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Review article: Drug development in inflammatory bowel disease: budesonide — a model of targeted therapy

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SUMMARY

The use of non-specific anti-inflammatory drugs such as the glucocorticoids is the foundation of medical therapy for inflammatory bowel disease. Although conventional steroid drugs are highly effective, their use is associated with the adverse effects of Cushing's syndrome. However, the therapeutic index of these drugs can be improved by chemical modification of the steroid nucleus and the use of new drug delivery systems that target the bowel wall as the pharmacokinetic compartment of interest. Budesonide is a novel glucocorticoid compound that illustrates the potential of this approach to identify effective and safe new treatments. Regional therapy for inflammatory bowel disease is an important pharmacological concept for the future development of the new glucocorticoids and other classes of drugs.

INTRODUCTION

Crohn's disease and ulcerative colitis are idiopathic inflammatory disorders of the bowel which have a worldwide distribution. In these conditions, chronic inflammation of the intestinal mucosa causes oedema and ulcer formation. This process produces the common clinical symptoms of diarrhoea, bleeding and abdominal pain. In ulcerative colitis, the inflammation is confined exclusively to the colon. Crohn's disease may occur at any site in the gastrointestinal tract, but more frequently in the terminal ileum and the proximal colon.

The two conditions are pathologically distinct. Inflammation in ulcerative colitis begins in the anal canal, is continuous to a variable degree through the colon, and is superficial. In contrast, Crohn's disease is usually characterized by segmental involvement of the colon or small bowel with transmural inflammation. Endoscopically, linear ulcerations surrounded by areas of normal mucosa are seen. The clinical course of both diseases is unpredictable, and usually consists of intermittent exacerbations of symptoms interspersed with periods of remission.[1]

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MEDICAL THERAPY FOR INFLAMMATORY BOWEL DISEASE

As the cause of inflammatory bowel disease (IBD) is unknown, current medical treatment is directed towards suppressing the pathological inflammatory response. The most important classes of drugs are 5-aminosalicylates (5-ASAs), glucocorticoids and immunosuppressives.[2] Surgery is used to treat complications of either disease or as a means of controlling symptoms in those individuals who do not respond to drug therapy. In the case of ulcerative colitis, colectomy is curative. Surgery does not cure Crohn's disease; the inflammation recurs following resection of a segment of inflamed bowel.

Glucocorticoids are the most important class of drugs for the treatment of active ulcerative colitis and Crohn's disease. The efficacy of steroid therapy has been confirmed by randomized, controlled trials.[3,4] Glucocorticoids exert their anti-inflammatory effects through multiple mechanisms, including suppression of both humoral and cellular immunity, inhibition of neutrophil and macrophage chemotaxis and reduction of cytokine production.[5] However, glucocorticoids also have powerful metabolic effects, which include the regulation of carbohydrate, protein, and mineral homeostasis. As glucocorticoid receptors are ubiquitous in human tissue and the

interaction of these steroids with the glucocorticoid receptor is not tissue-specific,[6] adverse drug effects from glucocorticoids are a common occurrence. The cosmetic effects that characterize Cushing's syndrome are almost uniform with chronic steroid use. The most common side-effects are moon faces, acne, swollen ankles, easy bruising, and hirsutism.[7] More serious adverse events, such as diabetes mellitus, hypertension and osteoporosis may also occur.[8,9] Thus, glucocorticoid therapy is a two-edged sword; its efficacy for the suppression of inflammation is coupled to other unwanted metabolic effects. These considerations have led to a search for new glucocorticoids with enhanced anti-inflammatory activity and decreased systemic toxicity.

CHARACTERISTICS OF AN IDEAL GLUCOCORTICOID FOR USE IN INFLAMMATORY BOWEL DISEASE

The pharmacological profile of an ideal glucocorticoid for use in inflammatory bowel disease (IBD) is shown in Table 1. The drug should combine high potency at the site of inflammation with minimal systemic effects. One way of fulfilling these criteria is to employ localized therapy.

The initial formulations of steroids for localized therapy utilized rectal installation routes. Clinical trials have shown that topical formulations (enemas, suppositories, foams) of hydrocortisone or betamethasone are effective for the treatment of ulcerative colitis and infrequently cause systemic side-effects.[10–12] However, rectal administration formulations are effective only for those patients whose disease is distal to the splenic flexure of the colon.

The development of specific oral drug delivery systems involves a newer, alternative approach to deliver locally acting steroids in patients who have disease elsewhere in the colon or small bowel. The development of such formulations were pioneered during the 1980s for the 5-aminosalicylates. Sulfasalazine, which consists of a sulfonamide antibiotic (sulfapyridine) linked by an azo bond with an anti-inflammatory salicylate (mesalamine) is poorly absorbed in the upper gastrointestinal tract. Upon entering the colon, bacterial enzymes split the sulfasalazine diazo bond, liberating 5-ASA.[13] As the efficacy of 5-ASA is dependent on the drug concentration in the bowel lumen, this is a highly effective mechanism for delivery of the drug to the colon. However, the sulfapyridine moiety is associated with adverse effects. Newer 5-ASA delivery systems were designed which did not require a sulfur-based carrier molecule. These formulations prevent proximal absorption of 5-ASA and deliver the drug to specific sites of intestinal inflammation. The development of these compounds provide a model which can be exploited for use with other classes of drugs, including glucocorticoids.[15]

Table 1. Characteristics of an ideal glucocorticoid for treatment of IBD

- High anti-inflammatory activity
- Site selectivity
- Low systemic absorption
- Rapid degredation of absorbed drug to inactive metabolism

DRUG ABSORPTION: LOCAL AND SYSTEMIC

The site at which an oral drug is absorbed is affected by multiple factors (Table 2).[16] Differences in absorption rates are often not clinically important for systemically acting drugs, as the pharmacodynamic effect is primarily determined by the total amount of drug, not the rate of absorption. However, this is not the case for compounds which act topically in the gastrointestinal tract, because the luminal concentration of the drug may be the primary determinant of efficacy. Furthermore, the factors that govern drug absorption may vary between healthy individuals and those with IBD. This may result in marked differences in bioavailability between individuals. The two physiological factors that are of primary importance in regulating absorption in the gastrointestinal tract are pH and intestinal transit time. The site where water-soluble compounds are absorbed is dependent upon an ionic charge, which is in turn, sensitive to the environmental

Table 2. Factors affecting the absorption of drugs

Drug factors	Dosage form factors	Physiological factors
pKa	Disintegration time	Intestinal surface area and transit time
Solubility	Dissolution rate	pH of gastrointestinal fluids
Partitioning	Type of dosage form	Enterohepatic cycling first-pass effect

hydrogen ion concentration. The pH of the stomach in the fasting state is approximately 4.0–6.0, but can decrease to less than 2.0 after a meal. In the small bowel, the pH ranges from approximately 5.0 in the duodenum to nearly 8.0 at the ileocaecal valve. The rate of absorption of weak acids increases with decreasing pH; conversely, the rate of absorption of weak bases is increased with increasing pH. As the pH of the bowel contents governs the proportion of drug which exists in an ionized form, compounds that are acidic should, in theory, be absorbed to a greater extent in the stomach and compounds that are basic should be absorbed to a greater extent in the distal colon. However, other factors such as the much greater surface area available in the small bowel for absorption and the intestinal transit time are dominant.[17] These factors must be considered when designing drugs for targeting specific sites in the gastrointestinal tract. The presence of regional differences in pH can be used to either decrease or increase drug absorption. However, it should be recognized that the hydrogen ion concentration in specific regions of the gastrointestinal tract of patients with IBD may not be the same as in normal individuals. Fallingborg *et al.* have studied this question, using a radiotelemetry capsule as a pH probe.[17] Patients with ulcerative colitis had normal gastric and small bowel hydrogen ion concentrations. However, three of the six individuals evaluated showed very low pH values (2.3–3.4) in the proximinal colon. Increased concentrations of faecal lactate were noted in this area. Fallingborg *et al.* hypothesized that this abnormally low pH was the result of a decreased capacity of the epithelium to metabolize butyrate. In normal individuals, butyrate is the primary source of energy for enterocytes; however, the presence of inflammation may impair cellular metabolic pathways. This could result in an increased production of lactate in the colon.[18,19] The finding may be important for the design of locally acting therapy because the abnormally acidic environment present in active ulcerative colitis could significantly alter the pharmacokinetics of an orally administered drug. Another important determinant of drug absorption is intestinal transit time. A drug that is absorbed in the gastrointestinal tract outside of the area of inflammation is not available to act as a local therapy. Thus, the absorption of a drug which is intended for this purpose, either proximal or distal to a site of inflammation, is undesirable. The high degree of variability in intestinal transit time noted in normal individuals is more pronounced in patients with intestinal diseases. Reddy *et al.*, used both radioisotopes and manometry to compare the colonic motility of patients with active ulcerative colitis to healthy controls.[20] In the latter group, an increase in colonic pressure was demonstrated after eating and was greatest in the descending colon. In contrast, patients with ulcerative colitis had decreased colonic pressure in all areas of the colon, and no pressure gradient was observed between adjacent colonic segments. The transit of intestinal contents in the control group was reduced in the fasting state. However, following the ingestion of a standardized meal, both antegrade and retrograde transit of intestinal contents were increased. In contrast, intestinal transit in the patients with ulcerative colitis was variable both before and after a meal. An increase in low amplitude contractions was associated with a more rapid antegrade transmission of bowel contents into the sigmoid colon. Reddy *et al.* speculated that these findings would result in a decreased time for the bowel contents to be in contact with the rectal mucosa. Other manometric studies are also consistent with the notion that abnormalities of motility are common in patients with IBD. Rao and Read studied 62 patients with active ulcerative colitis and 20 healthy controls using rectal manometry.[21] These investigators demonstrated that the resting motor activity was significantly lower in patients with active ulcerative colitis than in the healthy controls. Rectal contractions of higher amplitude than normal were demonstrated following infusion of saline into the distal bowel. The investigators postulated that the diarrhoea in ulcerative colitis is a result of both an increase in rectal sensitivity and more vigorous muscular contractions. These abnormalities have important implications for drug development, as locally acting drugs require adequate time to enter the bowel wall compartment. An adequate concentration of drug must be delivered to the site of inflammation without proximal absorption. Sufficient time must be available for the drug to be in contact with the intestinal epithelium. This presents a challenge for time-dependent delivery systems. If a topically active drug is released at a site which is either proximal or distal to the target site, efficacy is likely to be compromised.

Drug determinants: implications for gastrointestinal drug-delivery systems

For an orally administered, topically active drug to be effective, it must be in solution.[16] Orally administered drugs are usually in the form of capsules or tablets. Free drug is released from these products through an initial

process of disintegration. The rate of disintegration is governed by the physical formulation of a product. Tablets consist of granules of drug in a matrix of inert ingredients (excipients). Disintegration results in the release of small particles that can provide a large surface area for solubilization of the drug. Gelatin capsules dissolve rapidly (less than 10 min) and release fine particles of drug that are easily solubilized. Following solubilization, the drug is available for absorption. Many drugs are poorly soluble, so that the rate of dissolution is rate-limiting for absorption. Oral drugs may be altered in several ways to modify dissolution and absorption characteristics. Prodrugs may be designed to influence the site at which absorption takes place. For systemically active drugs, it is desirable to enhance proximal drug absorption. Weak acids which are poorly absorbed in the proximal small bowel may be conjugated with lipophilic side-chains to enhance absorption. Following absorption, the modified drug is metabolized and the parent compound is released. Another drug factor which regulates absorption is its lipid solubility. Lipophilic compounds are absorbed more rapidly across epithelial cell membranes than polar molecules. Absorption occurs in accordance with the pH partition coefficient. This value reflects the relative concentrations of drug present at an organic solvent/water interface. A drug with a partition coefficient of 1 has equal solubility in the organic and liquid phases. Drugs that are well absorbed have partition coefficients of 10:1 (octanol/water) or greater. For drugs which act locally in the gastrointestinal tract, proximal drug absorption is undesirable. Carrier molecules can be attached to the active compound, which, because of their polar nature, are poorly absorbed in the proximal small bowel. As discussed previously, sulfasalazine is a prototypic example of a drug that exploits this concept. Osalazine is an example of a 5-ASA prodrug that exploits a similar approach.[22] Another approach is to design specific gastrointestinal transport systems which are based on physical strategies. These drugs may be designed to maintain more constant drug levels for systematically acting drugs. Natural polymers are available which release a drug according to zero-order (i.e. a constant rate of release) or first-order kinetics. The result is lower drug absorption and less variability in serum concentrations. Osmotic mini-pumps have been used recently in the oral formulation of several drugs, including nifedipine.[23] In this system, water enters the drug tablet by osmosis. This results in an increase in pressure within the tablet. The drug is slowly forced out of a laser-drilled outlet, which yields a constant rate of drug release. Similar systems can be designed to deliver drug to specific regions of the gastrointestinal tract in a time-dependent fashion. Eudragit coatings are commonly used.[24] Eudragit is a synthetic polymer which has pH-dependent dissolution properties. Two forms of Eudragit; R and L, have significantly different dissolution properties. Eudragit L dissolves at pHs of greater than 7.0, whereas Eudragit S is optimally released at under pH 6.0.

Determinants of systemic absorption: implications for toxicity

Systemic toxicity is dependent both on the degree of absorption and the extent to which the drug is metabolized in the liver as it passes from the portal circulation. The liver is the primary site of drug metabolism.[25] Hepatic enzyme systems facilitate the excretion of lipid-soluble drugs by converting them to more polar metabolites. However, it has recently been recognized that the intestine also plays an important role in drug metabolism.[26] The epithelial cells of the small bowel express cytochrome P450 (CYP)3A enzymes, which metabolize glucocorticoids and other drugs. A wide variation exists among individuals in the expression of these enzymes.[27] Thus, the intestinal phase of drug metabolism in a population may be highly heterogeneic. Commonly prescribed drugs may interact with these enzyme systems. Rifampicin is a potent inducer of CYP3A expression in enterocytes.[28] Erythromycin[29] and grapefruit juice[30] inhibit these enzymes. Some important clinical correlates of these pharmacokinetic considerations have been identified. Drugs such as cyclosporin and felodipine are highly sensitive to intestinal metabolism. Cytochrome P450 enzymes may be important to the pharmacokinetics of regionally active glucocorticoids, however, no data are currently available which address this issue. Following transport across the epithelial cell, orally administered drugs are transported to the liver via the portal circulation. The absorption and subsequent metabolism of drugs is sensitive to changes in mesenteric blood flow. Bolondi *et al.*, using Doppler ultrasound measurements, have demonstrated a significant increase in splanchnic venous return in patients with active IBD, in comparison to healthy individuals.[31] In patients with Crohn's disease, the mean velocity of portal venous blood was 28.2 ± 7.7 cm/sec in comparison to 19.4 ± 2.2 cm/sec in healthy individuals ($P < 0.001$). Accordingly, the values in patients with ulcera-

tive colitis were 27.7 ± 5.8 cm/sec as compared with 19.4 ± 2.2 cm/sec ($P < 0.05$) for the control group. The increased flow in these patients with IBD normalized following treatment.

First pass metabolism

Only a small fraction of a systematically administered, absorbed drug is initially exposed to hepatic metabolism. In contrast, all of an orally administered, absorbed drug which is absorbed is susceptible to hepatic metabolism. This occurs because the venous blood from the gastrointestinal tract returns to the systemic circulation through the portal system and the liver. In contrast, only 25–30% of blood in the systemic circulation passes through the liver with each transit of the circulation. Thus, there is approximately a four-fold increase in exposure to the effects of hepatic metabolism in orally administered drugs compared to those given parenterally. In order to minimize the undesirable systemic effects of glucocorticoids, topically actings drugs should have a high, first-pass metabolism. Hepatic CYP3A enzyme systems are primarily responsible for glucocorticoid metabolism.[25] This family of enzymes is involved in the metabolism of many other commonly used drugs. Thus, interactions with drugs that either induce or inhibit these enzymes may be clinically important.

Pharmacokinetic properties of budesonide

Chemical modification to the glucocorticoid nucleus can enhance anti-inflammatory effects while minimizing undesirable mineralicorticoid activity. Two methods are available for the assessment of the potency of glucocorticoid drugs. One is the *in vitro* measurement of the binding affinity for the glucocorticoid receptor.[6] To achieve optimal anti-inflammatory activity, a candidate drug should have a high affinity for this receptor. The other measure is a bioassay in which a range of concentrations of a candidate compound is applied to the skin of a healthy volunteer. Blanching of the skin from steroid-induced vasoconstriction is assayed visually in comparison with a laboratory standard, fluocinolone acetonide. This bioassay evaluates both the anti-inflammatory activity and tissue penetration of a drug. Esterification at the 17-α position markedly enhances the potency of a glucocorticoid. However, despite potent anti-inflammatory effects, compounds such as betamethasone and dexamethasone are unsuitable for the treatment of skin disease because of poor tissue penetration. The introduction of lipophilic constituents at the 17-α and 16-α positions enhances tissue penetration. The resultant compound, triamcinolone acetonide, is a highly effective drug for the treatment of dermatoses.[32] Similar modifications resulted in the development of budesonide.

Budesonide is a 17-α substituted steroid that has many desirable characteristics for use as a regional anti-inflammatory drug. Budesonide has a topical anti-inflammatory effect approximately five times that of prednisone. This increase in potency was achieved by modifying the 6-α-hydroxy-prednisolone nucleus through the addition of 16α and 17α acetyl groups. Budesonide has a systemic bioavailability of 9.3–15% when administered orally as a controlled, ileal-release capsule or rectally as an enema.[33] The drug undergoes extensive first-pass metabolism in the liver and possibly the intestinal epithelium. The two major metabolites, 6β-hydroxy-budesonide and 16α-hydroxy-prednisolone, have minimal glucocorticoid activity.[34] The highest concentration of metabolites are excreted via the kidneys. A smaller amount of conjugated metabolites are eliminated through the bile. Formulations of budesonide have been designed to target specific regions of the gastrointestinal tract that are of relevance to the treatment of IBD. An enema formulation is available for the treatment of distal ulcerative colitis or proctosigmoiditis.[35,36] The development of a budesonide enterocapsule (budesonide controlled ileal release) has facilitated delivery of the drug to the distal small bowel and proximal colon for use as a treatment in Crohn's disease. This formulation contains acid-stable micro-granules of budesonide which are suspended in ethyl cellulose. The enterocapsule is coated with a layer of metho-acrylic acid copolymer that dissolves at a pH above 5.5. Approximately 50–79% of the absorption of budesonide occurs in the distal small bowel and proximal colon.[14] Recently, a colonic preparation of budesonide has been described, which consists of budesonide capsules containing acid-resistant pellets of drug.[37] This formulation has a sustained-release profile which delivers active drug during passage of the capsule through the colon.

Budesonide: results of clinical studies

A large number of clinical trials have evaluated the use of budesonide enemas in patients with distal ulcerative colitis or proctosigmoiditis. The oral controlled, ileal-

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