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ORAL FORMULATIONS OF BUDESONIDE: A NOVEL TREATMENT FOR INFLAMMATORY BOWEL DISEASE

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Summary

Budesonide is a promising drug for a variety of documented applications and has potential in gastroenterology. Its unique local mechanism of delivery and efficient first-pass metabolism, resulting in fewer systemic adverse effects than with conventional glucocorticoids, makes this a desirable drug for clinical practice. This drug has shown promise in treating a wide spectrum of inflammatory diseases from inflammatory bowel disease and other colitides to autoimmune liver diseases. Future research should focus on ways to increase delivery methods to promote long-term usage for maintenance therapy for the disease entities listed above, as well as for other potential nongastrointestinal conditions.

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Introduction

Inflammatory bowel disease (IBD), which has no clear and proven etiology, can be very challenging to treat and adequately control. Both ulcerative colitis (UC) and Crohn's disease (CD) can cause significant morbidity in affected individuals. Multiple drugs, including aminosalicylates,

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corticosteroids, immune modulators and antibiotics, have been used alone or in combination in the treatment of IBD. Newer drugs, such as infliximab and adalimumab with activity directed toward tumor necrosis factor-α, have recently been added to our therapeutic armamentarium.

Corticosteroids have a long history in the treatment of both types of IBD to control the inflammation in the bowel, as well to manage the extraintestinal manifestations of IBD such as pyoderma gangrenosum and erythema nodosum. Since glucocorticoid receptors are distributed throughout the body, it is not surprising that systemic administration of glucocorticoids can cause a wide array of adverse events (1). Some of these include Cushingoid appearance, acne and emotional disturbances including mania, depression, psychosis and insomnia. Ocular complications include glaucoma and cataract formation (2). Patients can also develop a spectrum of bone disease from osteoporosis to osteomalacia, which can arise both from the use of corticosteroids or the underlying IBD (3, 4). Any use of systemic steroids puts patients at risk for serious complications related to immunosuppression, such as bacterial and/or fungal sepsis, which can occur with systemic use of high-dose corticosteroids (5). Use of systemic steroids is also associated with disruption of the hypothalamic-pituitary axis (2). Treatment with corticosteroids prior to surgery is shown to significantly increase the risk of postoperative sepsis and death (6). Patients with IBD treated chronically with systemic corticosteroids may become refractory to therapy. Corticosteroid dependence has been reported in as many as 36% of patients treated with systemic steroids and is defined as a relapse within 30 days of finishing treatment or relapse with prednisolone dose reduction, impeding discontinuation of medication for more than 1 year (7). Rogler *et al*. (8) have shown that the number of peripheral leukocyte receptors is decreased in patients with IBD who have previously been treated with corticosteroids. These same authors also noted that mucosal glucocorticoid receptor levels were decreased in steroid treated IBD patients compared with healthy controls.

This article discusses the use of the novel, controlled-release steroid compound budesonide in the treatment of CD and UC; in addition, the use of budesonide for other medical conditions will be discussed.

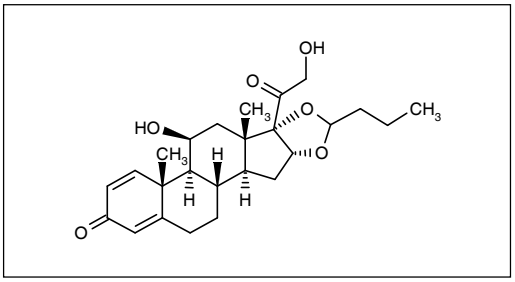

Fig. 1. Chemical structure of budesonide.

Pharmacokinetics

Budesonide is a glucocorticosteroid with a high first-pass effect and low systemic bioavailability (Fig. 1). This drug has high antiinflammatory activity but low systemic activity because of extensive hepatic metabolism. Budesonide is a topical corticosteroid that is successfully used as an inhaler in the treatment of asthma and rhinitis. This topical effect was proven in 1990 by Toogood *et al.* (9) when these authors showed that inhaled budesonide reduced asthma relapse for a longer duration than oral treatment. There are several reasons for this, including high water solubility, the good intrinsic activity of the drug, and a very strong affinity for glucocorticosteroid receptors noted in rat muscle. In fact, budesonide has a 200-fold stronger affinity than hydrocortisone and a 15-fold difference compared with prednisolone (10). Based on the work of Miller-Larsson *et al*. (11), this appears to increase mucosal retention. In this experiment, H^3-prednisolone and H^3-budesonide were perfused in rat ileums for 10 minutes then washed continuously. The mucosal retention for budesonide was 15-fold greater than for prednisolone at 20 minutes and 50-fold greater at 4 hours. Even the submucosa had evidence of activity indicating deep tissue penetration of locally delivered budesonide. Since the vast majority of IBD treatments are formulated for systemic effect, this localized delivery makes the drug highly appealing in the treatment of mild to moderate Crohn's disease of the ileum and ascending colon.

The most important aspect of topical or locally delivered corticosteroid therapy is the reduction in systemic adverse effects. With budesonide, this is accomplished in two ways: biotransformation in the liver and gut via cytochrome P450 3A (CYP3A) and efflux from intestinal cells via P-glycoprotein (12–14). In healthy humans, the systemic bioavail-

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ability of oral budesonide has been shown to be near 10% (15). In addition, budesonide undergoes a highly efficient first-pass hepatic extraction by CYP3A. After first-pass hepatic metabolism budesonide is converted to its metabolites, 16α-hydroxyprednisolone and 6β-hydroxybudesonide. These have < 1% of the glucocorticosteroid receptor affinity and antiinflammatory activity of budesonide (12). These metabolites are excreted in the urine. There is no evidence that intact budesonide is excreted *via* the kidneys (15, 16). This was confirmed by Edsbäcker *et al.* (17), who documented the efficiency of the first-pass metabolism of budesonide with less than 0.1% found in urine samples of patients taking an ^{111}Indium (^{111}In)-labeled drug.

Another important mechanism in the clinical pharmacology of a drug is the precision of delivery. Budesonide was originally used in IBD in Europe as a retention enema. This compound was then formulated into Budenofalk tablets and Entocort EC with pH-dependent release of active medication in the ileum and ascending colon. Entocort EC is composed of 3 mg of budesonide in tablet form. Budesonide is contained in an insoluble ethylcellulose polymer, which releases the medication in a time-dependent fashion and is enclosed by a gelatin capsule with Eudragit L, which starts dissolving in a pH medium > 5.5, *i.e.* in the proximal small intestine under physiologic conditions (10). Edsbäcker and Andersson found no difference in targeted delivery to the distal small bowel and proximal colon in the fed *versus* fasting state. Therefore, gastric retention from a meal did not cause early dissolution of the capsule. The same authors also confirmed the precision of this formulation, noting 20–25% delivery of drug to the ileum, 40% to the ascending colon, and 40% to the remaining colon using ^{111}In-labeled pharmacoscintigraphy (17).

Budesonide in the treatment of Crohn's disease

Oral budesonide has been studied for the treatment of mild to moderate Crohn's disease involving the ileum and/or ascending colon. These studies include several randomized, double-blind, placebo-controlled trials comparing different doses of budesonide or comparison with prednisolone and mesalamine in "double-dummy" protocols. Tremaine *et al.* (18) compared budesonide 9 mg given once daily or divided into twice-daily dosing to placebo with a dose reduction during weeks 9 and 10 to 6 mg daily in the budesonide group. Their study demonstrated higher clinical remission rates with budesonide (49% with once-daily *vs.* 53% with the twice-daily divided dose) compared with placebo (33%). This difference, however, did not reach clinical significance (18). Another study by Greenberg *et al.* (19) compared varying doses of budesonide with placebo. These authors showed that budesonide 9 mg/day produced a remission rate of 51% and 15 mg/day produced a remission rate of 43%. Dosing at 3 mg/day was lower at 33%, but still higher than placebo (20%). When compared with prednisolone in a randomized, double-blind, double-dummy protocol, Rutgeerts *et al.* (20) found no statistically significant differences in remission rates when budesonide was compared with oral prednisolone (60% and 74% respectively). Budesonide was administered as 9 mg/day dosing for 8 weeks with a decrease to 6 mg/day at weeks 9 and 10. Prednisolone was given orally at 40 mg/day for 2 weeks, then at 35 mg/day for 2 weeks, and then at 30 mg/day for 2 weeks. This was followed by a decreasing dose taper of 5 mg/day per week until discontinuation at week 10. However, glucocorticoid-related adverse effects were significantly higher in the prednisolone group (33% *vs.* 55%; $P = 0.003$). Interestingly, the steroid-associated adverse effects in the abovementioned placebo studies showed no statistical differences when the two were compared overall (18, 19). When compared with mesalamine, budesonide also demonstrated superiority in establishing remission in mild to moderate CD of the ileum and/or ascending colon. Thomsen *et al.* (21) compared oral budesonide 9 mg/day with oral mesalamine 2 g twice daily for 16 weeks. Higher budesonide remission rates were statistically significant for 8 (69% *vs.* 45%), 12 (64% *vs.* 42%) and 16 weeks (62% *vs.* 36%) with a shorter time to remission on average (21). However, after recalculation, the time to achieve remission was not statistically significant (28 *vs.* 58 days) (22, 23).

A randomized, double-blind, placebo-controlled trial was also performed that examined the effect on quality of life during treatment of mild to moderate CD with mesalamine *versus* budesonide. Thomsen *et al.* (24) included 182 patients, of which 93 received CIR budesonide 9 mg/day *versus* 89 who received SR mesalamine 2 g b.i.d. for 16 weeks. No other CD medications were

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allowed in this study. Thirty percent of the patients in the mesalamine group failed to complete the study due to worsening CD compared with 11% in the budesonide group. Quality of life was assessed at 2, 4, 6, 8, 12 and 16 weeks using the Psychological General Well-Being (PGWB) index. Significantly higher scores were found at weeks 2, 8, 12 and 16 with CIR budesonide compared with SR mesalamine, with the highest discrepancy at 12 weeks (24).

The overwhelming message is that budesonide can be used to achieve control in more than 50% of patients with CD involving the ileum and/or ascending colon. Consequently, the European Crohn's and Colitis Organization (ECCO) consensus on the management of CD has recommended budesonide 9 mg per day as the first-line treatment for mildly or moderately active CD involving the ileocecal area (25).

Budesonide has also been studied as an agent to provide continued remission after induction with medical therapy. Several studies (18–20, 26) investigated pooled data from 4 trials using 3 mg/day and 6 mg/day compared with placebo for maintenance therapy in mild to moderate CD. There were 380 patients enrolled in these 4 combined trials, all of which were in remission due to medical therapy with a CD activity index of ≤ 150. Neither budesonide dose was able to achieve remission for 54 weeks with a time to relapse for 6 mg/day of 268 days and of 170 days for 3 mg/day. The placebo control median time to relapse was 154 days (27). In 2002, Mantazaris *et al.* (28) compared azathioprine with budesonide in 67 patients who achieved remission with prednisolone. These patients were followed for 1 year. The clinical remission rate was similar for budesonide and azathioprine (25% *vs.* 30%, respectively). Histologic and endoscopic remission was higher in the azathioprine group.

Diarrhea is a common symptom associated with IBD, especially in patients with active disease and mucosal inflammation. However, diarrhea can occur in high volume even in the absence of active inflammation, especially in the setting of prior surgery, such as ileostomy for CD or proctocolectomy for UC (29, 30). Budesonide has been evaluated for use in these patients. Two studies by Ecker *et al.* (31, 32) have analyzed ileostomy output in CD patients without evidence of active inflammatory mucosal disease. Both demonstrated a decrease in ileostomy output with pH-modified release capsules of budesonide for short- and long-term treatment.

Budesonide in the treatment of ulcerative colitis

As mentioned previously, systemic glucocorticoids have been a staple in the treatment of active UC. However, the majority of patients (80%) can be controlled with 5-aminosalicylic acid (ASA) therapy in different application forms (33). Conventional corticosteroids have been used in either oral or intravenous dosing to treat the spectrum of severe to moderate UC. Few studies have looked at the possible use of budesonide in pH-controlled release form in the treatment of UC, with current ongoing trials including the BUC-57 trial. Initially, budesonide was studied in enema form administered in 2 mg/100 ml doses to treat distal active UC and proctitis, which was shown by Danielsson *et al.* (34) to be superior to placebo, but rectally delivered 5-ASA preparations appeared to be superior to steroids of any form in a meta-analysis (35). When evaluating the pH-controlled release form, Kolkman *et al.* (36) demonstrated that budesonide reached the distal part of the colon and rectum. Two other studies have also demonstrated the efficacy of controlled release budesonide in treating various levels of active UC including pancolitis to proctitis, even allowing patients to discontinue their conventional glucocorticoid therapy (37, 38). In UC patients who have undergone ileo-pouch anal anastomosis surgery follow total proctocolectomy, budesonide has also been shown to be effective in the treatment of antibiotic refractory pouchitis (39).

Other uses for budesonide

Primary biliary cirrhosis

Due to budesonide's high glucocorticoid receptor binding affinity and low frequency of systemic adverse effects when compared with prednisolone, it is an attractive drug and is also used for treatment in early primary biliary cirrhosis (PBC) (stages I-III). A 3-year randomized trial demonstrated that the combination of ursodeoxycholic acid (UDCA) and budesonide was more effective than UDCA alone in improving liver histology in early PBC (40). This trial also demonstrated that adjunctive therapy with budesonide did not significantly depress bone mineral density in comparison with monotherapy with UDCA in the early stages of

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PBC (41). However, studies have shown that hepatic dysfunction affects the pharmacokinetics of budesonide, which in turn could increase the risk of deleterious effects of budesonide on bone mass density and glucose metabolism (42, 43). Therefore, it is very important that bone mass density be monitored during budesonide therapy.

Autoimmune liver disease

Autoimmune hepatitis is a chronic inflammatory liver disease that usually responds to immunosuppressive therapy. The treatment of choice includes prednisone with or without azathioprine. However, many patients become intolerant to this regimen. One study showed that budesonide was able to induce biochemical and histological remission in patients with treatment-naïve autoimmune hepatitis and that it can also be used as salvage therapy in those cases in which prednisone and azathioprine fail or patients become intolerant to this drug (45). In this study, the majority (15 of 18) of patients went into complete remission with significant improvement of liver histology. The 3 who did not benefit from treatment with budesonide included 2 patients with liver cirrhosis and 1 with severe corticosteroid-dependent disease. Also of note was that only patients with advanced liver fibrosis or cirrhosis had severe adverse events, which was thought to be due to the reduced hepatic metabolism of the drug (43).

Celiac disease

Celiac disease is an autoimmune enteropathy triggered by ingestion of gluten. The mainstay of treatment is a gluten-free diet. However, up to 7–30% of patients have a poor response to this dietary therapy (46). Treatment for these patients with refractory celiac disease includes corticosteroids alone or together with immunomodulatory agents such as azathioprine, ciclosporin or infliximab. However, the disadvantage of systemic steroids is the associated systemic adverse effects. Therefore, with the aim of minimizing the systemic adverse effects of steroids, Brar *et al*. (47) showed that budesonide is useful in the management of refractory celiac disease. A beneficial clinical response to budesonide was observed in 76% of patients in the study.

Microscopic colitis

Microscopic colitis is a common cause of chronic diarrhea and mainly includes the two diseases collagenous colitis and lymphocytic colitis. This disease is most commonly seen in elderly women and has been shown to have a significant impact on the patient's quality of life. Budesonide is currently the best documented short-term treatment for collagenous colitis (48) and is the drug that has shown the strongest evidence of effectiveness in decreasing the volume and frequency of stools and in improving quality of life (49). However, after cessation of successful short-term treatment with budesonide, the relapse risk is high and occurs in 61–80% of treated patients (50, 51). One study showed that the median time to clinical relapse was only 2 weeks after cessation of treatment (52). Therefore further studies are needed to assess the long-term efficacy and safety of budesonide as maintenance therapy.

Oral chronic graft-versus-*host disease*

Oral chronic graft-*versus*-host disease (cGVHD) is a common long-term complication of allogeneic hematopoietic stem cell transplantation. This disease can occur in 25–70% of patients despite GVHD prophylaxis with ciclosporin and methotrexate, which is the first-line therapy for oral cGVHD (51). However, even with routine administration of systemic agents, many patients with oral manifestations of cGVHD do not have resolution of their disease and may benefit from adjuvant local therapy. The possibility of using budesonide for oral GVHD was first explored by Bertz *et al*. (53) after initially using the drug as a topical treatment for acute intestinal GVHD. A recent study showed that, when combined with systemic agents, topical budesonide was more effective in treatment for oral cGVHD than systemic agents alone (54). However, additional studies are needed to document the use of budesonide in this setting.

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