USE OF ANTI-INFLAMMATORY STEROIDS FOR THE TREATMENT OF CHRONIC INFLAMMATORY INTESTINAL DISEASES

The present invention relates to the use of therapeutic agents for the manufacture of a medicament for the treatment of inflammatory intestinal diseases.

Ulcerative colitis (UC) and Crohn's disease are chronic intestinal diseases also called Inflammatory Bowel Disease (IBD), characterized by inflammation of unknown etiology. Environmental, genetic and immunological factors are thought to be involved in the etiology of these diseases. Crohn's disease has also been called regional enteritis because of the frequent involvement of the terminal ileum. UC most often affects the descendens and sigmoideum segments of the colon.

The diseases are characterized by exacerbations and remissions. The inflammation in Crohn's disease is discontinuous with uninvolved areas of normal bowel between diseased areas, and transmural, involving all layers of intestinal tissue from the mucosa to the serosa. Because the inflammatory process is transmural, nonadjacent loops of bowel may adhere to each other and develop masses, fistulas, or obstruction. The inflammatory infiltrate in the thickened bowel wall contains lymphocytes, macrophages, neutrophils, and, in about half of the cases, granulomas. The epitheleum in UC is typically infiltrated with neutrophils and exhibits diffuse inflammation. There is an increased risk of colon cancer in patients with Ulcerative colitis. The primary manifestations are rectal bleeding, diarrhea, urgency, fever, weight loss and sometimes abdominal pain.

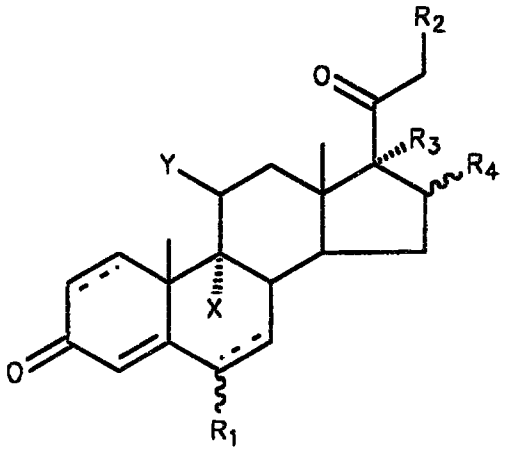
Current therapies involve the use of steroids , immuno-suppressants and-amino-salicylates that may cause a broad range of side-effects. Thusfar steroids have the best over-all effect in reducing active inflammation but also have the most significant side-effects.

The beneficial effects of glucocorticoids are attributable mainly to their anti-inflammatory activity, which is manifested as a reduction in the production and activity of pro-inflammatory cytokines and in the decreased production of the enzymes phospholipase A2, 5-lipoxygenase and cyclo-oxygenase, thereby inhibiting the arachidonic acid cascade and preventing the generation of prostaglandins and leukotrienes. In addition glucocorticoids have some non-specific anti-inflammatory actions.

Use of anti-flammatory steroids, however, is not without risk. Chronic use of these compounds often induce side-effects of systemic nature. One of the major ones is the suppression of the hypothalamopituitary-adrenal axis which may result in the inability to respond to stress. Therefore, it is to be preferred to locally treat the afflicted part of the colon. Thus, there is a need to develop pharmaceutical compositions which are devoid of systemic side effects.

It is the main object of the present invention to provide pharmaceutical compositions to be used in a local treatment of IBD without the risk of side-effects.

The present invention therefore relates to compounds of general formula I:



I,

wherein X is a member of the group consisting of H and halogen;

Y is a member of the group consisting of H(OH), H(O(C_{1-6})Acyl) and O;

R_1 is a member of the group consisting of H, CH_3 and halogen;

R_2 is (C_{1-4})Alkyl;

R_3 is a member of the group consisting of H, O((C_{1-6})Acyl), O((C_{1-6})Alkyl) and CH_3;

R_4 is a member of the group consisting of H and (C_{1-4})Alkyl and C_1-C_2 and C_6-C_7 are saturated or unsaturated bonds,

for the manufacture of a medicament for chronic intestinal inflammatory diseases.

The term acyl means an acyl group derived from an organic carboxylic acid having 1-6 carbon atoms as is also indicated by the affix (C_{1-6}). The number of C-atoms in the alkyl group is indicated by the affix (C_{1-4}) or (C_{1-6}).

The compounds are disclosed in US patent No. 3,947,478 for alkylated 3,20-diketo-delta-4 steroids. This patent, which is fully incorporated herein by reference, describes the method for the preparation of these compounds. The compounds are described to have anti-inflammatory dermatological utility. In addition, US patent 4,686,214 describes an ophtalmatic utility for the same compounds.

Especially preferred is a compound according to formula I wherein X is H, Y is H(OH), R_1 is H, R_2, R_3 and R_4 are CH_3, C_1-C_2 is a double bond and C_6-C_7 is a single bond. This compound is called rimexolone.

Rimexolone is a non halogenated glucocorticoid which has been shown to suppress joint-swelling in fibrin-induced mono-articular arthiritis in rabbits and to have little systemic side effects after topical administration (J. Clin.Pharm.(1990) *30*, 476-679). Once present in the blood stream, it is rapidly metabolized and excreted.

The compound have an extremely poor solubility in aqueous media. Oral toxicology experiments have indicated that the compounds are poorly absorbed after oral administration and that a large amount of unchanged steroid was excreted with the faeces.

Nevertheless, the compound has an effect on the diseased areas of the bowel comparable with that of dexamethasone.

Depending on the route of administration and the formulation used, the compounds have a long mean residence time. They have a very pronounced anti-inflammatory effect and a long duration of beneficial effect.

The compounds of the invention can be used in mammals as a medicament to ameliorate inflammation of inflammatory bowel diseases. Preferably, the compounds according to the invention are used in the treatment of ulcerative colitis. The mammal, preferably, is a human.

Compounds according to formula I, and pharmaceutical preparations based thereon, have a beneficial effect on the accumulation of mediators of mucosal inflammation such as PGE_2 ,LTB_4 and TXB_2. The compounds according to the invention therefore are suitable for therapeutic use in the treatment of colitis. The present invention therefore provides a method of reducing the process of chronic inflammation of the bowel comprising

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

administering to a mammal, preferably to a human, an effective amount of compounds according to general formula I, preferably rimexolone.

A daily dose can be administered in one or more dosage units through for example the oral route, the rectal route or through injection. Preferably, a single dosage unit a day is administered by the rectal route. Alternatively, a controlled release preparation, releasing the daily required total dose can be used.

The pharmaceutical preparations for use according to the invention can be prepared in accordance with standard techniques such as for example are described in the standard reference, Gennaro et al. (Ed.), Remmington's Pharmaceutical Sciences, (18^{th} ed. Mack Publishing Company, 1990, e.g. Part 8: Parmaceutical Preparations And Their Manufacture). For the purpose of making the pharmaceutical preparations according to the invention, compounds according to general formula I, rimexolone, or pharmaceutically acceptable salts thereof, are mixed with or dissolved in a pharmaceutical acceptable carrier. Examples of such preparations are tablets, pills, suppositories, (micro-)capsules, powders, emulsions, creams, ointments, suspensions, solutions.

Examples of pharmaceutically acceptable carriers are: starch (for example potato or corn starch), sugars (for example lactose), lubricants (for example magnesium stearate), binders (for example amylopectine or polyvinyl pyrrolidone), water, alcohol, glycerol and its derivatives, vegetable-, animal- and mineral oils and fats, fatty alcohols, silicones, polyalkylene glycols, cellulose derivatives, silica, dispersants, emulsifiers, surfactants, anti-oxidants, colorants and preservatives. In fact, any conventional pharmaceutical carrier that does not interfere with performance of the active ingredient can be used in the preparations according to the present invention.

A formulation for a enema typically contains approximately 100 ml water, a buffer (such as a phosphate-buffer) and salts (such as sodium chloride) to

obtain a neutral and iso-osmotic solution. In case the solubility of the active compound is too low to achieve full dissolution a thickener (such as a cellulose like methylcellulose or such as polyvidon) is added to the suspension to limit the degree of sedimentation and caking. A detergent (such as polysorbate 20) may be used to increase the availability of the active material to the tissues. Finally, a preservative (such as methyl and propyl oxybenzoate) is added.

The anti-inflammatory properties of rimexolone have been described at earlier occasions. Relative anti-inflammatory properties in relation to the invention are revealed in a rabbit model.

The invention is illustrated by the following examples:

Legends to the figures:

Figure 1: Rimexelone in a rabbit colitis model.

Low and high refer to low and high concentrations of rimexolone (as indicated in example 1). Dex refers to dexamethason. PGE_2 is prostaglandin E_2 and TXB_2 is thromboxane B_2.

Example 1

Induction of colitis

Male New Zealand White (SPF) rabbits weighing 2.5-3 kg were anaesthesized with hypnorm 0.4 mg/kg i.m. (Janssen, Belgium) after which a 22G canula was inserted in a marginal ear vein. Four milliliters of dilute formalin (0.65% vol/vol) were instilled per rectum through a 10Fr feeding-tube, 15 cm in length (time 0), followed (two hours later) by an intravenous

infusion (ear vein) of 0.85 ml heat aggregated rabbit immunoglobulin (10 mg/ml, at 63°C for 20 minutes) (Dako, Denmark).

All animals were sacrificed 24 hours after induction of colitis by intravenous injection of 150 mg/kg sodium pentobarbitol, following pre-medication with Hypnorm. Rectal dialysis was performed two hours prior to sacrifice. Visking dialysis tubing, diameter 6.3 mm, length 6 cm (Medicell Int., London), filled with Rheomacrodex (NBPI, The Netherlands), was inserted to 18 cm and left in-situ for two hours. Following removal, the dialysate volume was measured, and stored at - 20 °C for processing within twenty four hours.

Treatment regimen

Fourty-eight rabbits were randomized into 4 groups. Treatment consisted of a rectal application of rimexolone at a dose of 10 mg/kg (low dose group; N=12) or 40 mg/kg (high-dose group, N=12), one hour before and four and eight hours after induction of colitis. Control animals received a rectal instillation of 0.9% saline (n=12) or 40 mg/kg Dexamethason (n=12).

Sample collection and processing

The distal colon was excised, opened and washed free of faeces in ice-cold phosphate buffered saline. Dialysis fluid was extracted for thromboxane B_2 (TXB_2) and prostaglandin E_2 (PGE_2) through Amprep C_2 and C_{18} (Amersham, England) solid phase columns respectively. Eluents were vacuum dried, resuspended, diluted and assayed using Biotrak ELISA (Amersham). The lower detection limits for these assays were TXB_2 10 pg/ml and PGE_2 20 pg/ml. Plates were read using a Thermomax plate reader (Molecular Devices, USA) and results analyzed with Softmax software (Molecular Devices).

Results

The anti-inflammatory effect of rimexolone is studied over a 24 hour period. The dialysate PGE_2 and TXB_2 levels are shown in figure 1. It can be concluded that the levels of PGE_2 and TXB_2 are reduced in animals when treatment with Rimexolone as compared with the control group. Furthermore, the effect is dosage-dependent. The high dosage effect is almost similar to the effect obtained with dexamethasone.

Example 2

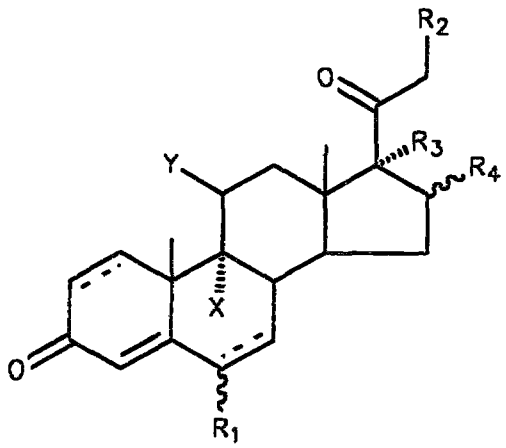
Composition of enema:

Rimexolone	10-100 mg
phosphate buffer	to pH 7
NaCl	to isotonicity
methylcellulose	1-2%*
polysorbate 20	1%
MOB	0.15%
water	100 ml

*) depending upon the viscosity grade

Claims:

1. Use of compounds of general formula I



I,

wherein X is a member of the group consisting of H and halogen;
Y is a member of the group consisting of H(OH), H(O(C_{1-6})Acyl) and O;
R_1 is a member of the group consisting of H, CH_3 and halogen;
R_2 is (C_{1-4})Alkyl;
R_3 is a member of the group consisting of H, O((C_{1-6})Acyl), O((C_{1-6})Alkyl) and CH_3;
R_4 is a member of the group consisting of H and (C_{1-4})Alkyl, and C_1-C_2 and C_6-C_7 are saturated or unsaturated bonds,
for the manufacture of a medicament for chronic inflammatory bowel diseases.

2. Use of compounds of general formula I for the manufacture of a medicament for Crohn's disease.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

3. Use of compounds of general formula I for the manufacture of a medicament for ulcerative colitis.

4. Use of rimexolone for the manufacture of a medicament for chronic inflammatory bowel diseases.

5. Use of rimexolone for the manufacture of a medicament for Crohn's disease.

6. Use of rimexolone for the manufacture of a medicament for ulcerative colitis.

7. A method of ameliorating colitis comprising administering to a mammal an effective amount of a compound having the general formula I.

8. A method of ameliorating colitis comprising administering to a mammal an effective amount of a rimexolone.

9. The method according to claims 7-8 wherein the mammal is human.

THIS SHEET HAS BEEN REPLACED