

Pharmacokinetics and pharmacodynamic action of budesonide in children with Crohn's disease

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Publication data

Submitted 24 October 2005
First decision 13 November 2005
Resubmitted 20 November 2005
Accepted 20 November 2005

SUMMARY

Background

Budesonide is effective as initial therapy of mild to moderate Crohn's disease in adults. Superior tolerability to conventional corticosteroids might be attributed to extensive first-pass metabolism of budesonide by cytochrome P450 3A.

Aim

To evaluate biotransformation and pharmacodynamic action of budesonide in children.

Methods

Drug disposition and effects on endogenous cortisol were evaluated in 12 children with Crohn's disease (5–15 years) after first intake of 3 mg budesonide (single dose), and again after 1 week of thrice daily dosing (steady-state). The parent drug and cytochrome P450 3A-dependent metabolites were analysed in blood and urine.

Results

Pharmacokinetic parameters of budesonide following single-dose administration (e.g. $AUC_{0-\infty}$ 7.7 ± 5.1 h ng/mL, C_{max} 1.8 ± 1.2 ng/mL) did not change upon multiple dosing. Overall systemic elimination of budesonide reflected by clearance and half-life was not different between children and adults. After 1 week of treatment reversible adrenal suppression was observed – most pronounced in children aged below 12 years.

Conclusions

Disposition of oral budesonide appears to be similar between children and adults, but the doctor has to be aware of an increased risk for adrenal suppression in paediatric patients.

Aliment Pharmacol Ther 23, 387–395

INTRODUCTION

Use of drugs in children requires a thorough consideration of the pharmacokinetics and pharmacodynamic action in the paediatric population. Variation in body composition, and maturity of liver and kidney are predominant factors accounting for differences in drug disposition between children and adults.¹ Simplified dosing approaches for paediatric patients based on extrapolation from adult data do not consider age-associated changes in absorption and drug elimination or pharmacodynamics. Lack of comprehensive evaluations of drugs to treat children with inflammatory bowel diseases is a concern. Inflammatory bowel diseases primarily affect young adults, but in 15–25% of cases, the initial disease starts in childhood.²

Budesonide is a newer synthetic glucocorticoid with a high ratio of local to systemic anti-inflammatory activity.³ Oral formulations of budesonide are effective as initial therapy of mild to moderate Crohn's disease of the ileum and ascending colon in adults.^{4, 5} Two recent investigations in paediatric Crohn's disease reported similar remission rates with budesonide and prednisone or prednisolone treatment; budesonide was suggested as an alternative to conventional corticosteroids in children because of superior tolerability.^{6, 7} The decreased risk for adverse drug reactions might be attributed to the very low absolute bioavailability of budesonide of about 10% which results from gastrointestinal efflux mediated by P-glycoprotein, the product of the multidrug resistance 1 (*MDR1*) gene, and from extensive biotransformation via cytochrome P450 3A (CYP3A) in gut and liver.^{8, 9} CYP3A enzymes are the most important enzymes in human drug metabolism.¹⁰ However, changes in CYP3A activity during childhood and adolescence are incompletely characterized.¹¹ Data concerning developmental expression of P-glycoprotein which is the major drug transporter in human intestine are scarce.¹² Therefore, clinical studies on disposition of budesonide in children including characterization of the relevant metabolic pathways are required.

Recently, paediatric gastroenterologists discussed a trend to higher incidence of certain steroid-associated side-effects such as moon face in children when compared with adults during both prednisolone and budesonide treatment.⁷ Symptoms of adrenal suppression are dose-related in adults,¹³ but may be a special problem in childhood and during puberty. To support

safe dosing and weaning of budesonide in children, effects on endogenous cortisol production have to be examined carefully.

Thus, the aim of our trial was to determine the pharmacokinetic profile and pharmacodynamic action of oral budesonide following single dose and steady-state dosing in children with Crohn's disease. A profound analysis of metabolite kinetics (formation of 6 β -hydroxybudesonide and 16 α -hydroxyprednisolone via CYP3A) and comparison with data in adults will be provided. This is the first report in children on pharmacokinetics of a modified release formulation of budesonide dissolving at pH 6.4.

MATERIALS AND METHODS

Patients

Twelve female and male children aged below 16 years with a diagnosis of mild or moderate Crohn's disease, confirmed by history, endoscopy, or histology evidence, and negative stool culture were enrolled in the study. Disease activity was assessed by the paediatric Crohn's disease activity index (PCDAI) at screening.¹⁴ The patients were eligible if, at the investigator's discretion, they had to start treatment with a corticosteroid. Exclusion criteria were: (i) severe Crohn's disease; (ii) any other disease of bacterial, fungal or viral origin; (iii) hepatic or renal disease or other pathological findings, which might interfere with pharmacokinetics or drug safety; (iv) administration of corticosteroids within 3 months prior to the study drug; (v) concomitant treatment with methotrexate, infliximab, antacids or colestyramine (cholestyramine); (vi) use of drugs during the last week prior to the first administration or during the trial, which might influence biotransformation of budesonide.¹⁵ For concomitant azathioprine or mercaptopurine (6-mercaptopurine), the dose must have been stable prior to study entry for at least 8 weeks. Mesalazine (mesalamine) was allowed in dosages of 30–50 mg/kg. Intake of grapefruit in the week prior to the first study day precluded participation.

Study design

The children ingested 3 mg budesonide as a single oral dose on day 1, thrice daily from days 2 to 7, and once in the morning of day 8. On day 1 and on day 8, single-dose and steady-state pharmacokinetic and

pharmacodynamic profiling were performed by determination of budesonide, CYP3A-dependent metabolites (6 β -hydroxybudesonide, 16 α -hydroxyprednisolone), and cortisol in plasma and urine before and during 24 h after drug administration. On day 1, one separate blood sample was collected for deoxyribonucleic acid extraction in order to determine MDR1 single nucleotide polymorphisms (2677G>T,A and 3435C>T).¹⁶ All children were hospitalized during two study days (days 1 and 8). After an overnight fast, a standardized lunch was served but not until 4 h after intake of budesonide. Blood samples were taken just before and 1, 2, 2.5, 3, 4, 4.5, 5, 6, 8 and 24 h after administration of the study drug. For safety reasons, in one children aged 5 years blood collection for determination of cortisol had to be restricted to two samples (0 and 24 h). Blood samples (ethylenediaminetetraacetic acid tubes) were centrifuged immediately. Urine was collected in two consecutive samples (0–8 and 8–24 h). Plasma and urine were stored at –20 °C (<1 month) until analysis. To ensure compliance during days 2–7, patients had to use a dispenser and fill in a medication diary. Any concomitant medication was administered with a difference of at least 2 h to the study medication. Adverse drug reactions were recorded in all children throughout the study.

Analytical methods

Concentrations of budesonide, 6 β -hydroxybudesonide, and 16 α -hydroxyprednisolone in plasma and urine were determined by validated liquid chromatography tandem mass spectrometry.¹⁷ After extraction from the matrix, budesonide and its metabolites were quantified using a triple-stage mass spectrometer SCIEX API III PLUS (SCIEX, Thornhill, ON, Canada). The chromatography column was coupled via a heated nebulizer interface to an atmospheric pressure ionization chamber of the mass spectrometer. For determination of 16 α -hydroxyprednisolone a turbo ion spray interface was used instead. The lower limit of quantification in plasma (urine) was 0.1 ng/mL (0.5 ng/mL) for budesonide and 6 β -hydroxybudesonide, and 0.4 ng/mL (2 ng/mL) for 16 α -hydroxyprednisolone. Between-day and within-day coefficients of variation of quality controls were below 15%. Cortisol in plasma and in urine was determined using a fluorescence polarization immunoassay (TDx/TDxFLx, Abbott Laboratories, Abbott Park, IL, USA). Sensitivity of the test was 0.77 μ g/dL.

Pharmacokinetic and pharmacodynamic analysis

Pharmacokinetic analysis was based on plasma concentrations above the limit of quantification. Peak plasma concentration (C_{\max}), trough plasma concentration (C_{\min}) and time of C_{\max} (t_{\max}) were taken directly from the plasma concentration–time curves. Area under the plasma concentration–time curve (AUC) as well as terminal elimination half-life ($t_{1/2} = \ln[2]/\lambda$), apparent oral clearance ($Cl/f = \text{dose}/AUC_{0-\infty}$), and apparent volume of distribution ($V_d/f = \text{dose}/[AUC_{0-\infty} \lambda]$) were calculated using standard non-compartmental analysis (WINNONLIN v. 3.1A, Pharsight Corporation, Mountain View, CA, USA). Cl/f and V_d/f were normalized for body weight. The elimination rate constant (λ) was determined by linear regression analysis of the terminal log-linear phase of the plasma concentration–time curve. AUC describes the extent of systemic drug exposure; Cl/f characterizes the ability to remove budesonide from the plasma in a given period; V_d/f is a function of plasma and tissue protein-binding properties of the substance, but does not necessarily refer to any physiological compartment in the body. Rate of accumulation was obtained by the following ratio:¹⁸ $R_{ac} = AUC_{ss,0-8h,d8}/AUC_{0-8h,d1}$. A linearity factor of pharmacokinetics after repeated administration was calculated as the ratio of $AUC_{ss,0-8h,d8}$ and $AUC_{0-\infty,d1}$. Ratios of metabolite formation ($AUC_{Met}/AUC_{Budesonide}$, where Met is the metabolite) such as AUC_{0-24h} of 6 β -hydroxybudesonide to AUC_{0-24h} of budesonide were used as indices of CYP3A metabolic activity. Urinary recoveries of the analytes were based on the cumulative amount of the analyte excreted during the 24 h collection period (Ae_{0-24h}), and were expressed as percentage of the budesonide dose administered. Clearances to metabolites (Cl_{Met}) being a measure of elimination of budesonide via biotransformation were calculated by dividing Ae_{0-24h} of the respective metabolite by AUC_{0-24h} of budesonide in plasma. Effects of budesonide on endogenous cortisol production were evaluated in each individual by (i) measuring morning cortisol plasma levels (8 AM), by (ii) calculating AUC of cortisol in plasma during 24 h and by (iii) measuring the cumulative amount of cortisol excreted into urine during 24 h.

Statistical analysis

It has been demonstrated that in a paediatric pharmacokinetic study with frequent blood collection a group

of 12 subjects will provide reliable information on the parameters reported.¹⁹ The pharmacokinetic and pharmacodynamic parameters are given as mean \pm s.d. or median with 95% confidence interval in parentheses. Wilcoxon test was used to compare the parameters on day 1 (single dose) with the corresponding parameters on day 8 (steady-state). Morning concentrations of cortisol in plasma were compared across treatment ($C_{0h,d1}$, $C_{24h,d1}$, $C_{0h,d8}$, $C_{24h,d8}$) by non-parametric ANOVA. In addition, differences in our results on disposition of budesonide and formation of metabolites in children and our previously published results on pharmacokinetics of oral budesonide in adults were tested for significance by Mann–Whitney test; in eight healthy adults (44.4 ± 8.6 years), pharmacokinetic parameters of budesonide and its metabolites following single-dose administration of 3 mg of budesonide are available from baseline of a drug interaction study using the same methods.²⁰ The *P*-value of <0.05 was regarded as statistically significant. Statistical comparison was carried out by use of the software package GRAPHPAD INSTAT (GraphPad Software, Inc., San Diego, CA, USA).

Ethical considerations

The study protocol was approved by the Institutional Ethics Committees of the respective centres. The trial was conducted in accordance with the ethical guide-

lines of the Declaration of Helsinki, and International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). Details of the study drug and study design were outlined to the child and the parents by the investigator prior to screening. All parents or legal guardians gave written informed consent. Children gave either written consent or assented verbally.

RESULTS

Patients

Four female and eight male children with Crohn's disease (PCDAI, 16.9 ± 11.7) completed the study according to the protocol with excellent compliance. Individual demographic and clinical characteristics are presented in Table 1. The study drug was well tolerated. There was no serious adverse drug reaction.

Pharmacokinetics

Pharmacokinetic parameters of oral budesonide and two CYP3A-dependent metabolites are given in Table 2 for comparison of single-dose administration and steady-state dosing. Plasma concentration–time curves of budesonide, 6β -hydroxybudesonide and 16α -hydroxyprednisolone are illustrated in Figures 1–3. Mean *Cl/f* of budesonide describing the ability of the body to remove

Table 1. Demographic and clinical features of the paediatric population

Patient	Age (years)	Sex (M/F)	Height (cm)	Weight (kg)	Weight for height (% of normal)	Localization of Crohn's disease	Concomitant medication on days 1–8
1	11	M	150	47	118	Colonic	5-ASA
2	13	F	139	31	98	Ileocolonic	5-ASA
3	15	M	177	62	91	Ileal	5-ASA
4	15	M	159	44	94	Ileocolonic	5-ASA*, AZT*
5	14	F	156	49	110	Ileocolonic	5-ASA*, AZT*
6	15	F	166	68	116	Ileocolonic	5-ASA*, AZT*
7	13	M	153	46	111	Colonic	5-ASA
8	9	M	146	37	101	Ileocecal	5-ASA
9	15	F	174	57	87	Ileocolonic	5-ASA
10	15	M	171	49	84	Ileocecal	5-ASA
11	15	M	182	59	83	Colonic	Sulfasalazine
12	5	M	116	26	127	Ileal	–
Mean (s.d.)	12.9 (3.1)		157 (18.5)	48 (12.4)	102 (14.6)		

5-ASA, mesalazine; AZT, azathioprine.

* Not on the study days (days 1 and 8).

Table 2. Pharmacokinetic parameters of budesonide and two CYP3A-dependent metabolites in 12 children with Crohn's disease

	Budesonide	6 β -OH-budesonide	16 α -OH-prednisolone
3 mg single dose (day 1)			
C_{max} (ng/mL)	1.76 \pm 1.17	2.3 \pm 1.0	16.2 \pm 6.0
t_{max} (h)	4.5 (4.0–5.3)	4.8 (4.4–6.0)	4.5 (3.9–5.2)
$AUC_{0-\infty}$ (h ng/mL)	7.7 \pm 5.1	18.1 \pm 6.5	72.4 \pm 25.6
$t_{1/2}$ (h)	1.9 (1.6–3.6)	5.1 (4.3–6.4)	1.5 (1.4–3.1)
Cl/f (L/min/kg)	0.18 \pm 0.08		
V_d/f (L/kg)	40.1 \pm 23.2		
Ae_{0-24h} (% of dose)	0.001 \pm 0.003	1.9 \pm 0.74	9.9 \pm 2.9
3 \times 3 mg multiple dose (day 8, steady-state)			
$C_{ss,max}$ (ng/mL)	1.8 \pm 1.1	3.3 \pm 1.1	22.1 \pm 11.3
$t_{ss,max}$ (h)	4.5 (4.3–5.2)	4.8 (4.4–5.3)	4.6 (4.4–5.1)
$C_{ss,min}$ (ng/mL)	0.29 \pm 0.14	1.2 \pm 0.38	2.3 \pm 1.9
$AUC_{ss,0-8h}$ (h ng/mL)	6.7 \pm 4.0	16.4 \pm 4.6	72.5 \pm 24.4

Data are given as mean \pm s.d. or as median with 95% confidence interval in parentheses.

C_{max} , peak plasma concentration; t_{max} , time of peak plasma concentration; $AUC_{0-\infty}$, area under the plasma concentration–time curve extrapolated to infinity; $t_{1/2}$, terminal elimination half-life; Cl/f , apparent oral clearance; V_d/f , apparent volume of distribution; Ae_{0-24h} , amount excreted into urine during 24 h; $C_{ss,max}$, peak plasma concentration at steady-state; $t_{ss,max}$, time of peak plasma concentration at steady-state; $C_{ss,min}$, trough plasma concentration at steady-state; $AUC_{ss,0-8h}$, area under the plasma concentration–time curve at steady-state during the dosing interval of 8 h; CYP3A, cytochrome P450 3A.

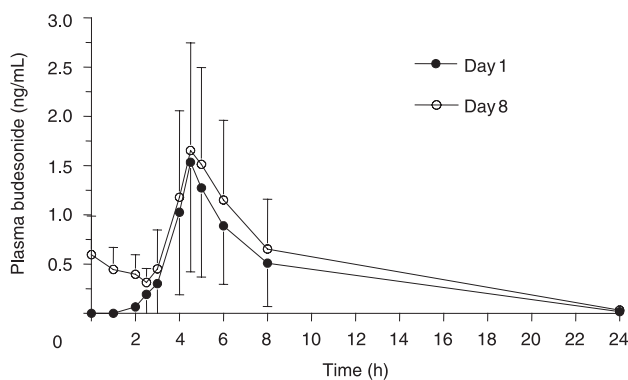


Figure 1. Plasma budesonide concentration–time curves in 12 children with Crohn's disease following a single oral dose of 3 mg budesonide on day 1 (solid circle) and on day 8 (open circle) after thrice daily dosing during days 2–7. Data are presented as mean \pm s.d.

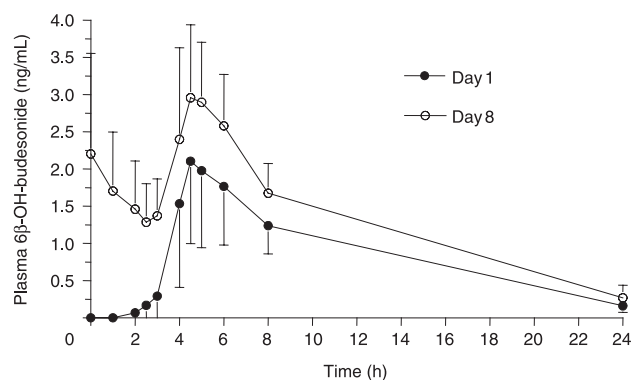


Figure 2. Plasma 6 β -hydroxybudesonide concentration–time curves in 12 children with Crohn's disease following a single oral dose of 3 mg budesonide on day 1 (solid circle) and on day 8 (open circle) after thrice daily dosing during days 2–7. Data are presented as mean \pm s.d.

the drug from plasma was 0.18 L/min/kg in children following a single oral dose of 3 mg. Median $t_{1/2}$ of budesonide was 1.9 h on day 1, and it was not significantly longer on day 8 (2.5 h, 95% CI: 2.0–4.3 h). Steady-state dosing did not result in relevant systemic

drug accumulation (1.5 \pm 0.6, budesonide; 2.2 \pm 0.8, 6 β -hydroxybudesonide; 1.5 \pm 0.4, 16 α -hydroxyprednisolone; R_{ac}). The linearity factor based on AUC was 1.0 \pm 0.5 for budesonide, 0.9 \pm 0.2 for 6 β -hydroxybudesonide and 1.1 \pm 0.3 for 16 α -hydroxyprednisolone,

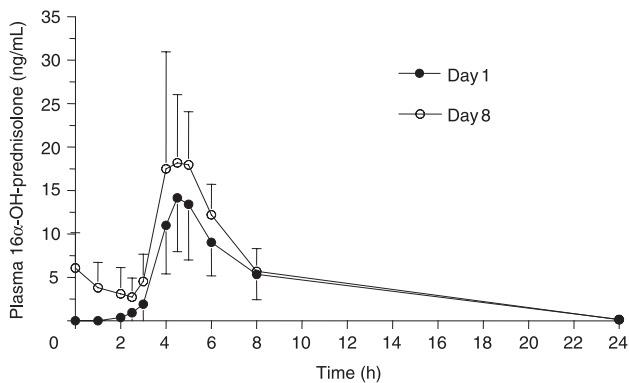


Figure 3. Plasma 16 α -hydroxyprednisolone concentration–time curves in 12 children with Crohn's disease following a single oral dose of 3 mg budesonide on day 1 (solid circle) and on day 8 (open circle) after thrice daily dosing during days 2–7. Data are presented as mean \pm s.d.

which means that multiple-dose pharmacokinetic behaviour of budesonide might be well predicted by single-dose pharmacokinetics.

There were no significant differences in the pharmacokinetic parameters following a single dose of 3 mg budesonide between children with Crohn's disease and healthy adults²⁰ (e.g. C_{max} , 1.76 \pm 1.17 ng/mL vs. 1.07 \pm 0.63 ng/mL; Cl/f , 0.18 \pm 0.08 L/min/kg vs. 0.22 \pm 0.11 L/min/kg; V_d/f , 40.1 \pm 23.2 L/kg vs. 46.7 \pm 27.9 L/kg; children vs. adults). In accordance with results in adults,²⁰ mean urinary recovery of budesonide (sum of budesonide and both metabolites) in children was about 12% of the dose administered. The amount of unchanged budesonide excreted into urine is negligible. Ratios of metabolite formation ($AUC_{Met}/AUC_{Budesonide}$) reflecting activity of CYP3A were not different between single-dose administration and steady-state dosing in children. Formation of 6 β -hydroxybudesonide was significantly increased in children when compared with recent data in adults²⁰ (2.9 \pm 1.0 vs. 1.9 \pm 0.9, $P = 0.0373$, Figure 4). In the paediatric population, Cl_{Met} were 0.24 \pm 0.12 L/h/kg for 6 β -hydroxybudesonide, and 1.2 \pm 1.2 L/h/kg for 16 α -hydroxyprednisolone; comparison with adults²⁰ revealed no significant difference.

To assess a pharmacogenetic impact on disposition of budesonide, we contrasted opposite homozygous MDR1 genotypes. All children with MDR1 3435 CC genotype (patients 1–3) were also carriers of MDR1 2677 GG, and one patient with the variant MDR1

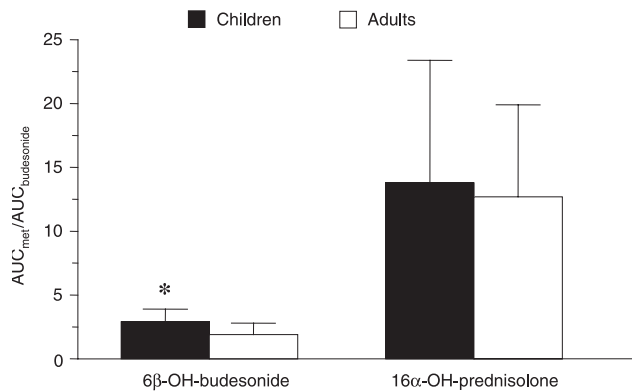


Figure 4. Ratios of cytochrome P450 3A (CYP3A)-dependent metabolite formation ($AUC_{Met}/AUC_{Budesonide}$ where Met is the metabolite) following a single oral dose of 3 mg budesonide in 12 children with Crohn's disease (black) and eight healthy adults²⁰ (white). Data are presented as mean values and s.d. (* $P < 0.05$).

3435 TT genotype (patient 9) was carrier of MDR1 2677 TT. Looking over the plasma concentration–time curves in these children, absorption of budesonide was not found to be lower in MDR1 3435 CC with putatively high intestinal expression of P-glycoprotein²¹ than in MDR1 3435 TT. Remarkably delayed absorption of budesonide was observed in a boy (patient 10) who took oral metronidazole (1.2 g/day during 12 days) until the evening before first administration of budesonide. On day 1 but not on day 8, budesonide in plasma was below the limit of quantification during 6 h in that patient.

Pharmacodynamic action

Effects of budesonide on endogenous cortisol are summarized in Table 3. After 1 week of thrice daily dosing of 3 mg budesonide, morning cortisol levels in plasma decreased significantly (17 \pm 13 μ g/dL vs. 9 \pm 12 μ g/dL, day 1 vs. day 8, $P < 0.01$). Likewise, areas under the effect curves (AUC_{0-24h}) were lower on day 8 when compared with day 1 ($P < 0.05$). On day 8, in five of 12 children (the three youngest patients, and two older children; patients 1, 3, 8, 10 and 12) plasma cortisol at 8 AM was below the limit of detection. In each subject, withdrawal of budesonide resulted in a return to normal values of morning plasma cortisol within 24 h ($C_{24h,d8}$). Urinary excretion of cortisol was not affected by intake of budesonide.

Table 3. Effect of budesonide on endogenous cortisol in 12 children with Crohn's disease

Evaluation of cortisol	Day 1	Day 8
<i>C</i> _{0h} (µg/dL)		
All children (<i>n</i> = 12)	17 ± 13	9 ± 12**
5–11 years (<i>n</i> = 3)	11 ± 2	<LOQ
12–15 years (<i>n</i> = 9)	19 ± 14	12 ± 13*
<i>C</i> _{24h} (µg/dL)		
All children (<i>n</i> = 12)	15 ± 11	12 ± 9
5–11 years (<i>n</i> = 3)	9 ± 0.02	9 ± 5
12–15 years (<i>n</i> = 9)	17 ± 12	14 ± 10
<i>AUC</i> _{0–24h} (h µg/dL)†		
All children (<i>n</i> = 11)	239 ± 239	183 ± 195*
9–11 years (<i>n</i> = 2)	121 ± 21	95 ± 45
12–15 years (<i>n</i> = 9)	266 ± 259	202 ± 212
<i>Ae</i> _{0–24h} (µg)		
All children (<i>n</i> = 12)	301 ± 89	299 ± 82
5–11 years (<i>n</i> = 3)	213 ± 82	257 ± 127
12–15 years (<i>n</i> = 9)	330 ± 73	313 ± 67

On day 1 and on day 8, a single oral dose of 3 mg budesonide was given after thrice daily dosing during days 2–7. Data are given as mean ± s.d.

*C*_{0h}, predose cortisol plasma concentration (8 AM); *C*_{24h}, cortisol plasma concentration at 24 h (8 AM); *AUC*_{0–24h}, area under the cortisol plasma concentration–time curve during 24 h; *Ae*_{0–24h}, amount of cortisol excreted into urine during 24 h; LOQ, limit of quantification (0.77 µg/dL).

P* < 0.05 vs. day 1; *P* < 0.01 vs. day 1.

† No profiling in one children aged 5 years.

DISCUSSION

This study provides comprehensive data on the pharmacokinetics and pharmacodynamic action of oral budesonide in children with Crohn's disease. The pharmacokinetic parameters of budesonide following single-dose administration did not change significantly upon multiple dosing. We observed no relevant drug accumulation during steady-state dosing. Therefore, in the paediatric population plasma concentration of budesonide at steady-state may be predicted from single-dose data. After short-term treatment with budesonide, 3 mg thrice daily during 1 week, reversible adrenal suppression was observed in the paediatric patients; morning plasma cortisol below the limit of detection in each patient below 12 years of age was striking.

Budesonide is a high extraction drug. It undergoes extensive first-pass metabolism by CYP3A enzymes forming 6β-hydroxybudesonide and 16α-hydroxyprednisolone. Glucocorticoid activity of the metabo-

lites amounts to only 1–10% of the parent drug.⁹ Overall systemic elimination of budesonide reflected by *Cl/f* and *t*_{1/2} was not different between children and adults. Conversion to 6β-hydroxybudesonide (*AUC* ratio) was found to be 1.5-fold higher in children than in adults. Difference in formation of 16α-hydroxyprednisolone did not reach statistical significance. Metabolite formation of budesonide (*AUC*_{Met}/*AUC*_{Budesonide}) has been proven to be a good measure of CYP3A activity.²⁰ However, it is difficult to gain insight into age-related differences in CYP3A activity comparing children with Crohn's disease and healthy adults. Consistent with our data, absolute bioavailability of a different delivery system of oral budesonide was similar (9 ± 5% vs. 11 ± 7%) in eight children with Crohn's disease (12.4 ± 1.8 years) and six adults with Crohn's disease (33.2 ± 12.6 years).²² The trend to lower bioavailability of oral budesonide in the paediatric population observed by those investigators might now be explained by enhanced biotransformation via CYP3A enzymes in children. However, metabolic pathways of budesonide were not analysed in that trial.

CYP3A is the most abundant human CYP enzyme accounting for approximately 30% of the total CYP content in adult liver.²³ Clinical trials with substrates of CYP3A are needed to evaluate precisely if developmental changes necessitate dose adjustments across the span of childhood and adolescence. The CYP3A subfamily, which comprises three functional genes, CYP3A4, CYP3A5 and CYP3A7, is variably expressed at different stages of life. CYP3A4 is the major isoform in the adult liver, whereas expression of CYP3A5 is low in adult Caucasians due to a genetic polymorphism.²⁴ CYP3A7 is expressed in the fetal liver, peaks shortly after birth and then declines rapidly to levels that are undetectable in most adults.²⁵ Clearly, the most dramatic developmental changes occur during the first year of life.²⁶ The few data available comparing duodenal and hepatic expression of CYP3A in older children and adolescents with that in adults are conflicting.^{12, 25, 27, 28} Many healthy children of different ages would be needed in a clinical trial aiming at an accurate examination of maturational changes of CYP3A.

It remains to be determined if Crohn's disease affects duodenal CYP3A activity. Mean absolute bioavailability of a high dose of oral budesonide (18 mg) was reported to be significantly increased (21% vs. 12%, *P* < 0.05) in six adult patients with Crohn's disease in comparison with eight healthy adults.²⁹ Therefore, it

might be speculated that the difference in formation of metabolites we observed between children with Crohn's disease and healthy adults is further enlarged between children with Crohn's disease and adults with Crohn's disease. Inflammatory bowel diseases might not only affect intestinal CYP3A but also intestinal drug efflux by P-glycoprotein. To date, investigations in Crohn's disease addressing the interplay between drug-metabolizing enzymes and transporter proteins are missing.

MDR1 genotyping was performed due to the particular relevance of intestinal P-glycoprotein for oral drug therapy.³⁰ It has been shown that a 2677G>T, A single nucleotide polymorphism in exon 21 and a 3435C>T single nucleotide polymorphism in exon 26 of the *MDR1* gene affect expression of P-glycoprotein and thereby pharmacokinetics of commonly used drugs.³¹ There was no hint for a pharmacogenetic effect on absorption of budesonide in our study population. Considering the small number of children, our preliminary results of MDR1 genotyping should be interpreted with caution.

The finding that in one child receiving metronidazole the lag time of enteric-coated budesonide was considerably prolonged is interesting and warrants further investigation. Unfortunately, repetition of the study in that subject (boy) was impossible because of resection of the ileum a short time later. One might consider an unexpected drug interaction of budesonide and metronidazole in this case. Alternatively, absorption on the first study day might have been affected by altered intraluminal pH, delayed gastric emptying or intestinal transit independent of a concomitant drug.

Both in adults and in children with Crohn's disease, the frequency of adverse drug reactions following effective doses of budesonide has been found to be lower than that following effective doses of conventional steroids.³² From the pharmacodynamic analysis of our study it is apparent that children with Crohn's disease who are prescribed budesonide have to be monitored very carefully for steroid-related adverse

reactions. Vigilance of healthcare professionals is the most important factor in avoiding adverse drug reactions. Plasma cortisol concentrations are a sensitive measure of systemic corticosteroid effects in children.³³ The method is used to detect adrenal suppression before the appearance of clinical symptoms. Therefore, the finding that morning plasma cortisol was not detectable on day 8 in five of 12 children including all children below 12 years of age needs special attention. The extent of adrenal suppression in adults is known to be related to the dose of budesonide.¹³ Using the standard dosage of oral budesonide in Crohn's disease which is 9 mg/day, our children with a mean body weight of 48 kg received obviously a higher dose per kilogram body weight than adults. The observation that youngest but not most light-weighted children displayed highest adrenal suppression might indicate particular sensitivity in the subset of young children. Although all children recovered from adrenal suppression within 24 h, a prolonged effect cannot be excluded after longer treatment with budesonide. Thus, it seems advisable to reduce the dose gradually at the end of treatment with budesonide and monitor morning plasma cortisol levels before complete weaning.

In conclusion, our pharmacokinetic and pharmacodynamic data may be used to ensure effective and safe treatment with budesonide in children with Crohn's disease. Disposition of oral budesonide appears to be similar between children (5–15 years) and adults. However, the doctor has to be aware of an increased risk for adrenal suppression during and after intake of budesonide in paediatric patients. It is important to note that in children corrections in dosing made for body weight or body surface may not accurately reflect differences in pharmacodynamics.

ACKNOWLEDGEMENTS

The study was supported by Dr Falk Pharma GmbH, Freiburg, Germany. Genotyping was performed by Dr G. Schaeffeler, Stuttgart, Germany.

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