1130-0108/2006/98/5/362-373
REVISTA ESPAÑOLA DE ENFERMEDADES DIGESTIVAS

REV ESP ENFERM DIG (Madrid)
Vol. 98. N.° 5, pp. 362-373, 2006

POINT OF VIEW

Budesonide for ulcerative colitis

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ABSTRACT

In this review, we examined studies published on oral and topical formulations of budesonide (Entocort® and Budenofalk®, in Spain: Entocord® and Intestifalk®) for the treatment of ulcerative colitis. This glycocorticosteroid has a potent local action and an important first-pass liver metabolism. It has proven successful over the last years as a controlled-release formulation. It obtained results similar to prednisolone, without the latter's significant suppression of plasma cortisol. Many publications exist on the effects of oral budesonide for the treatment of Crohn's disease (CD). These have led to the registration of this drug for the treatment of CD. Studies on oral formulations of budesonide for the treatment of ulcerative colitis (UC) are scarce. After reviewing published evidence, we suggest the conduction of controlled trials for the treatment of UC to obtain evidence-based efficacy and safety results in order to benefit patients with this form of inflammatory bowel disease (IBD).

Key words: Budesonide. Ulcerative colitis. Inflammatory bowel disease. Treatment.

Marín-Jiménez I, Peña AS. Budesonide for ulcerative colitis. Rev Esp Enferm Dig 2006; 98: 362-373.

INTRODUCTION

The notorious frequent adverse effects associated with the use of classical glycocorticosteroids (GCSs) prompted the development of a new group of drugs with equivalent efficacy and a safer profile. The pharmacological development of novel GCSs has been more difficult in UC than in other diseases because of variations in colonic pH, transit time, and the effects of bacterial metabolism. Friend (1) has evaluated prednisolone metasulfobenzoate, fluticasone propionate, tixocortol pivalate, beclomethasone dipropionate, and budesonide. Budesonide, with its high topical activity and high rate of first-pass metabolism in oral controlled-release formulations, can reach different bowel compartments. This has led to the qualification of "a model of targeted therapy" (2). Two commercially available enteric-coated pH-dependent release oral formulations have been marketed, Entocord® EC and Budenofalk® (in Spain Entocord® and Intestifalk®). The latter will be available in Spain in 2006. Budesonide gives an overall treatment result approaching that of prednisolone but without the suppression of plasma cortisol levels (3). Many studies have been published on the effects of oral budesonide in Crohn's disease (CD) (4-6), but there is little evidence on the efficacy of oral budesonide in UC. The importance of fewer side effects in the case of GCSs will undoubtedly help improve patient compliance regarding treatment (7). In a recent study of the incidence of UC in northern Spain, disease extension was limited to proctitis in 11% of patients, left-side colitis in 53%, and extensive colitis in 36% of patients (8). This suggests that both topical and oral therapy with GCSs need optimization.

The efficacy and fewer side effects of enema/foam preparations of budesonide for the treatment of distal disease in UC are encouraging. An excellent review of budesonide published in 1999 by Gomollón et al. has analyzed the value of this drug in the treatment of CD and UC (9). Since then, new papers with novel data exist, although some uncertainties remain. In this revision, we wish to reassess data published in abstracts from different national and international congresses, as well as the bibliography provided by pharmaceutical companies. We

Recibido: 04-11-05.
Aceptado: 08-11-05.

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used Medline's systematic search tools for the use of topical GCSs in CD and UC, and we screened for studies published on the presently available enteric-coated pH-dependent release oral formulations, as well as on the topical preparations for distal IBD.

We divided information into the following sections:

1. Budesonide Pharmacology.
2. Studies of Budesonide for Ulcerative Colitis:

—Topical budesonide: pharmacokinetic studies.

—Topical budesonide compared with placebo.

—Topical budesonide compared with topical corticosteroids.

—Topical budesonide compared with topical aminosalicylates.

—Topical budesonide compared with oral metronidazole.

—Oral budesonide.

3. Future perspectives.

BUDESONIDE PHARMACOLOGY

In contrast to other steroids such as hydrocortisone, prednisolone and dexamethasone (10), budesonide is a non-halogenated synthetic corticosteroid with the highest affinity for the glycocorticoid receptor. Budesonide is a 1: 1 mixture of two epimers (22R and 22S). Both epimers are rapidly eliminated with a terminal half-life of 2.7 ± 0.6 hours (11). Budesonide is extensively metabolized by hydroxylation, while the cytochrome P450 isoenzyme CYP3A4, expressed in high amounts in hepatocytes and epithelial cells of the intestinal wall, is the main responsible isoenzyme for its rapid elimination (12).

Budesonide circulates in the plasma mainly bound to proteins (88%). With a dosage range of 3-15 mg/day, it shows a linear pharmacokinetic behavior (13,14). Due to the high clearance of budesonide, which approaches the clearance of liver blood flow, a low oral bioavailability has to be expected. After oral administration and absorption, budesonide undergoes a 90% first-pass hepatic metabolism (15). It is transformed into 6-beta-hydroxibudesonide and 16 alpha-hydroxiprednisolone; both of these contain less than 1% of the parent compound. This explains the mere 10% of oral bio-availability and the low systemic action of budesonide. When administered as an enema to humans, budesonide reaches the splenic flexure (16). Its bioavailability then averages 15% in patients with UC. Some animal experiments (17) have revealed that budesonide has a longer retention in the colonic mucosa *versus* systemic corticosteroids; 20 minutes and 4 hours after perfusion of the rat colon, higher concentrations of budesonide were detected when compared to prednisolone.

There are three different forms of oral controlled-released preparations of budesonide (18): controlled ileal-release capsules, a pH-modified release formulation, and a budesonide prodrug (budesonide-beta-D-glucuronide). The latter preparation is not available yet (18). The controlled ileal-release formulation (Entocort® EC) is composed of a hard gelatin capsule with acid-resistant pellets covered with Eudragit L 100-55; it has a delayed release at pH > 5.5. The pH-modified release formulation (Budenofalk®) is also composed of a gelatin capsule and acid-resistant pellets; however the pellets are covered with Eudragit L, S, LS, and RS, and have a delayed release at pH > 6.4. Budesonide-beta-D-glucuronide is an oral prodrug targeted to deliver budesonide specifically to the colon, since this prodrug is not absorbed in the small intestine. Budesonide-beta-D-glucuronide is hydrolyzed by colonic bacterial and mucosal beta-glucuronidase in order to release free budesonide into the colon (19). Hydrolysis rates of budesonide-beta-D-glucuronide in human fecal samples from patients with UC and normal volunteers are similar (20), but it is not clear whether a pH reduction in the colon of IBD patients may inhibit the bacterial hydrolysis of this prodrug.

STUDIES OF BUDESONIDE IN ULCERATIVE COLITIS

Topical budesonide: pharmacokinetic studies

In table I we summarized a compilation of four studies in which different pharmacokinetic aspects of budesonide in UC patients were evaluated (16,21-23). The first study (21) showed that budesonide does not accumulate in the human body after 4 weeks of treatment; also, mean plasma cortisol values did not change during this period of time. The second study (16) showed that a low viscosity formulation of budesonide had an improved capacity to reach the more proximal parts of the colon, reaching the splenic flexure in 15 minutes. In the third study (22), a dose of 2 mg/day showed the same efficacy as the 4 mg/day dosage, but with less plasma cortisol suppression. This third study also demonstrated that budesonide enemas given twice weekly appear to be sufficient to maintain remission and prevent relapses in patients with quiescent disease during some months after suppressing active disease. The fourth, recently published study (23) showed that budesonide foam (20 ml) reaches the sigmoid colon after rectal application. Noteworthy is the fact that patients preferred this foam to enemas.

Topical budesonide compared with placebo

In the first of the two studies (24), shown in table II, budesonide is significantly more effective than placebo to achieve endoscopical, histological and clinical improvement in UC patients without causing a decrease in plasma cortisol levels. The second study (25), apart from comparing budesonide with placebo also evaluated three different enema dosages –0.5, 2 and 8 mg. This study proved that

Table I. Pharmacokinetic studies of topical budesonide

Year of publication	*Author reference*	*n*	*Ulcerative colitis characteristics*	*Medication (dose)*	*Time Evaluation parameters*	*Results/conclusions Cortisol depression*
1993	Danielsson et al. (21)	28	Distal active UC and proctitis	Budesonide ENE (2 mg)	4 weeks Pharmacokinetic assessment; E + H	Improvement of E + H Budesonide does not accumulate Mean plasma cortisol values did not change during treatment
1994	Nyman-Pantelidis et al. (16)	5	Distal active UC and proctitis	Budesonide ENE (two different formulations: low and high viscosity)	– Area of spread of enema	Low viscosity ENE gets to splenic flexure in 15 minutes; high viscosity ENE get less far and spending much more time
2002	Lindgren et al. (22)	149	Distal active UC	Budesonide ENE -acute phase: 2 mg (q.d. or t.i.d) until 8 weeks/remission -Maintenance: 2 mg/twice weekly until 24 week or relapse	Acute phase: 8 weeks Maintenance: 24 weeks	Remission rates at week 4 and 8 the same in 2 and 4 mg groups 4 mg group much adrenal alteration Budesonide for maintenance at this intervals is not effective to prevent relapse
2005	Brunner et al. (23)	12	Proctosigmoiditis and left sided colitis	Budesonide FO (2 mg/20 mL)	– Area of spread of the drug	Foam gets to sigma in all patients Drug is detected 4 hours after instillation

VN: number of patients; E: endoscopic evaluation; H: histologic evaluation; Clin: clinical evaluation. ENE: enema. FO: foam.

Table II. Studies comparing topical budesonide with placebo

Year of publication	*Author reference*	*n*	*Ulcerative colitis characteristics*	*Medication (dose)*	*Time Evaluation parameters*	*Results/conclusions Cortisol depression*
1992	Danielsson et al. (24)	41	Distal active UC and proctitis	Budesonide ENE (2 mg/100 ml) *vs.* placebo ENE	4 weeks E + H + Clin	Budesonide more effective than placebo. Budesonide not decrease cortisol plasma levels
1998	Hanauer et al. (25)	233	Distal active UC and proctitis	Budesonide ENE (0.5, 2, 8 mg/100 ml) *vs.* placebo ENE	6 weeks E + H + Clin	Budesonide (dose: 2 and 8 mg) better than placebo in E, H and Clin. 90% patients on budesonide maintain normal plasma cortisol levels

N: number of patients; E: endoscopic evaluation; H: histologic evaluation; Clin: clinical evaluation. ENE: enema. FO: foam.

budesonide is significantly superior to placebo in UC patients with distal active UC and proctitis. The 2-mg dose enema was recommended, as this proved to be the minimum dose to show a significant effect when compared to placebo. At week 6, a remission rate of only 19% was reported. This low rate of remission is the result of strict criteria to define "remission" in this study.

Topical budesonide compared with topical corticosteroids

Table III shows the results of budesonide for UC patients compared with the results obtained with classic corticosteroids. In two (26,27) of the nine studies summarized in this table, foam was used as a vehicle for the drug. In almost all nine studies, budesonide showed a similar efficacy as compared to classic topical steroids, although with a better safety profile. Budesonide did not decrease plasma cortisol levels. When budesonide foam was compared with betamethasone enema (27), no significant differences in terms of quality of life were observed; however, betamethasone reduced plasma cortisol levels. Two meta-analysis which evaluated the efficacy of rectal budesonide *versus* classic corticosteroids for the treatment of distal ulcerative colitis (28,29) concluded that no significant differences exist in efficacy between budesonide and classic topical corticosteroids, and that budesonide induces less endogenous cortisol suppression.

Topical budesonide compared with topical aminosalicylates

In the three studies shown in table IV, budesonide enema and foam were compared with topical 5-ASA

Table III. Studies comparing topical budesonide with topical corticosteroids

Year of publication	*Author reference*	*n*	*Ulcerative colitis characteristics*	*Medication (dose)*	*Time Evaluation parameters*	*Results/conclusions Cortisol depression*
1987	Danielsson et al. (30)	64	Distal active UC	Budesonide ENE (2 mg/100 ml) *vs.* prednisolone ENE (31.25 mg/100 ml)	4 weeks E + H + Clin	Budesonide > prednisolone in E, H and Clin evaluations Prednisolone reduces cortisol, but not budesonide
1991	Danish Budesonide Study Group (31)	146	Distal active UC	Budesonide ENE (1,2 or 4 mg/100 ml) *vs.* prednisolone ENE (25 mg/100 ml)	2 weeks E + H + Clin	All treatments improved E + Clin (less the 1 mg budesonide group). Prednisolone reduces cortisol, but not budesonide
1994	Bianchi Porro et al. (32)	88	Distal active UC	Budesonide ENE (2 mg/100 ml) *vs.* methylprednisolone ENE (20 mg/100 ml)	4 weeks E + H + Clin	All treatments improved E, H, and Clin, without significant differences between them. Prednisolone reduces cortisol, but not budesonide
1994	Ostergaard et al. (33)	26	Distal active UC	Budesonide ENE (2 mg/100 ml) *vs.* prednisolone ENE (25 mg/100 ml)	8 weeks Adrenal gland suppression	Prednisolone reduces cortisol, but not budesonide
1994	Lofberg et al. (34)	100	Distal active UC	Budesonide ENE (2,3 mg/115 ml) *vs.* prednisolone ENE (31.25 mg/125 ml)	8 weeks E + H + Clin	All treatments improved E, H, and Clin, without significant differences between them. Prednisolone reduces cortisol, but not budesonide
1994	Tarpila et al. (35)	72	Proctitis	Budesonide ENE (2 mg/100 ml) *vs.* hydrocortisone acetate FO (125 mg/125 ml)	4 weeks E + H + Clin	All treatments improved E, H, and Clin, without significant differences between them. Prednisolone reduces cortisol, but not budesonide
1995	Bayless et al.* (36)	184	Distal active UC	Budesonide ENE (2 mg) *vs.* hydrocortisone ENE (100 mg) *vs.* placebo	6 weeks E + H + Clin	E: budesonide similar to hydrocortisone (both better than placebo) H and Clin: non significant differences between , budesonide prednisolone and placebo. Prednisolone reduces cortisol significantly more than budesonide
2003	Bar-Meir et al. (26)	251	Proctosigmoiditis	Budesonide FO (2 mg) *vs.* hydrocortisone acetate FO (100 mg)	8 weeks E + H + Clin	All treatments improved E, H, and Clin, without significant differences between them. Prednisolone reduces cortisol, but not budesonide
2004	Hammond et al. (27)	38	Distal active UC	Budesonide FO (2 mg/50 ml) *vs.* beta-methasone ENE (5 mg/100 ml)	4 weeks QOL + E + H + Clin	Similar efficacy and QOL with budesonide and bethametasone. Bethametasone reduces cortisol, but not budesonide

N: number of patients; E: endoscopic evaluation; H: histologic evaluation; Clin: clinical evaluation. ENE: enemas. FO: foam. QOL: quality of life. * Just published in abstract form.

(37-39). These studies demonstrated similar results in terms of efficacy with an excellent safety profile.

Topical budesonide compared with oral metronidazole

Only one study for the treatment of active pouchitis (40) reported the use of topical budesonide (Entocort® enema) compared with oral metronidazole. Budesonide was as efficacious as metronidazole, and showed a better adverse effects profile. Although more clinical trials are needed on this subgroup of patients, budesonide could be a good alternative to the existing therapies.

Oral budesonide

Only three clinical studies have been published using oral budesonide in patients suffering from UC (Table V). In the first study (3), oral budesonide (Entocort®, 10 mg/day) showed a similar efficacy when compared to

Table IV. Studies comparing topical budesonide with topical aminosalicylates

Year of publication	*Author reference*	*n*	*Ulcerative colitis characteristics*	*Medication (dose)*	*Time Evaluation parameters*	*Results/conclusions Cortisol depression*
1991	Lamers et al.* (39)	62	Proctosigmoiditis and proctitis	Budesonide ENE (2 mg/100 ml) *vs.* 5-ASA ENE (4 g/60 ml)	4 weeks E + H + Clin	Similar efficacy in E + H + Clin No adverse effects in both groups
1995	Leman et al. (37)	97	Distal active UC and proctosigmoiditis	Budesonide ENE (2 mg/100 ml) *vs.* 5-ASA ENE (mesalazine 1 g/100 ml)	4 weeks E + H + Clin	Similar efficacy in E + H + Clin No adverse effects in both groups
2000	Rufle et al. (38)	33	Distal active UC proctosigmoiditis and proctitis	Budesonide FO (1 mg/50 ml) (bid) *vs.* mesalazine ENE (4 g/60 ml o.d.)	6 weeks E + H + Clin	Similar efficacy in E + H + Clin No influence of both treatments in cortisol plasma levels

N: number of patients; E: endoscopic evaluation; H: histologic evaluation; Clin: clinical evaluation. ENE: enemas. FO: foam. *Just published in abstract form.

Table V. Studies with oral budesonide

Treatment compared	*Year of publication*	*Author*	*n*	*Ulcerative colitis characteristics*	*Medication (dose)*	*Time Evaluation parameters*	*Results /conclusions Cortisol depression*
Oral budesonide compared to predisolone	1996	Lofberg et al. (3)	72	Active extensive and left sided UC	Budesonide (10 mg) *vs.* prednisolone (40 mg)	9 weeks E and plasma cortisol levels	Same E results Prednisolone supresses cortisol, but not budesonide
Oral budesonide alone	1997	Keller et al. (41)	14	Steroid dependent UC (7 pancolitis, 3 extensive colitis, 3 left sided colitis and 1 proctitis)	Budesonide 3 mg t.d.s.	6 months Clin. and reduction of systemic steroid dose	11 out of 14 Clin. improvement and ended systemic steroid treatment
Oral budesonide alone	2004	Kolkman et al. (42)	15	Distal active UC	Budesonide 9 mg o.d. *vs.* budesonide 3 mg t.i.d	8 weeks Pharmacokinetics, pharmacodynamics, safety and efficacy	Better results in 9 mg o.d group. Budesonide reaches the distal part of colon and the rectum

N: number of patients; E: endoscopic evaluation; H: histologic evaluation; Clin: clinical evaluation. ENE: enemas. FO: foam.

prednisolone (40 mg/day) in active extensive and left-sided UC. Budesonide did not modify plasma cortisol levels. The second study (41) reported the use of oral budesonide (Budenofalk®) for steroid-dependent UC patients with disease extension from pancolitis to proctitis. Eleven out of fourteen patients achieved clinical improvement. Budesonide allowed ending the steroid treatment. The third study, in patients with distal active UC, oral budesonide (Budenofalk®) showed encouraging clinical results (42). This study, particularly designed to study the pharmacokinetics and pharmacodynamics of Budenofalk®, found significant levels of budesonide in the distal colon and rectum. This suggests that this formulation could be of value in the treatment of distal disease.

FUTURE PERSPECTIVES

The data reviewed have shown that topical budesonide is a good alternative for topical 5-ASA, the present therapy of choice, in the treatment of distal active UC. Budesonide is as effective as topical 5-ASA, with also a good safety profile. Budesonide does not decrease plasma cortisol levels, which differentiates it from classic GCSs. This would suggest that budesonide could be the GCS of choice in the treatment of distal active UC. However, no evidence for the efficacy of oral budesonide in UC is yet available. Budenofalk®, which dissolves at pH > 6.4 and delivers budesonide in acceptable quantities to the distal colon and rectum in UC patients, may be useful for the treatment of UC patients (42). Since Entocort® can reach the transverse and descending colon (43) a comparative trial, as some authors have already suggested (6), between the two oral formulations of budesonide would be of interest. Further studies on this topic are necessary. Advances in the field of GCSs such as nitrosoglycocorticoids and selective glycocorticosteroid-receptor agonists may further improve the benefit-risk ratio (44).

ACKNOWLEDGEMENT

Dr. Marín-Jiménez has spent six months studying inflammatory bowel disease in the Laboratory of Immunogenetics, VU University Medical Center in Amsterdam (the Netherlands), thanks to a fellowship from "Fundación para la Investigación en Gastroenterología y Hepatología", Department of Gastroenterology, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

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