Research and Clinical Forums

VOLUME 20 NUMBER 1 1998
ISSN 0143-3083

IBD AND SALICYLATES – 3

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The Publishing Editor
Research and Clinical Forums
Speldhurst Place, Speldhurst Road
Royal Tunbridge Wells
Kent TN4 0JB

British Library Cataloguing in Publications Data
Research and Clinical Forums
Volume 20, No. 1
1. Inflammatory Bowel Disease 2. Crohn's Disease 3. Ulcerative Colitis 4. Salicylates 5. Sulphasalazine
610'.5 R31
ISSN 0143-3083

Research and Clinical Forums is in indexed in *Directory of Published Proceedings*, *Excerpta Medica/EMBASE*, *Current Contents Proceedings - Medical, Biological, Agricultural* and *Index to Scientific and Technical Proceedings®*.

New data on inflammatory bowel disease treatment with topical steroids

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SUMMARY

Glucocorticosteroids (GCSs) remain the mainstay primary treatment of active inflammatory bowel disease (IBD). These agents usually result in a rapid suppression of symptoms but due to the ubiquitous nature of the GCS receptor, they also cause systemic side-effects. Recently, new GCSs developed mainly for asthma (eg., budesonide) have been found to counter the problem of systemic side-effects due to a greater first-pass metabolism and an increased affinity for the GCS receptor, resulting in a predominantly topical mode of action. Budesonide seems particularly suitable for IBD conditions. It has been developed for both rectal and oral delivery to the gut and has been shown to have good efficacy in both Crohn's disease and ulcerative colitis with a mild side-effect profile.

INTRODUCTION

Effects and side-effects of glucocorticosteroids

Glucocorticosteroids (GCSs) remain the mainstay of medical treatment in active inflammatory bowel disease (IBD). The anti-inflammatory effects of GCSs in acute attacks of ulcerative colitis (UC) as well as in Crohn's disease (CD) are unsurpassed by any other type of drug and a rapid and substantial effect on clinical symptoms is usually seen during the first few days of treatment. Glucocorticosteroids exert their actions by binding to the intracellular GCS-receptor which is uniformly distributed in all types of human cells. Activation of the receptor will evoke a number of responses and effects, including inhibition of the production and action of certain key pro-inflammatory cytokines.

The anti-inflammatory effects of conventional GCSs in IBD are commonly offset by systemic side-effects: eg., cosmetic or psychological problems such as acne, moonface, striae and mood disturbances including insomnia. Others, like hypertension, dyspepsia and impaired glucose tolerance, may be of substantial clinical importance. Long-term treatment is precluded by the risk for hazardous and sometimes also irreversible complications such as osteoporosis and osteonecrosis, cataracts and diabetes mellitus. The suppression of endogenous cortisol levels and impairment of the hypothalamic-pituitary-adrenal gland function, with delayed recovery, are other issues of concern.

Development of GCSs for topical action

Recent steroid development, primarily aimed at refinement of topical inhalation therapy in asthma, has provided us with new GCS compounds such as budesonide and fluticasone, which have 100–200 times higher affinity for the GCS receptor compared with hydrocortisone, enabling treatment with much reduced doses. If the drug is administered in the gut, the major portion will be cleared through the portal vein to the liver where it is, to a large extent, inactivated during the hepatic first-pass metabolism. The systemic availability of the new GCSs will therefore be substantially reduced compared with that of older GCSs, and this improved ratio of efficacy at the target level *vs* decreased systemic load is the principle on which new topical steroids for IBD rely[1,2]. Furthermore, other GCS prerequisites for optimal topical action in IBD conditions include sufficient water solubility for adequate distribution in the bowel lumen, a high mucosal uptake and deep penetration. These enhanced properties of new GCSs are dependent on the introduction of lipophilic substitutions in the 16-α and 17-α positions on the GCS skeleton.

Several new GCSs have been evaluated for use in IBD during the last years[2], but after review[3], only a few compounds remain on the market for topical IBD applications.

BECLOMETHASONE

Beclomethasone, 17-α and 21–dipropionate, given in enema form for active distal UC, has previously been shown to have equal efficacy but reduced suppression of plasma cortisol levels in comparison with conventional GCS enemas[4]. Beclomethasone was recently compaired with 5–aminosalicylic acid (5-ASA) in a randomised controlled trial (RCT); the two drugs were equally effective when given as monotherapy for active ulcerative proctitis, but significantly improved results were obtained when a combination of the two different compounds (3 mg GCS + 2 g 5-ASA in 100 ml) was used[5]. The results need confirmation, but are still of great clinical interest as they indicate that therapeutic synergism may be obtained by combining drugs utilising different modes of action, maintaining a low toxicity profile[6]. However, as beclomethasone is now out of patent, the commercial interest for a study using this particular drug is probably low and it is uncertain if further development for UC will be continued.

BUDESONIDE

To date, the best documented of the new generation of highly potent 17-α substituted GCSs for the treatment in IBD, is budesonide. It is now approved in several countries, both as an enema and in an oral preparation (Entocort®, Astra, Sweden). Due to its relatively high water solubility, budesonide is readily dissolved, facilitating transport to the bowel wall. These hydrophilic properties ensure a high tissue uptake, resulting in high concentrations and high activity in the target tissues when the drug is applied topically. As shown in animal studies, budesonide has a greater topical uptake and remains within the mucosa for a longer period of time than prednisolone[1]. The drug is biotransformed rapidly in the liver *via* the cytochrome P450 CYP3A4 enzymes, with 80–90% metabolised in the first pass resulting in low systemic availability.

positive results[7–11]. In an American RCT comprising 184 patients with distal UC, the budesonide enema was compared with standard hydrocortisone enema. Budesonide showed similar therapeutic efficacy, but had significantly less impact on the response to an adrenocorticotropic hormone (ACTH) test after 6 weeks of treatment[12]. Another large US study with 223 patients evaluated the budesonide enema in a dose-ranging RCT *vs* placebo, comparing doses of 0.5, 2 and 8 mg given at bedtime. The optimal dose was confirmed to be 2 mg/100 ml, although the 8 mg dose provided slightly higher remission rates[13]. In line with these results, a recent, Swedish, multicentre RCT investigating active distal UC and proctitis treatment using administration of the enema bd. could not demonstrate a significant advantage in remission rate over the standard, once-daily dose (62% *vs* 57% bd.) after 8 weeks[14]. Furthermore, in those patients achieving remission, a prolonged treatment with the budesonide enema given twice weekly for up to 6 months was not significantly superior to placebo in maintaining remission (38% *vs* 53% relapse rate)[14]. A clinical trial comparing budesonide enema 2 mg/100 ml to Pentasa® (mesalazine) 1 g/100 ml in acute distal UC or proctitis for 4 weeks[15] showed equal efficacy in inducing endoscopic and histological remission; however, the Pentasa® enema was superior in obtaining clinical remission (60% *vs* 38%; $P = 0.03$).

BUDESONIDE FOR ORAL USE

A refined, slow-release delivery system developed for budesonide by Astra Draco AB, Sweden uses mm-sized enteric coated (Eudragit L) pellets with a rate-limiting polymer containing the active drug[16]. This time-dependent and pH-dependent delivery system (controlled ileal release, [CIR]) results in an absorption of around 70% of the given drug in the distal ileum and the caecum, making it appropriate for treatment of active distal ileal and/or right-sided colonic CD. Encouraging results in a small pilot trial were confirmed by two large multicentre RCTs. The optimal dose of the oral preparation for active ileal or ileocaecal CD was found to be 9 mg in a Canadian placebo-controlled, dose-ranging study of 258 patients[17]. Special attention was made to monitor GCS-associated side-effects, but interestingly, no significant differences were found between the active treatment groups compared with placebo in this respect. The 9 mg dose had the best clinical efficacy and a GCS-associated side-effect incidence similar to that of placebo (26%); however, significantly lower plasma cortisol was seen after 8 weeks treatment in the budesonide group compared to placebo (69% *vs* 14%; $P < 0.001$). In a European, multicentre, double-blind, double-dummy RCT, comparing 9 mg budesonide CIR given with a standard regimen of 40 mg/day of oral prednisolone tapering over a 10-week period[18], no statistical difference in overall remission rate (as determined by a Crohn's disease activity index [CDAI]-score < 150) was seen (52% *vs* 65%; $P = 0.12$). While clinical efficacy was comparable, morning plasma cortisol levels were markedly suppressed in the prednisolone group after 8 weeks ($P = 0.02$). In line with this, GCS-associated side-effects were milder and significantly less frequent in the budesonide group (33% *vs* 55%; $P = 0.003$) during the study period.

These results have recently been confirmed and reinforced by an international comparative RCT[19], involving 177 patients with active ileocaecal CD. The study evaluated two different dosing regimens for budesonide. A once daily *vs* a twice daily

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