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Pharmacokinetics after single and multiple oral dosing of budesonide pH-modified-release capsules in patients with distal ulcerative colitis

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INTRODUCTION

Budesonide has been identified as a suitable topical steroid and is currently used for the treatment of Crohn's disease and ulcerative colitis, given as enteric-coated pellets in gastric juice-soluble capsules or as enemas[1–3]. Gastric juice-soluble hard gelatine capsules, each containing 3 mg budesonide distributed in about 350 gastric juice-resistant pellets with a diameter of about 1 mm for pH-modified release of budesonide (Budenofalk® pH-modified release capsules, PMR) (pH $\geqslant$6.4) based on the encapsulation of budesonide in methacrylic polymers, has recently been introduced. This delivery form releases the active drug during passage through the ileum and ascending colon, and this has been shown to improve clinical and functional outcomes as quickly and efficiently as systemically acting glucocorticoids such as prednisolone or prednisone in patients with inflammatory bowel diseases[4,5]. Two pilot studies showed that Budenofalk® had a therapeutic effect on the activity of steroid-dependent ulcerative colitis, had a significant steroid-sparing effect, and beneficial effects could be demonstrated by combining the new oral budesonide formulation with budesonide enemas in patients with steroid-dependent ulcerative colitis[6,7]. In an open clinical trial including 72 patients with active ulcerative colitis, it was found that the effects of another formulation of oral budesonide were comparable to prednisolone but, in contrast to prednisolone, budesonide did not change the plasma cortisol level[8].

A case report of a 14-year-old girl suffering from a steroid-dependent chronic active, severe ulcerative colitis demonstrated complete remission after changing from prednisolone to oral Budenofalk® 3 × 3 mg/day, and the progression of osteopenia and growth retardation caused by the prednisolone treatment could be stopped[9].

Previous reports have described the pharmacokinetics and pharmacodynamics of the topically acting budesonide after single and multiple dosage regimens of Budenofalk® in healthy volunteers and patients with Crohn's disease, and in ileostomy patients[10].

The aim of the present study was to investigate the clinical efficacy and safety of the topically acting budesonide in patients with mildly to moderately active left-sided ulcerative colitis using the dosage regimens of 3 × 3 mg or 1 × 9 mg budesonide per day, to provide pharmacokinetic results on budesonide and its two major metabolites and to assess the budesonide concentrations in biopsy specimens of the rectum, sigmoid and descending colon before treatment and at steady state.

PATIENTS AND METHODS

Fifteen patients with mildly to moderately active proctitis, proctosigmoiditis or left-sided ulcerative colitis were included in the study after diagnosis was confirmed by colonoscopy and histology. The CAI (clinical activity index) score had to be more than 4, and the EI (endoscopic index) score had to be 4 or more[11]. The patients were not allowed to receive any concomitant active medication for ulcerative colitis such as glucocorticoids or an immunosuppressant. In Group A receiving 3 × 3 mg Budenofalk® capsules, the eight patients (six female, two male) with ulcerative colitis included in the evaluation were 30.4 ± 16.54 years old (range 17–67 years), had a body weight of 66.5 ± 13.73 kg (range 48–79 kg) and an average height of 172.9 ± 10.78 cm (range 158–190 cm). In Group B receiving 1 × 9 mg Budenofalk® capsules, the seven patients (four female, three male) with ulcerative colitis included in the evaluation were 48.6 ± 16.38 years old (range 27–69 years), had a body weight of 81.6 ± 17.64 kg (range 56–107 kg) and an average height of 170.6 ± 9.07 cm (range 163–182 cm).

Patients were randomly assigned to receive treatment with either 3 × 3 mg budesonide per day or 1 × 9 mg budesonide per day for 8 weeks or for 4 weeks where there was remission after this treatment period, respectively. The patients enrolled in this study were hospitalized on the evening of day 4 for performance of the pharmacokinetic studies (budesonide, 6β-OH-budesonide and 16α-OH-prednisolone concentrations) on day 5, and they stayed until the morning of day 6 for the last blood withdrawal at 7 a.m. In addition, budesonide concentrations were determined in biopsy material of the descending colon (±50 cm), the sigmoid colon (±25 cm) and the rectum (±10 cm) at baseline (day 0) and on day 56 of treatment. The CAI was determined at baseline and after 4 and 8 weeks of treatment in symptomatic patients.

A sensitive, rapid and selective liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS-MS) method has been developed and validated for the simultaneous quantification of budesonide (BUD) and its major metabolites, 6ß-hydroxybudesonide (6ß-OH-budesonide) and 16α-hydroxyprednisolone (16α-OH-prednisolone) in human plasma.

The pharmacokinetic analysis was performed using non-compartmental approaches using the Kinetica® software (version 3.1, InnaPhase Corporation, Philadelphia, PA) which did not differ in pharmacokinetic principles from

previously employed Excel® spreadsheets. Data below the limit of detection were not considered, and the following parameters were derived:

1. T_{max} (time of peak concentration) and C_{max}-values (peak concentration) were obtained directly from the concentration vs. time data.

2. The time lag of absorption (t_{lag}) was defined as the time after drug administration at which concentrations increased above baseline values.

3. The area under the concentration–time profile between 0 h (day 5) and the last measurement point after 24 h on day 6 ($AUC_{0-24\ h}$) was calculated by the trapezoidal rule.

4. The terminal elimination rate constant k_e was determined for each individual subject from the terminal slopes of semi-logarithmic plots of serum concentration–time profiles. For the 3 × 3 mg dosing regimen, generally the time window of 12–24 h was used. The elimination half-life was calculated as $t_{\frac{1}{2}} = 0.693/k_e$.

5. Apparent clearance (Cl) not adjusted for the systemic bioavailability (f) was calculated from $AUC_{0-24\ h}$ and the administered dose (D = 9 mg).

6. The clinical efficacy response was defined as CAI ⩽ 4 (presence of clinical remission) at day 28 (second control) and day 56 (final control). Non-response was defined as CAI > 4 (absence of clinical remission) at the same time. Patients who were not in remission and had discontinued the therapy on day 24 or earlier were considered to be non-responders at both times of assessment.

RESULTS

Only patients with active ulcerative colitis distal to the splenic flexure were included for the assessment of the clinical activity index (CAI > 4). After 4 weeks a complete response (CAI ⩽ 4) was reached in 0 patients of group A, but in three patients of group B. The overall response rate after 8 weeks (CAI ⩽ 4 or decrease CAI 30%) was better with 9 mg o.d. (71%) compared to 3 mg t.i.d. (38%). The endoscopic index (EI) improved from 8.8 ± 2.1 to 3.8 ± 4.7 (p = 0.02) in 3 mg t.i.d. and from 9.7 ± 2.1 to 2.0 ± 2.9 (p < 0.001) in 9 mg o.d.

Mean budesonide and 6β-OH-budesonide serum profiles were markedly different between treatment groups, with higher peak concentrations obtained following the single 9 mg dose compared to the more sustained drug profile obtained when the same dose was administered in three divided portions at 5 h intervals as shown in Figure 1. The similar profiles for budesonide and 6β-OH-budesonide, in conjunction with higher levels of 16α-OH-prednisolone and a lag-time of about 3 h, are consistent with prolonged absorption of drug.

Concentrations measured in biopsy specimens obtained on day 0 and day 56 of the clinical trial showed increased budesonide levels after treatment, with no distinct differences between regional concentrations and dosing regimens, when the distinct variability in the concentrations is considered (results not shown).

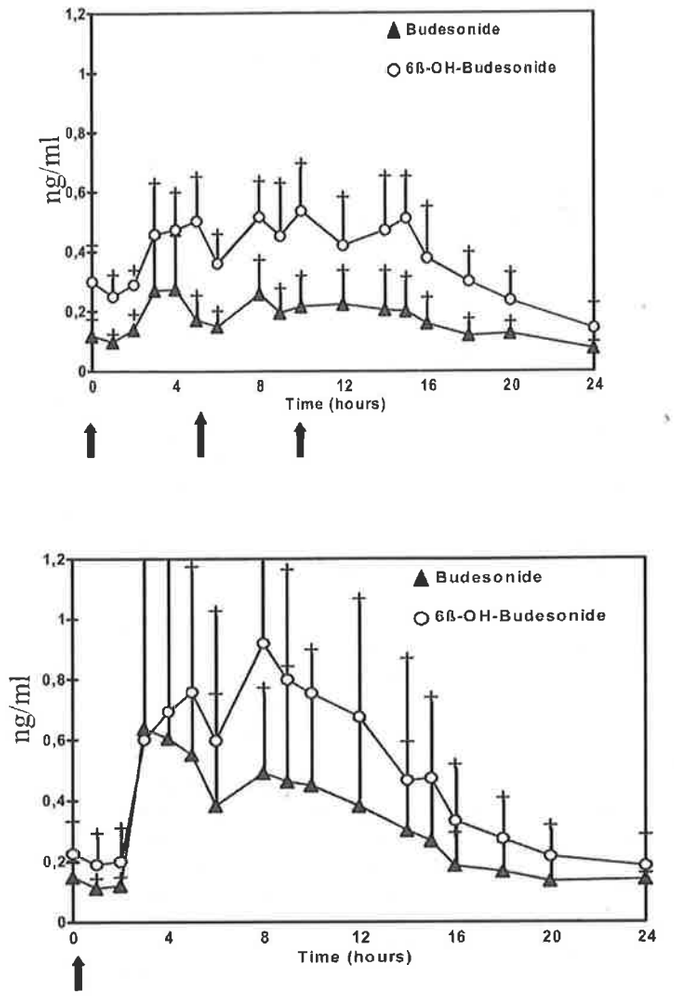

Figure 1 Mean serum budesonide and 6β-OH-budesonide (±SD) on day 5 of dosing in patients with left-sided ulcerative colitis. Group A (above): 3 mg budesonide oral capsules three times daily at 0, 5 and 10 h as indicated by arrows; group B (below) 9 mg budesonide as oral controlled-release capsules at 0 h

DISCUSSION

The present clinical study on oral budesonide in patients with mildly to moderately active distal ulcerative colitis shows that the pH-modified release formulation of budesonide (Budenofalk® 3 mg capsules) induces a treatment effect in about two-thirds of patients, comparable to that of mesalazine, the standard drug in this indication[12]. For the first time an efficacy of oral budesonide could be demonstrated in ulcerative colitis patients with inflammation limited to the distal parts of the colon. Obviously, the therapeutic effect is dependent on the dosage regimen. After 4 weeks of treatment, remarkably better results were found in the 1×9 mg dosage regimen than in the 3×3 mg regimen: 57% vs 0% were in remission or showed clinical improvement. This difference was smaller after 8 weeks of treatment at the end of the study, when 57% (group B) vs 38% (group A) were in remission. The onset of response indicated that the 1×9 mg treatment was not only more effective than the 3×3 mg treatment, but was also much faster in inducing remission or clinical improvement. The efficacy of oral budesonide demonstrated in this study is in agreement with the results of two earlier trials in ulcerative colitis as indicated in the introduction. Another study on oral budesonide in ulcerative colitis investigated the efficacy and safety of the pH-modified release formulation (Budenofalk® 3 mg capsules) in steroid-dependent patients. A daily dose of 9 mg budesonide was well tolerated, significantly improved clinical symptoms and allowed for sparing conventional, systemically acting steroids[13].

Results for budesonide mean pharmacokinetic parameters are in reasonable agreement with an early publication that calculated budesonide kinetics after intravenous administration in healthy volunteers[14]. The similar profiles for budesonide and 6β-OH-budesonide, in conjunction with higher levels of 16α-OH-prednisolone and a lag-time of about 3 h, are consistent with prolonged absorption of drug.

Concentrations measured in biopsy specimens, when the distinct variability in the concentrations is considered, obtained on day 0 and day 56 of the clinical trial showed increased budesonide levels after treatment, with no distinct differences between regional concentrations and dosing regimens[15]. The study indicated higher oral bioavailability after the 1×9 mg dose than after the 3×3 mg dose at comparable t_{max}: 5.7 h vs. 5.3 h. The difference in $AUC_{0-24\ h}$ and Cl/f between the two groups, however, barely reached significance because of the distinct variability in $AUC_{0-24\ h}$ estimates for the two dosing regimens. Results from this study indicate that higher peak concentrations of parent drug and metabolites are obtained when a single 9 mg dose of budesonide is administered as controlled-release capsules compared to administration of 9 mg in three divided doses over 10 h. Although the data suggest increased total absorption of drug with a single administration, AUC values were not significantly different due to the high variability between patients with ulcerative colitis[15].

The study also assessed the drug levels in biopsy specimens after 56 days of treatment. Considering the limited amount of data, and the distinct variability, it is difficult to assess whether regional differences in the budesonide content between descending and sigmoid colon or rectum exist.

Since all patients in this study suffered from inflammation limited to the left-sided colon and/or rectum, and the pharmacokinetic investigations demonstrated therapeutically adequate mucosal budesonide concentrations in these regions, it can be concluded that the active drug from both dosage regimens of Budenofalk® 3 mg capsules used in this study is effective in the whole colon, even reaching far distal gut regions. The good tolerability profile without serious drug-related adverse events as compared to the conventional, systemically acting steroids suggests that this topically acting, pH-modified release formulation of budesonide could be a treatment option in active ulcerative colitis.

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