Gastroenterol Hepatol. 2018;41(7):458–471

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

REVIEW

Reviewing the therapeutic role of budesonide in Crohn's disease☆

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Received 20 March 2018; accepted 3 May 2018
Available online 3 August 2018

KEYWORDS
Budesonide;
Crohn's disease;
Ulcerative colitis;
Inflammatory bowel disease

PALABRAS CLAVE
Budesonida;
Enfermedad de Crohn;
Colitis ulcerosa;

Abstract Oral budesonide is a glucocorticoid of primarily local action. In the field of digestive diseases, it is used mainly in inflammatory bowel disease, but also in other indications. This review addresses the pharmacology, pharmacodynamics and therapeutic use of budesonide. Its approved indications are reviewed, as well as other clinical scenarios in which it could play a role, in order to facilitate its use and improve the accuracy of its prescription.

Revisando el papel terapéutico de la budesonida en la enfermedad de Crohn

Resumen La budesonida oral es un glucocorticoide de acción fundamentalmente local. En la especialidad de Aparato Digestivo, se emplea sobre todo en la enfermedad inflamatoria intestinal, aunque también en otras indicaciones. Esta revisión aborda aspectos acerca de la farmacología, la farmacodinámica y el empleo terapéutico de la budesonida. Se contemplan sus

☆ Please cite this article as: López-Sanromán A, Clofent J, Garcia-Planella E, Menchén L, Nos P, Rodríguez-Lago I, et al. Revisando el papel terapéutico de la budesonida en la enfermedad de Crohn. Gastroenterol Hepatol. 2018;41:458–471.

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Enfermedad inflamatoria intestinal

indicaciones reconocidas y se especula acerca de otras situaciones en las que podría desempeñar un papel de interés, con el objeto de facilitar su uso y mejorar la exactitud de su prescripción.

Introduction

Budesonide (BUD) is the only recognised pharmacological alternative for the treatment of mild, active ileal or ileocolic Crohn's disease (CD). Despite this, in the 2 decades since the publication of the controlled trials that led to its approval in this indication, relatively few publications or conferences have focused on updating its use in CD. Its idiosyncrasies (indication according to location and inflammatory activity of the disease, steroid with an optimised safety profile) make it a *rara avis* in the therapeutic arsenal of CD, particularly in the era of selective immunosuppressants (IS). In view of this situation, in 2016 a group of experts in CD met to reassess the role of BUD in the management of CD. In a second meeting held in 2017, we decided to prepare a document addressing issues surrounding both the indications (approved, suggested and potential) and mode of use (dosage, regimens, use of mineral and vitamin supplements) of BUD in inflammatory bowel disease (IBD) in order to bring gastroenterologists up to date with the latest evidence.

The aim of this article is to review the pharmacological characteristics of BUD and its accepted indications for the management of CD, and to evaluate treatment regimens and clinical situations for potential use based on the available evidence and expert opinion.

Description and pharmacological properties of budesonide

BUD is considered the prototype ''second generation'' topical glucocorticoid. It is characterised by greater potency and lower systemic bioavailability, and is the most widely studied therapeutic option in IBD.[1] Its affinity for glucocorticoid receptors is 195 times greater than hydrocortisone and 15 times greater than prednisolone.[2,3] This means that 5 mg BUD is therapeutically equivalent to 12 mg prednisolone.[4] Its rapid elimination, thanks to a high (90%) first-pass hepatic metabolism, results in a low systemic bioavailability which reduces its adverse effects (AE),[5] something that does not occur in patients with portosystemic shunt, such as those with portal hypertension. Its metabolites are mainly excreted in the urine, and, to a lesser extent, in the faeces.[6–8]

The metabolism of BUD, which is mainly CYP3A4-mediated, can be affected by several factors that interfere with its clearance and systemic bioavailability (Table 1).

Indications for budesonide in gastrointestinal diseases. Guidelines for use in inflammatory bowel disease

BUD is marketed in different formulations: as a nasal spray, oral tablets, or suppositories.[9,10] In gastrointestinal disease, delayed-release tablets and suppositories are used to treat various intestinal diseases, including IBD and microscopic colitis, as well as autoimmune hepatitis. Orodispersible tablets are indicated to treat eosinophilic oesophagitis,[9,10] although they are not currently available in Spain.

BUD is indicated to induce remission in patients with mild or moderate CD that affects the ileum, the ascending colon, or both. For this purpose, it is presented as enteric-coated (ethylcellulose matrix) pH-dependent modified release capsules that dissolves at pH > 5.5.[7,8,11] This enables most of the drug (59–68%) to be absorbed in the ileum and caecum.[7,8,11] The recommended daily dose to induce remission in adults is 9 mg, administered in a single morning dose for up to 8 weeks, reaching its peak effect within 2–4 weeks.[7,8] In Spain, BUD for this indication (Entocort® and Budenofalk®) is available in 2 formulations, which only differ in 2 aspects: start of release, which in the case of Entocort® is more proximal, although peak release occurs in both simultaneously; and the presence of lactose in Entocort® but not in Budenofalk®.[7,8] BUD is not yet available in multi-matrix (MMX) formulation in Spain.

Table 2 summarises the existing recommendations for the use of BUD in IBD in the principle guidelines.[12–18]

Efficacy and safety of budesonide in Crohn's disease

Several controlled clinical trials have shown that BUD is superior to placebo in inducing remission of CD, and equivalent to prednisolone for the control of mild to moderately active right-sided Crohn's disease.[6] Although BUD is less effective in the short-term than conventional steroids, particularly in patients with severe disease or more extensive colonic involvement, there is less likelihood of AEs and adrenal suppression with BUD.[19] The most important controlled trials in induction of clinical remission in CD with BUD are shown in Table 3.

Systemic glucocorticoids are associated with various AEs, ranging from aesthetic changes, such as moon facies, hirsutism and acne, to psychic disturbances (nervousness, insomnia) and even more permanent and serious conditions, such as reduced growth rate, infections, hypertension, diabetes, osteoporosis and glaucoma.[28]