

# PEDIATRIC PHARMACOTHERAPY



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## Budesonide Use in Children and Adolescents with Crohn's Disease

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**O**n April 29, 2016, the Food and Drug Administration extended the approval of controlled ileal release budesonide (Entocort® EC) to include the treatment of mild to moderate active Crohn's disease in the ileum and/or ascending colon in children 8 years of age and older.<sup>1,2</sup> Corticosteroids have long been recommended for inducing remission in children with active Crohn's disease.<sup>3</sup> Controlled ileal release budesonide, first approved by the FDA in 2001, produces less systemic corticosteroid exposure than prednisolone and may reduce the incidence of adverse effects. Use of budesonide in children result in less reduction in growth velocity than prednisone. In the 2014 European Crohn's and Colitis Organization and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ECCO/ESPGHAN) consensus guidelines on the management of Crohn's disease, 96% of the experts on the panel agreed that budesonide may be used as an alternative to systemic corticosteroids for children with ileal or ascending colonic disease.<sup>4</sup>

### Mechanism of Action

Budesonide, (RS)-11 $\beta$ , 16 $\alpha$ , 17, 2-tetrahydroxy pregna-1, 4-diene 3, 20-dione cyclic 16, 17-acetal butyraldehyde, is a high-potency nonhalogenated glucocorticoid with weak mineralocorticoid effects. Budesonide has an intrinsic potency approximately 200-fold greater than that of cortisol and 15-fold greater than prednisolone.<sup>2</sup>

### Pharmacokinetics and Pharmacodynamics

Entocort® EC provides a high degree of topical glucocorticoid activity in the distal ileum compared to its systemic effects. This local effect is the result of its low bioavailability (approximately 10%) caused by substantial first-pass metabolism via CYP3A4 enzymes in the

gut mucosa and liver. In premarketing pharmacokinetic studies, the mean peak plasma concentration and area under the concentration time curve (AUC) following a dose of 9 mg given once daily were  $5.3 \pm 1.8$  nmol/L and  $37.0 \pm 14.6$  nmol·h/L in healthy adults, and  $4.0 \pm 2.1$  nmol/L and  $35.0 \pm 19.8$  nmol·h/L in adults with active Crohn's disease. Time to peak concentrations varied from 30 to 600 minutes. Administration with a high-fat meal delayed the time to peak concentration but did not alter AUC, suggesting that the drug may be taken with or without food. The mean volume of distribution varied from 2.2 to 3.9 L/kg, with 85-90% bound to plasma proteins. Budesonide has an elimination half-life of 2 to 3.6 hours. The primary metabolites, 6 $\beta$ -hydroxy budesonide and 16 $\alpha$ -hydroxy prednisolone, have no significant corticosteroid activity and are excreted in the urine.<sup>2</sup>

The pharmacokinetic and pharmacodynamic profiles of budesonide were compared in six adults and eight children ranging in age from 9 to 14 years.<sup>5</sup> After a week of 9 mg budesonide given once daily, the median peak plasma concentration in the children was  $6.0 \pm 3.5$  nmol/hr, with a mean AUC of  $41.3 \pm 12.2$  nmol·h/L, approximately 17% higher than that seen in the adult subjects. The mean bioavailability of budesonide in the children was 9.2%. The mean volume of distribution was  $2.2 \pm 0.4$  L/kg, with a weight-normalized clearance of 20.5 mL/min/kg, compared to 15.9 mL/min/kg in adults. The mean half-life was  $1.9 \pm 0.2$  hours. There was a greater decrease in plasma cortisol AUC in the children compared to the adults ( $64\% \pm 18\%$  in versus  $50\% \pm 27\%$ ), but the difference was not statistically significant. The authors summarized that budesonide pharmacokinetics are similar in

children and adults; however, there was a trend towards a greater degree of cortisol suppression in the pediatric patients.

#### Clinical Studies

##### **Induction of Remission**

In 2001, Kundhal and colleagues at Toronto's Hospital for Sick Children published the first retrospective study of controlled ileal release budesonide in children with mild to moderate Crohn's disease.<sup>6</sup> Thirty-two children 8 to 18 years of age with a Pediatric Crohn's Disease Activity Index (PCDAI) between 12.5 and 40 points were enrolled. Twenty-three patients had disease localized to the ileum and nine had both ileal and colonic involvement. All patients received 9 mg budesonide once daily. The five newly diagnosed patients received budesonide alone while the patients with relapsed disease received budesonide in addition to their other maintenance medications (5-aminosalicylic acid, sulfasalazine, metronidazole, ciprofloxacin, or azathioprine).

At the first follow-up visit (a mean of  $8.7 \pm 6$  weeks after initiation of therapy), 59% of the patients had a positive response to treatment as determined by physician global assessment and PCDAI scores. Eight patients (25%) were classified as having a complete response, with another eleven children (34%) having a partial response. In the 22 patients with complete documentation, the mean PCDAI decreased from  $33 \pm 14$  to  $22 \pm 16$  ( $p = 0.001$ ). The PCDAI fell to  $< 15$ , indicating remission, in six patients. Following the acute phase of treatment, six patients continued to receive 6 mg budesonide daily as maintenance therapy. Only one of the six experienced an exacerbation during treatment. The other five children experienced good control of their symptoms and had gained weight at follow-up. All six patients on maintenance therapy had a slowed growth velocity, with a rate of linear growth  $< 4$  cm/year, more than two standard deviations less than the mean for prepubertal children. The mean rate of growth during the 6-month treatment period was similar to that prior to treatment  $2.3 \pm 1.0$  cm/year, compared to  $3.0 \pm 1.8$  cm/year prior to starting budesonide ( $p = 0.31$ ). It is not clear at this time this indicates drug-induced growth impairment or the presence of active disease despite normal PCDAI scores.

In 2003, Escher and colleagues from the European Collaborative Research Group on Budesonide in Paediatric Inflammatory Bowel Disease published the results of their multicenter prospective randomized, double-blind active comparator trial. Forty-six children 6 to 16 years of age with active Crohn's disease were enrolled.<sup>7</sup> All of the children had disease

involving the ileum and/or the ascending colon and a standard Crohn's Disease Activity Index (CDAI)  $\geq 200$ , indicating significant disease. Patients received either controlled ileal release budesonide 9 mg once daily for 8 weeks followed by 6 mg per day for 4 weeks or prednisolone 1 mg/kg/day for 4 weeks followed by a taper over 8 weeks. The primary endpoint for the study was the percentage of patients in remission, defined as a CDAI of  $\leq 150$ , at 8 weeks.

Remission rates were similar between the groups at 8 weeks: 55% of the children receiving budesonide and 71% of the prednisone group ( $p = 0.25$ ). These findings were similar to both the Kundhal study and remission rates reported in adult trials. Approximately half of the patients in both groups achieved remission within 2 weeks. Both treatment groups achieved maximal clinical effect at week 8. Mean CDAI scores remained higher in the budesonide group throughout the study, with a mean of 149 at 8 weeks compared to 97 in the prednisolone group ( $p = 0.047$ ). Adverse effects were common in both groups, with abdominal pain and headache being the most frequently reported. Other glucocorticoid adverse effects, including acne and moon face occurred in fewer of the children receiving budesonide (5% and 23%, respectively, compared to the 27% and 58% in the prednisolone group,  $p = 0.01$  and  $0.033$ ). The mean erythrocyte sedimentation rate (ESR) decreased to a greater extent in the prednisolone group than in the budesonide group ( $-13$  mm/hr compared to  $-5$  mm/hr,  $p < 0.05$ ) suggesting less systemic corticosteroid exposure with budesonide over time. The mean morning cortisol level was significantly higher in the budesonide group, 200 nmol/L (6.3 mcg/dL), compared to 98 nmol/L (2.6 mcg/dL) in the prednisolone group ( $p = 0.0028$ ), confirming less adrenal suppression.

Additional information on the effectiveness and safety of budesonide has been gained with the study of an alternative dosage formulation available in Canada and Europe.<sup>8,9</sup> This product, sold as Budeson<sup>®</sup> or Budenofalk<sup>®</sup>, is designed to dissolve at a pH  $> 5.5$ , making it available to the lower ileum. In 2003, Levine and colleagues, writing for the Israeli Pediatric Budesonide Study Group, evaluated this product in 33 children and adolescents (mean age 14.3 years).<sup>8</sup> The patients were randomized to receive either 9 mg pH-dependent release budesonide or 40 mg prednisone per day for 12 weeks. Remission rates were similar, 47% in the budesonide group and 50% in the prednisone group. The reduction in PCDAI scores at week 12 was also similar ( $9.3 \pm 14.8$  for budesonide and  $13.4 \pm 10.6$  for prednisone). There were significant differences,

however, in the percentage of patients experiencing adverse effects (32% in the budesonide group and 71% in the prednisone group,  $p < 0.05$ ). As in the study of controlled ileal release budesonide, there were lower rates of cosmetic adverse effects (moon face, acne, and hirsutism) with pH-dependent release budesonide when compared to prednisone ( $p < 0.01$ ). Significant adverse effects were uncommon; one patient receiving prednisone developed a herpetic skin infection and one patient in each group was diagnosed with depression. Although not a statistically significant difference, muscle pain or proximal muscle weakness occurred more often in the prednisone group (36%) than in the budesonide group (8%).

These investigators conducted a follow-up study in 2009 comparing two regimens for pH-dependent release budesonide.<sup>9</sup> Seventy children were randomized to either a standard regimen of 9 mg once daily for 7 weeks followed by 6 mg daily for 3 weeks (group 1) or induction with 12 mg once daily for one month followed by the standard regimen used in group 1 (group 2). The primary outcomes were remission rate and the change in PCDAI at week 7. Clinical response was reported in 51.4% of the patients in group 1 versus 74.3% in group 2. Remission rates at the end of treatment were 42.9% and 65.7% in the two groups, respectively ( $p = 0.054$ ). The authors concluded that an induction dose of budesonide may produce higher rates of remission without an increase in steroid-induced adverse effects. While the results from these two studies cannot be extrapolated to controlled ileal release budesonide, they confirm the ability of budesonide to produce rates of symptom control and remission similar to those produced by systemic corticosteroids in children with Crohn's disease.

A summary of clinical experience with budesonide was published by the Pediatric Inflammatory Bowel Disease Collaborative Research Group in 2012.<sup>3</sup> The group maintains a registry of patients from 21 North American pediatric gastroenterology centers. Of the 932 patients < 16 years of age with Crohn's disease in the registry, 119 (13%) received a total of 148 courses of budesonide. Both the pH-dependent release and controlled ileal release preparations were included. The mean age of the patients was  $12.5 \pm 2.1$  years. Thirty-five percent of the patients had ileum and/or ascending colon disease, while 65% had more widespread disease. The most commonly prescribed dose was 9 mg once daily (105 patients), followed by 6 mg (10 patients), 3 mg (9 patients), and 12 mg (one patient). Budesonide was typically prescribed as adjunctive therapy with 5-

aminosalicylates or immunomodulators in patients with active disease, or as a means of weaning from systemic corticosteroids. Of the 56 newly diagnosed patients, only five took budesonide as monotherapy. In the 63 children with established disease, only one patient received budesonide alone. The authors concluded that the use of budesonide is increasing, primarily as initial treatment in newly diagnosed children or as adjunctive therapy for patients to minimize exposure to systemic corticosteroids, 5-aminosalicylates, azathioprine, or methotrexate.

### **Maintenance Therapy**

While approved for maintenance of clinical remission for up to 3 months in adults, budesonide has not been approved for maintenance therapy in children. The prescribing information for the drug states that an open-label study of controlled ileal release maintenance therapy for children 5 to 17 years of age did not meet the requirements to establish safety and efficacy.<sup>2</sup> As demonstrated in the Kundhal study of controlled ileal release budesonide, as well as Levine study of pH-dependent release budesonide, long-term administration in children and adolescents with Crohn's disease has the potential to produce clinically significant reductions in linear growth velocity.<sup>5,6</sup>

### Warnings and Precautions

Hypersensitivity reactions, including anaphylaxis, are rare but have been reported with budesonide. As a result, it is contraindicated in patients with previous evidence of hypersensitivity to any form of budesonide or any of the product's other ingredients. As with all corticosteroids, use of budesonide may increase the risk for infection. Chronic corticosteroid administration has been associated with increased cortisol levels and suppression of the adrenal axis. In patients receiving budesonide who are undergoing surgery or significant stress, supplementation with a systemic corticosteroid is recommended. Patients transitioning from a corticosteroid with higher systemic absorption, such as prednisone, to budesonide should be closely monitored for signs of steroid withdrawal. Gradual tapering of the systemic corticosteroid dose is recommended.<sup>2</sup>

### Adverse Effects

The most commonly reported adverse effects with controlled ileal release budesonide in adults include headache (21%), respiratory infection (11%), nausea (11%), back pain (7%), dizziness (7%), dyspepsia (6%), abdominal pain (6%), flatulence (6%), vomiting (6%), fatigue (5%), and pain (5%).<sup>2</sup> The most frequent adverse effects in the 22 budesonide patients in the Escher study were headache (18%), abdominal

pain (14%), fatigue (14%), emesis (14%), and myalgias, pharyngitis, or nausea (9%). Similar results were observed in the 2004 Levine study.<sup>8</sup> Budesonide data from the Pediatric Inflammatory Bowel Disease Collaborative Research Group included no reports of fractures, opportunistic or serious infections, or other serious adverse effects.<sup>3</sup>

#### Drug Interactions

Budesonide is a CYP3A4 substrate and should not be used with CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, cyclosporine, and grapefruit juice. Concomitant use with ketoconazole may increase budesonide serum concentrations eight-fold. A similar degree of CYP3A4 is produced by the furocoumarin derivatives in grapefruit juice. As a result, it should not be ingested at any time during treatment in order to avoid elevated budesonide concentrations resulting from CYP3A4 inhibition in the bowel. Conversely, administration with strong CYP3A4 inducers, such as phenobarbital, phenytoin, or rifampin, may result in subtherapeutic concentrations.<sup>2</sup> The clinical significance of reduced serum budesonide concentrations is not known.

#### Availability and Dosing

Entocort<sup>®</sup> ED is available in 3 mg capsules. The recommended dose for children and adolescents 8 to 17 years of age is 9 mg taken once daily in the morning for up to 8 weeks, followed by 6 mg once daily for 2 weeks. In adults, a 9 mg daily dose may be taken for up to 8 weeks and repeated as necessary for recurrence of active disease. It may then be continued at a dose of 6 mg for up to 3 months to maintain remission.<sup>2</sup> The 2014 ECCO/ESPGHAN guidelines recommend an initial dose of 9 mg, but add that doses up to 12 mg may be used for the first 4 weeks of induction, based on the Levine study with pH-dependent release budesonide.<sup>4,9</sup> The guidelines recommend tapering budesonide within 10-12 weeks of initiation.

Controlled ileal release budesonide capsules should be swallowed whole and not chewed or crushed. For patients unable to swallow the capsule, it may be opened and the contents mixed with a tablespoon of applesauce or pudding and swallowed without chewing.<sup>10</sup> The dose of oral budesonide should be reduced to 3 mg once daily in patients with moderate hepatic impairment (Child-Pugh Class B). It is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C).<sup>2</sup>

#### Summary

Corticosteroids are important tools for inducing remission in patients with Crohn's disease. While used in children and adolescents for over

15 years, budesonide has only recently been approved for this patient population by the Food and Drug Administration. Recently published pediatric studies demonstrate similar efficacy to oral prednisolone in inducing remission and lowering disease symptoms, with less systemic exposure. While this has resulted in a better adverse effect profile, studies conducted to date have failed to show a difference in corticosteroid-associated reductions in growth velocity. Larger, longitudinal studies are needed to establish the long-term benefit of budesonide in pediatric Crohn's disease.

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#### **References**

1. FDA approves drug to treat active Crohn's disease in pediatric patients. American Academy of Pediatrics, AAP News. August 2016. Available at: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM514457.pdf> (accessed 8/28/16).
2. Entocort EC prescribing information. Elan Pharma International Limited. May 2016. Available at: <https://www.drugs.com/pro/entocort-ec.html> (accessed 10/1/16).
3. Otley A, LeLeiko N, Langton C, et al. Budesonide use in pediatric Crohn disease. J Pediatr Gastroenterol Nutr 2012;55:200-4.
4. Ruemmele FM, Veres G, Holho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis 2014;8:1179-207.
5. Lundin PDP, Edsbäcker S, Bergstrand M, et al. Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with active Crohn's disease. Aliment Pharmacol Ther 2003;17:85-92.
6. Kundhal P, Zachos M, Holmes JL, et al. Controlled ileal release budesonide in pediatric Crohn disease: efficacy and effect on growth. J Pediatr Gastroenterol Nutr 2001;33:75-80.
7. Escher JC, European Collaborative Research Group on Budesonide in Paediatric IBD. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicenter trial. Eur J Gastroenterol Hepatol 2004;16:47-54.
8. Levine A, Weizman Z, Broide E, et al. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. J Pediatr Gastroenterol Nutr 2003;36:248-52.
9. Levine A, Kori M, Dinari G, et al. Comparison of two dosing methods for induction of response and remission with oral budesonide in active pediatric Crohn's disease: a randomized placebo-controlled trial. Inflamm Bowel Dis 2009;15:1055-61.
10. Institute for Safe Medication Practices. Oral dosage forms that should not be crushed 2015. Available at: <http://www.ismp.org/tools/donotcrush.pdf> (accessed 10/4/16).

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