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(54) **COMPOSITIONS POUR LE TRAITEMENT ET LA PREVENTION DE MALADIES INFLAMMATOIRES DU TRACTUS GASTRO-INTESTINAL, ET METHODES ET UTILISATIONS CONNEXES**

(54) **COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF INFLAMMATORY DISEASES OF THE GASTROINTESTINAL TRACT AND METHODS AND USES THEREOF**

(57) Novel compositions for the treatment of inflammatory diseases of the gastrointestinal tract, preferably ulcerative proctitis, ulcerative colitis, Crohn's colitis, radiation proctitis and pouchitis are described. Compositions comprising more than one active agent such as: 5-ASA; a topical steroid such as, budesonide or an R-epimer thereof; and optionally metronidazole, which are more effective than the use of any of these agents alone are also described.

ABSTRACT OF THE DISCLOSURE

Novel compositions for the treatment of inflammatory diseases of the gastrointestinal tract, preferably ulcerative proctitis, ulcerative colitis, Crohn's colitis, radiation proctitis and pouchitis are described. Compositions comprising more than one active agent such as: 5-ASA; a topical steroid such as, budesonide or an R-epimer thereof; and optionally metronidazole, which are more effective than the use of any of these agents alone are also described.

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Title: Compositions for the Treatment and Prevention of Inflammatory Diseases of the Gastrointestinal Tract and Methods and Uses Thereof

FIELD OF THE INVENTION

The invention relates to methods and compositions for the treatment and prevention of inflammatory diseases of the gastrointestinal tract, including without limitation to ulcerative proctitis, ulcerative colitis, Crohn's colitis, radiation proctitis and pouchitis, and uses thereof.

BACKGROUND OF THE INVENTION

Inflammation is part of many gastrointestinal diseases. Such diseases include but are not limited to Crohn's, ulcerative colitis, pouchitis and proctitis due to radiation, chemical infections and vasculitis.

Crohn's disease is an inflammatory disease of the gastrointestinal tract. It can occur in the mouth, esophagus, duodenum, jejunum, ileum and colon. Most commonly, it affects the terminal ileum and adjacent colon. Specifically, it can effect any portion of the gastrointestinal tract in a patchy, segmental fashion. It is a transmural inflammation affecting the full thickness of the bowel wall. Moreover, in 20% of cases histological granuloma are present. Its cause is unknown. It is routinely treated with anti-inflammatory medications including systemic steroids, 5-ASA, sulphasalzine, metronidazole, as well as non-specific anti-diarrheal and nutritional therapy. Surgery is also commonly required. Crohn's disease may be seen quite commonly in the rectum and perianal area. Enemas have been used that include salazopyrin, hydrocortisone, budesonide, betamethasone, 17 valerate, prednisone, and cyclosporin. These have all been effective in at least some, patients, but there still remain patients resistant to these medications.

Ulcerative colitis is an idiopathic inflammatory disease confined to the mucosal layer of the colon. It is a continuous disease that begins in the rectum and spreads upward. It is treated orally with 5-ASA, sulphasalzine, steroids and surgery, in that it always involves the rectum. When there is distal bowel involvement, it is often treated with enemas. More specifically,

it has been treated with 5-ASA enemas, sulfasalazine enemas, as well as steroid enemas. Despite the use of these enemas, many patients are not adequately treated.

Pouchitis is an inflammatory condition that occurs in a surgically created small bowel pouch when a colectomy is done for ulcerative colitis. Its cause is unknown, but may be related to bacterial colonization of the pouch. It is treated with metronidazole, but occasionally steroids are required.

Proctitis is inflammation of the rectum as a result of radiation treatment for prostate cancer. This is also treated with general anti-inflammatory enema preparations such as 5-ASA and occasionally with steroids.

The above described gastrointestinal disorders require anti-inflammatory therapy. The use of anti-inflammatory enemas for the treatment of such diseases is known. The use of 5-ASA and steroid enemas have been described in Frank Richter, MD, Wolfgang Scheppach, MD., "Innovations in Topical Therapy", Bailliere's Clinical Gastroenterology, vol. 11, No. 1, March 1997, pp97-109.

The mechanism of anti-inflammatory action of 5-ASA probably involves many aspects of the inflammatory cascade which includes thromboxane, leukotrienes, and interleukins.

It is known that the steroid entities primarily effect T cell mediated immunity which is causing the inflammatory reaction. Topical steroids have been used as enema preparations with good local effect. However, the more potent steroids cause systemic side effects.

Enema preparations for use in bowel disease should have a high topical effect and low or absent systemic effect to avoid systemic side effects.

Budesonide, a topical steroid, has a high topical potency and rapid rate of first pass liver metabolism and has been used in the past to treat certain inflammatory gastrointestinal diseases with reduced or no side effects.[Stephen L. Wolman, "Use of Oral Budesonide In A Patient With Small Bowel Crohn's Disease And Previous Pseudomotor Cerebri Secondary To Steroids", Scand, J. Gastroenterolgy, vol. 24, Suppl 15, pp. 146-147 (1989)]

Overall, a comparison of steroid enemas versus 5-ASA enemas show that the steroid enemas are less than or equally effective. A comparison of 5-ASA enemas and budesonide enemas show that these compounds have approximately equal efficacy.

Metronidazole has been shown to be useful in treatment of Crohn's colitis and perianal. Disease [Sutherland, L ., et. al., "Double Blind Placebo Controlled Trial Of Metronidazole In Crohn's Disease", Gut, vol. 32, pp. 1071-1075 (1991)], as well as pouchitis. It is occasionally useful for ulcerative colitis. Metronidazole has been tried as a suppository for chronic proctitis, [Davies, P.S. , Et al., "Metronidazole in The Treatment Of Chronic Proctitis: A Controlled Trial.", Gut, vol. 18, pp.680-681 (1977)]. It showed only a small effect. Metronidazole has known antiparasitic and antimicrobial effects, however its mechanism of action in the treatment of Crohn's colitis, perianal disease and pouchitis is not entirely understood. It is rapidly absorbed into the body and can result in significant side effects.

Unfortunately, existing treatments are not effective in many patients with inflammatory diseases of the gastrointestinal tract. Previously used preparations for the treatment of these diseases are single entity preparations (with a single active agent). Many suffer from ongoing inflammation despite the use of these single entity preparations. Furthermore, certain patients experience side effects from the use of these preparations There is a need for new and effective preparations for the treatment and prevention of inflammatory diseases of the gastrointestinal tract.

SUMMARY OF THE INVENTION

This invention provides for a pharmaceutical composition for use in treating inflammatory gastrointestinal diseases in an animal comprising an effective amount of a combination of compounds which suprisingly has enhanced effectiveness in the treatment of such diseases over treatment using the compounds alone.

The pharmaceutical composition of the present invention comprises 5-ASA and a steroid, preferably a topical steroid and preferably a high potency lipid soluble topical steroid, and a suitable pharmaceutical carrier. Preferably, the pharmaceutical composition is an enema composition.

In one embodiment, the steroid is preferably selected from the group of steroids consisting of budesonide or an R-epimer thereof, beclomethasone, diproprionate, tixocortal pivalate, butixicort, prednisolone, metasulphobenzoate, fluticasone and flunisolide. Most preferably, the steroid is budesonide or an R-epimer thereof which has a high level of topical potency and tissue penetration while causing no or minimal systemic side effects.

In a further embodiment of the invention, the composition further comprises metronidazole.

Preferably the composition of the invention comprises about 0.5-4g/100 ml 5-ASA, about 1-10mg/100 ml and more preferably about 1-4 mg/100 ml of the steroid, preferably, budesonide or an R-epimer thereof, and optionally about 0. 125 -1 g/100 ml and more preferably about 0.250 -1 g/100 ml of metronidazole. Most preferably the composition comprises 2g/100 ml 5-ASA, 2.3 mg/100 ml of budesonide or an R-epimer thereof and when present 500 mg/100 metronidazole.

The preferred compositions of the invention have a high topical effect and low or absent systemic effect to avoid systemic side effects.

The use of the effective combination of compounds in the treatment of inflammatory diseases of the gastrointestinal tract and methods of using the effective combination of compounds, preferably in the concentrations noted above, for the treatment of inflammatory diseases of the gastrointestinal tract are also encompassed within the scope of the present invention.

The treatment of inflammatory gastrointestinal diseases, include without limitation, ulcerative proctitis, ulcerative colitis, Crohn's colitis, radiation proctitis and pouchitis.

In one embodiment the invention provides for the use of a combination of compounds in the preparation of a medicament for the treatment of inflammatory gastrointestinal diseases.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

As discussed previously, many of the currently used treatments for inflammatory gastrointestinal diseases appear to work by different mechanisms. Prior treatments were single entity preparations and not effective or sufficiently effective for many patients with inflammatory gastrointestinal disease.

The present invention describes an effective amount of a combination of compounds, 5-ASA, a steroid, preferably a topical steroid, preferably a high potency and lipid soluble topical steroid, and optionally metronidazole, which can be used in the treatment of inflammatory diseases of the gastrointestinal tract and which suprisingly has enhanced effectiveness in the treatment of such diseases over treatment using the compounds alone. Methods of treatment of inflammatory gastrointestinal diseases comprising the adminstration of these compounds to an animal in need thereof and the uses of the compounds in the treatment of inflammatory gastrointestinal diseases are also encompassed within the scope of this invention.

In one embodiment, the steroid is preferably selected from the group of steroids consisting of budesonide or an R-epimer thereof, beclomethasone, diproprionate, tixocortal pivalate, butixicort, prednisolone, metasulphobenzoate, fluticasone and flunisolide. Most preferably, the steroid is budesonide or an R-epimer thereof which has a high level of topical potency and tissue penetration while causing no or minimal systemic side effects.

Reference to the compounds herein, is intended to include analogs and derivatives thereof which have similar functionality and mode of action. Analogs as used herein are compounds with similar chemical

structure but different atoms. Derivatives as used herein refers to chemical derivatives, compounds which can be derived from another by a simple chemical process.

The effective amount of combination of compounds of the invention can be used in treating inflammatory diseases of the gastrointestinal tract in an animal, including without limitation, ulcerative, proctitis, ulcerative colitis, Crohn's colitis, radiation proctitis and pouchitis.

"Animal" as used herein refers to any living organism which has a gastrointestinal tract and which can succumb to inflammatory diseases of the gastrointestinal tract, such as Crohn's colitis, ulcerative colitis, or the like, and may benefit from treatment disclosed herein. These animals can include, without limitation, mammals, such as mice, guinea pigs, rats, rabbits, dogs, monkeys, cotton top tamorin, and most preferably humans.

An "effective amount" is defined as an amount of the active ingredient, i.e., combination of compounds of 5-ASA and a topical steroid, and optionally metronidazole, effective at dosages and for periods of time necessary to achieve the desired result. An effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual to be treated. Although preferred dosage regimes are outlined below, a person skilled in the art would appreciate that the dosage regime may be altered to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The effective amount of combination of compounds can be formulated into pharmaceutical compositions for adminstration to animals in an effective amount and in a biologically compatible form suitable for adminstration *in vivo*, i.e., a form of the compounds to be administered in which any toxic effects are outweighed by the therapeutic effects.

The combination of compounds may be administered by oral administration, inhalation, transdermal application, or rectal administration, preferably by oral or rectal administration, preferably in the form of enemas. Depending on the route of administration, the compounds in the

pharmaceutical compositions may be coated in a material to protect them from the action of enzymes and to target specific areas of the gastroinstestinal tract. For instance, use of the acrylic resin Eudragit® may be used to protect the compounds and to deliver them to specific sites. Organic substances may also be included in the compositions to prolong the pharmacologic actions of the peptides. Examples of such organic substances include non-antigenic gelatin, carboxymethylcellulose, sulfonate or phosphate ester of alginic acid, dextran, polyethylene glycol and other glycols, phytic acid, polyglutamic acid, and protamine.

The pharmaceutical compositions of the invention can be prepared by per se known methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of the compounds is combined in a mixture with a pharmaceutically acceptable carrier. Examples of pharmaceutically acceptable carriers are described in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985).

Enema compositions can be prepared by methods known in the art. For instance, in addition to the active compounds, which are usually present from about 1-10% by weight, the composition may contain: viscosity enhancing substances preferably in an amount from about 0.05 to 2% by weight; preservatives, such as benoic acid; pH regulating substances, such as buffers; chelating agents, preferably from about 0.01 - 0.5% by weight, such as EDTA; and anti oxidants, preferably from about 0.05 - 0.5% by weight, such as bisulphites.

Further, a person skilled in the art would know that, non medical ingredients in the enema preparation may contain colloidal silicone dioxide lactose, lactose and hydrith, magnesium sterate, polyvidone, crosslinked riboflavin-5-phosphate sodium. The vehicle may contain methyl parahydroxybenzoate, proparahydroxybenzoate, sodium chloride and purified water, carboxypolyethylene polysorbate 80, methylparaben, and sodium hydroxide. Dibasic sodium phosphate and hydras and citric acid may also be used in the formulation.

Experiments have been done with the individual compounds and combinations thereof (i.e., 5-ASA, budesonide and metronidazole) and it appears that the combination of 5-ASA and budesonide is more effective than either one of these agents alone. In addition, the addition of metronidazole appears to enhance the effect in some patients. The metronidazole may work by having a direct antiinflammatory effect and/or by decreasing the anaerobic bacteria in the area allowing for greater bioavailability of the other anti-inflammatories used.

Preferred concentrations of the compounds are about 0.5-4 g/100 ml 5-ASA, about 1 to 10 mg/100 ml and more preferably about 1 to 4 mg/100 ml of a steroid, such as budesonide or an R-epimer thereof, and when present from about 250 mg to 1 g per 100 ml of metronidazole.

From experimentation, it appears that a preferred combination formulation is that of 2g of 5-ASA, 2.3 mg of budesonide and 500 mg of metronidazole in a 100 ml enema with associated antioxidants and preservatives. A person skilled in the art, as noted above, would know what other components could be present in the enema aside from the active ingredients of 5-ASA, a topical steroid and when present, metronidazole.

The following non-limiting examples are illustrative of the present invention:

EXAMPLES

The use of a composition comprising 5-ASA, and a topical steroid in the treatment of inflammatory gastrointestinal diseases is described. Also described is the use of a composition further comprising metronidazole. The use of metronidazole as an enema alone for its anti-inflammatory activity or for greater steroid bioavailability, presumably by increasing the anaerobic bowel flora of the rectum, has not before been previously described.

The results of experiments using a composition comprising 2 g of 5-ASA, 2.3 mg of budesonide and 500 mg of metronidazole in a 100 ml enema (combo #1) showing enhanced efficacy of the combinational enema composition of this invention in patients who have failed previous therapy with single entity compositions are illustrated in Table 1, below. Table 1 also illustrates the use of a composition comprising 2g of 5-ASA and 2.3 mg of

budesonide in a 100 ml enema (combo #2). This treatment also proved to be more effective than the use of either compound alone.

Table 1

Patient	Sex	Date of Birth	Composition of Previous Unsuccessful Enemas				Results with Combination Enema	Results with Combination Enema
			budesonide	5-ASA	betamethasone	cortisone	Combo #1*	Combo # 2*
Crohn's	F	9/6/67	+	+	+		Good	Excellent
Crohn's	M	27/1/68	+	+	+		Excellent	Excellent
UC	F	30/7/53	+	+	+		Excellent	
UC	M	12/4/58	+	+	+		Excellent	Excellent
UC	F	24/1/20	+	+	+	+	Excellent	
CCP	F	10/2/22		+		+	Excellent	Excellent
Crohn's	M	28/7/76	+				Excellent	
UC	F	25/01/51	+	+	+		Excellent	Excellent
UC	F	29/04/52					Excellent	
UC	F	19/04/60	+		+		Excellent	Excellent
UC	F	01/01/60					Excellent	
UC	F	11/11/47		+			Good	
CC	M	15/08/70	+				Excellent	
Crohn's	F	23/05/37	+				Excellent	Excellent
UP	F	13/02/37	+		+		Excellent	Excellent

* U.C. = Ulcerative Colitis
CCP = Colitis Cystica Profunda
CC = Crohn's Colitis
UP = Ulcerative Proctitis

Combo #3 = Salofalk® (ASA), Budesonide, Flagyl ® (metronidazole)
Combo #2 = Salofalk ® (ASA), Budesonide

The goal of treatment with this new enema preparation is primarily to induce symptomatic remission. Prior to treatment, the patients had frequent bowel movements that may be loose or liquid with associated blood and mucous. The chart indicates the prior commercially available single entity treatments received by the patient. The active agent of these previous enemas is indicated. These prior treatments were unsuccessful in these patients, as there was continuous presence of blood and mucous.

In grading the response of the patients to the combination enema of the invention, an excellent response indicates that the patient returned to previously normal number of bowel movements per day with no blood or mucous. A good response was a return to a lower number of bowel movements of at least less than 4 per day with no blood. Some mucous may be present. A fair response was one with no change or a decrease in the

number of bowel movements and a decrease in the presence of blood or mucous. A poor response was no change in the number of bowel movements or in the presence of blood or mucous.

As can be seen by the chart, the combination enema always lead to a marked improvement. Even in patients who have relapsed, the return to the use of the described combination enema resulted in renewed marked improvement.

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

What is claimed is:

1. A pharmaceutical composition for the treatment of an inflammatory disease of the gastrointestinal tract in an animal comprising: an effective amount of 5-ASA and a steroid, and a pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to claim 1 wherein the steroid is a topical steroid.

3. A pharmaceutical composition according to claim 2, wherein the steroid is a high potency lipid soluble topical steroid.

4. The composition of claim 1 wherein the steroid is budesonide or an R-epimer thereof.

5. The composition of any one of claims 1, 2, 3 or 4 further comprising an effective amount of metronidazole.

6. The composition of any one of claims 1, 2, 3, 4 or 5 comprising about 0.5.-4g/100 ml 5-ASA, and about 1-10mg/100 ml of the steroid.

7. The composition of claim 6 wherein the concentration of the steroid is 4mg/100 ml.

8. The composition of claim 6 further comprising about 0.125-1 g/ 100 ml of metronidazole.

9. The composition of claim 8 wherein the concentration of metronidazole is 0.250-1g/100 ml.

10. The composition of claim 8 comprising 2g/100 ml 5-ASA, 2.3 mg/100 ml of budesonide or an R-epimer thereof and 500 mg/100 ml metronidazole.

11. The composition of any one of claims 1-10 wherein the pharmaceutical composition is an enema composition.

12. The composition of any one of claims 1-11 wherein the inflammatory disease of the gastrointestinal tract is selected from the group consisting of ulcerative proctitis, distal ulcerative colitis, distal crohn's colitis, radiation proctitis and pouchitis.

13. A use of an effective amount of 5-ASA and a steroid in the preparation of a medicament for treatment of an inflammatory disease of the gastrointestinal tract in an animal.

14. A use according to claim 13, wherein a steroid is a topical steroid.

15. A use according to claim 14, wherein the steroid is a high potency lipid soluble topical steroid.

16. A use according to claim 13 wherein the steroid is budesonide or an R-epimer thereof.

17. A use according to any one of claims 13, 14, 15 or 16 further comprising administering an effective amount of metronidazole.

18. A use of any one of claims 13, 14 or 15 comprising administering about 0.5.-4g/100 ml 5-ASA, and about 1-10mg/100 ml of the steroid .

19. A use of claim 18 further comprising administering about 0.125 -1 g/ 100 ml of metronidazole.

20. A use of any one of the compositions of claims 1 to 12 in the treatment of treating an inflammatory disease of the gastrointestinal tract in an animal.

21. A composition of any one of claims 1 to 12 wherein the animal is human.

22. A use of any one of the claims 13-20 wherein the animal is human.