹¹¹In granules were prepared just before use and were mixed with the Entocort granules before being placed into capsules and subsequently administered. This technique of radiolabelling inert markers, followed by thorough pharmacoscintigraphic evaluation, has been used with success in the human pharmacology documentation of other controlled-release formulations.^{7–11} As in most studies where the pharmacoscintigraphic technique has been used to estimate the site of uptake, we assumed prompt trans-mucosal absorption. This assumption introduces a systematic error into the estimates of regional uptake, the extent of which is dependent on the trans-mucosal lag time of the drug being assessed. As there is a certain lag time between the release of the drug from the formulation and the appearance in the systemic circulation, calculated trans-mucosal absorption lag times, obtained from another study,¹⁷ were used to adjust for the time difference between scintigraphic and pharmacokinetic data. As expected, adjustment for the absorption lag time suggested a greater proximal uptake of budesonide from the controlled-release formulation. However, the effect of the adjustment factor was relatively small and, irrespective of adjustment for the uptake time, the results showed that a major part of the budesonide dose from Entocort capsules was released at the intended target sites: the ileum and colon.

When comparing the plasma concentration–time data for the controlled-release formulation of budesonide with that of the standard immediate-release formulation, the data showed a delay in plasma concentrations for the controlled-release formulation. This is consistent with the *in vitro* dissolution properties of the two formulations (AstraZeneca, data on file), as well as *in vivo* findings.^{20, 21} Similarly, pharmacoscintigraphic data provided evidence of a significant shift in the site of uptake towards the ileum and colon with the controlled-release formulation. Notably, the variability in the different data sets was not greater for the controlled-release than for the standard formulation.

In our study, we were able to recruit six patients with Crohn's disease, three of whom had active disease (patients P3, P4 and P5). Interestingly, although the SITT values of the patients with active disease (1, 4.5 and 1 h, respectively) were within the range reported for the other patients and healthy subjects (1–5.5 h), they had shorter ascending colon transit times (1, 7 and 1 h, respectively) than the rest of the patients (range, 11–15.5 h) and seven of the eight healthy subjects (range, 7–31 h). These patients also had the greatest relative uptake of budesonide in the distal colon: 48%, 8% and 92%, respectively, of the total budesonide uptake vs. 0–5% (range) in the rest of the fed patients and healthy controls. The patients with quiescent disease (P1, P2 and P6) had similar SITT values and relative uptake in the different segments to those of healthy controls (Tables 5 and 6). These findings are in concordance with other studies in patients with inflammatory bowel disease, reporting little impact of inflammation on SITT,²² but significant impact on colonic transit.²³ Entocort capsules have been developed to release budesonide in a time-dependent fashion in the ileum and throughout the colon. Hence, in the three patients with active disease in this study, the rapid transit through the proximal gut can explain reasonably well the limited budesonide uptake in this proximal region, and the subsequent extensive uptake of the remaining budesonide in the distal gut.

In both patients and healthy subjects given the controlled-release formulation, a major fraction of budesonide was absorbed in the ileum and colon. Although there were no major differences in overall uptake in these regions between the treatment groups, in the patients with active Crohn's disease, the uptake of budesonide from the controlled-release formulation

appeared to be more distal than that in healthy subjects or patients with quiescent disease. Therefore, Entocort capsules should be well suited for the local treatment of inflammatory bowel disease localized to the ileum and ascending colon, and, in patients with active Crohn's disease, possibly also for lesions extending beyond the hepatic flexure of the colon.

The systemic availability of oral budesonide is low — of the order of 10% in healthy subjects^{24, 25} — which was confirmed in the present study. As plain, oral budesonide is rapidly dissolved and absorbed, this low figure is a result of an extensive first-pass metabolism via cytochrome p450 3A (CYP3A) enzymes before entry into the systemic circulation.⁵ Gut metabolism by CYP3A has been shown to be significant for a number of drugs metabolized via this enzyme.²⁶ Interestingly, CYP3A activity appears to be most abundant in the upper small intestine and then gradually decreases throughout the intestine, with little or no activity in the colon.²⁷ In the present study, the first-pass metabolism of oral budesonide was virtually unaffected by its site of uptake. The systemic availability after the standard immediate-release formulation was almost identical to that after the controlled-release capsules, in spite of the fact that significantly more was absorbed in the proximal parts of the small intestine from the standard than from the controlled-release formulation. Any gradient in CYP3A expression throughout the gut apparently does not affect the metabolism of budesonide, suggesting that the gut CYP3A metabolism of budesonide is relatively small. In addition, this suggests that the uptake of budesonide is complete even when intestinal release is delayed through the use of Entocort capsules.

The observation that the systemic availability of budesonide was greater in patients than in healthy subjects was unexpected. In two recently published articles on patients with active Crohn's disease, the systemic availabilities of budesonide after a single dose of Entocort capsules were about 14%²⁸ and 11%,²⁹ i.e. lower than in our patients and closer to our healthy controls. In another study in patients with active Crohn's disease, the systemic exposure was significantly higher after the first dose than after repeated treatment for 8 weeks.³⁰ In our patients, the average cortisol suppression did not differ from that in healthy controls, somewhat contradicting the systemic exposure data in the two groups of subjects. However, the urine cortisol assessment was associated with a large variability, and

possible cortisol differences may not have been revealed in this small study. Liver CYP3A activity can be inhibited by inflammation.³¹ A similar phenomenon could have possibly contributed to our findings of increased budesonide availability in Crohn's disease patients, and also to the reduction in budesonide exposure following treatment, which was suggested in the study by Naber *et al.*³⁰

The present study showed that gastric emptying of the controlled-release granules was considerably delayed by food in the stomach, whereas the subsequent transit times through the small intestine into the ascending colon were practically uninfluenced by food. These data agree with previously published results for gastric residence and SITT.³² The site of uptake of budesonide was also little affected by food, indicating that the food-induced gastric retention had little or no detrimental effect on the enteric coating of the controlled-release formulation.

To conclude, a major fraction of budesonide was released in the ileo-colonic region, which is the intended target for the budesonide controlled-release formulation. Although systemic availability was higher in Crohn's disease patients than in controls, ileo-colonic uptake was similar. The prandial state had little effect on budesonide uptake.

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