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(54) **METHODS FOR TREATING GASTROESOPHAGEAL REFLUX DISEASE**

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(58) **Field of Classification Search** 514/179, 514/178

See application file for complete search history.

(56) **References Cited**

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(57) **ABSTRACT**

This invention relates to the discovery that agents capable of inhibiting the biological action of the glucocorticoid receptor can be used in methods for treating gastroesophageal reflux disease in a subject.

14 Claims, No Drawings

METHODS FOR TREATING GASTROESOPHAGEAL REFLUX DISEASE

CROSS REFERENCES TO RELATED APPLICATIONS

This application claims priority to U.S. 60/424,199, filed Nov. 5, 2002, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to the discovery that agents capable of inhibiting the biological action of the glucocorticoid receptor can be used in methods for reducing, eliminating, or preventing gastroesophageal reflux disease in a subject.

BACKGROUND OF THE INVENTION

Gastroesophageal reflux disease (GERD) is a chronic, relapsing condition with associated morbidity and an adverse impact on quality of life. The disease is common, with an estimated lifetime prevalence of 25 to 35 percent in the U.S. population. Psychological well-being questionnaires indicate that patients with GERD can have a poor quality of life. Indeed, the combination of symptoms, dietary restrictions, and functional limitations take their toll on an individual's sense of well-being.

In addition to the poor quality of life experienced by GERD sufferers, annual health care costs related to this disease are high. Individuals who suffer from GERD are prone to complications such as severe esophagitis, recurrent esophageal strictures, severe pulmonary symptoms, and Barrett's esophagus, which carries with it an increased risk for the development of adenocarcinoma of the esophagus.

Antacids remain the drugs of choice for quick relief of symptoms associated with GERD. These agents act primarily by rapidly increasing the pH of the gastric refluxate. Although antacids are effective in relieving symptoms, they cannot be used as sole agents for achieving esophageal healing because of the high dosage requirements and consequent lack of patient compliance.

Over-the-Counter H_2-Receptor Blockers may also be prescribed for the treatment and prevention of GERD. These agents are indicated for the prevention and relief of heartburn, acid indigestion and sour stomach. They do not act as rapidly as antacids, but they provide longer relief of symptoms. Unfortunately, standard dosages of these agents do not completely inhibit acid secretion, and so do not typically promote esophageal healing.

Clearly, there is a need in the art for a safe and effective GERD treatment that will reduce and/or eliminate the causes and/or symptoms of GERD. The ideal treatment would also promote healing of damaged esophageal tissues, thereby reducing health cost associated with the disease. Fortunately, the current invention addresses these and other needs. The invention is based, at least in part, on the surprising discovery that glucocorticoid receptor antagonists are effective agents for the treatment of GERD.

Corticosteroids are steroid hormones released by the adrenal glands. The most significant human adrenal corticosteroids are cortisol, corticosterone and aldosterone. Corticosteroids produce cellular effects following binding to receptors located in the cytoplasm of the cell. Two general classes of corticosteroid receptors are now recognized, the mineralocorticoid receptors (also termed type I, or MR) and the glucocorticoid receptors (also termed type II, or GR).

Mineralocorticoid receptors (MRs) bind cortisol with ten-fold higher affinity than glucocorticoid receptors (GRs) bind glucocorticoids. Thus, the activation of the two classes of receptors may differ depending on the corticosteroid (cortisol) concentration. Blood levels of the glucocorticoid cortisol vary over a wide range during the day. In general, normal cortisol concentrations in the blood range from about 0.5 nM to about 50 nM; however, in response to stress, cortisol concentration may exceed 100 nM.

Glucocorticoid blockers are agents that block or reduce the effects of glucocorticoids. Such interference with glucocorticoid action may, for example, be due to interference with binding of glucocorticoid agonists to glucocorticoid receptors (GR), or to interference with the action of agonist-bound GR at the cell nucleus, or to interference with expression or processing of gene products induced by the action of agonist-bound GR at the nucleus. Glucocorticoid receptor antagonists (GR antagonists) are compounds which inhibit the effect of the native ligand or of glucocorticoid agonists on GR. One mode of action of GR antagonists is to inhibit the binding of GR ligands to GR. A discussion of glucocorticoid antagonists may be found in Agarwal et al. "Glucocorticoid antagonists", FEBS Lett., 217:221-226 (1987). An example of a GR antagonist is mifepristone, (11β,17β) 11[4(dimethylamino)phenyl]-17hydroxy-17(1 propynyl)estra-4,9dien-3one, also known as RU-486 or RU-38486. See U.S. Pat. No. 4,368,085. Mifepristone binds specifically to GR with an affinity about 18 times that of the affinity of cortisol for GR. GR antagonists may be steroids, such as mifepristone, or non-steroids.

The present inventors have determined for the first time that glucocorticoid receptor antagonists are effective agents for the treatment of gastroesophageal reflux disease. Thus, the present invention fulfills the need for an effective method for the treatment of gastroesophageal reflux disease by providing methods of administering glucocorticoid receptor antagonists to a subject.

BRIEF SUMMARY OF THE INVENTION

The present invention is based at least in part, upon the discovery that administration of a glucocorticoid receptor antagonist provides an effective and improved treatment for gastroesophageal reflux disease. Thus, in one aspect, the invention is directed toward methods of treating gastroesophageal reflux disease in a subject, provided that the subject is not otherwise in need of treatment with a glucocorticoid receptor antagonist.

In one aspect of the invention, the glucocorticoid receptor antagonist comprises a steroidal skeleton with at least one phenyl-containing moiety in the 11-beta position of the steroidal skeleton. In one aspect, the phenyl-containing moiety in the 11-beta position of the steroidal skeleton is a dimethylaminophenyl moiety. In another aspect, the glucocorticoid receptor antagonist is mifepristone.

In one aspect of the present invention, the glucocorticoid receptor antagonist is selected from the group consisting of 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9-estradien-3-one and 17β-hydroxy-17α-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one. In another aspect, the glucocorticoid receptor antagonist is selected from the group consisting 4α(S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol and 4α(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol.

In another one aspect, the glucocorticoid receptor antagonist is (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

In another aspect of the present invention, the glucocorticoid receptor antagonist is administered in a daily amount of between about 0.5 to about 35 mg per kilogram of body weight per day. In another aspect, the glucocorticoid receptor antagonist is administered in a daily amount of between about 5 to about 15 mg per kilogram of body weight per day.

In one aspect of the present invention, the administration is once per day. In yet another aspect, the mode of administration is by a transdermal application, by a nebulized suspension, or by an aerosol spray. In another aspect, the mode of administration is oral.

In another aspect the invention also provides a kit for treating gastroesophageal reflux disease in a subject. The kit comprises a specific glucocorticoid receptor antagonist and an instructional material teaching the indications, dosage and schedule of administration of the glucocorticoid receptor antagonist to a patient suffering from gastroesophageal reflux disease.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "gastroesophageal reflux disease" or "GERD" refers to a condition resulting from food or liquid traveling from the stomach back up into the esophagus. This partially digested material is usually acidic and can irritate the esophagus, often causing heartburn and other symptoms. GERD can be associated with a number of conditions, including, but not limited to incompetent esophageal sphincters, hiatal hernia, obesity, recurrent or persistent vomiting, previous esophageal surgery or esophageal stricture

The term "prophylactic" refers to an agent that acts to prevent disease, such as gastroesophageal reflux disease. In one aspect, a glucocorticoid receptor antagonist of the invention is administered prophylactically to prevent the onset or recurrence of gastroesophageal reflux disease.

The terms "treating", "treatment", "to treat" refer to means for reducing or eliminating gastroesophageal reflux disease and or the accompanying symptoms in a subject. Treatment refers to any indicia of success in reduction, elimination, or amelioration of gastroesophageal reflux, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms, or lessening of symptoms or making the condition more tolerable to the subject; rendering the refluxate harmless, improving esophageal clearance, protecting the esophageal mucosa; or improving a patient's physical or mental well-being. For example, success of treatment by methods of the invention could be measured by comparing the severity of gastroesophageal reflux and the nature of the refluxant in the year before treatment with anti-glucocorticoids of the invention was initiated, with the year following the initiation of treatment. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, or any other appropriate means known in the art.

The term "cortisol" refers to a family of compositions also referred to as hydrocortisone, and any synthetic or natural analogues thereof.

The term "glucocorticoid receptor" ("GR") refers to a family of intracellular receptors also referred to as the cortisol receptor, which specifically bind to cortisol and/or cortisol analogs. The term includes isoforms of GR, recombinant GR and mutated GR.

The term "mifepristone" refers to a family of compositions also referred to as RU486, or RU38.486, or 17-β-hydroxy-11-β-(4-dimethyl-aminophenyl)-17-α-(1-propynyl)-estra-4,9-dien-3-one), or 11-β-(4dimethylaminophenyl)-17-β-hydroxy-17-α-(1-propynyl)-estra-4,9-dien-3-one), or analogs thereof, which bind to the GR, typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to a GR receptor. Chemical names for RU-486 vary; for example, RU486 has also been termed: 11β-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one; 11β-(4-dimethyl-aminophenyl)-17β-hydroxy-17α-(prop-1-ynyl)-estra-4,9-dien-3-one; 17β-hydroxy-11β-(4-dimethylaminophenyl-1)-17α-(propynyl-1)-estra-4,9-diene-3-one; 17β-hydroxy-11β-(4-dimethylaminophenyl-1)-17α-(propynyl-1)-E; (11β,17β)-11-[4-dimethylamino)-phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; and 11β-[4-(N,N-dimethylamino)phenyl]-17α-(prop-1-ynyl)-D-4,9-estradiene-17β-ol-3-one.

The term "specific glucocorticoid receptor antagonist" refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist, such as cortisol, or cortisol analogs, synthetic or natural, to a GR. By "specific", we intend the drug to preferentially bind to the GR rather than the mineralocorticoid receptor (MR) with an affinity at least 100-fold, and frequently 1000-fold.

A subject "not otherwise in need of treatment with a glucocorticoid receptor antagonist" is an individual or patient who is not being treated with antiglucocorticoid compounds for any disorder accepted by the medical community to be effectively treatable with antiglucocorticoid compounds. Conditions known in the art and accepted by the medical community to be effectively treatable with glucocorticoid receptor antagonists include: Cushing's disease, drug withdrawal, dementia, stress disorders, anxiety disorders (U.S. Pat. No. 5,741,787), depression, psychotic major depression (U.S. Pat. No. 6,150,349), schizoaffective disorder, diabetes, rheumatoid arthritis, autoimmune disease, HIV infection, dermatitis, inflammation, fibromyalgia, central nervous system disease, neurodegeneration, neural injuries, pelvic pain, and various cancers.

I. Introduction

This invention pertains to the surprising discovery that agents that can inhibit glucocorticoid-induced biological responses are effective for treating gastroesophageal reflux disease. In treating gastroesophageal reflux disease, the methods of the invention can ameliorate, eliminate, reduce or prevent the symptoms of gastroesophageal reflux disease. In one embodiment, the methods of the invention use agents that act as GR antagonists, blocking the interaction of cortisol with GR, to treat gastroesophageal reflux disease. The methods of the invention are effective in treating gastroesophageal reflux disease in an afflicted patient.

Cortisol acts by binding to an intracellular, glucocorticoid receptor (GR). In humans, glucocorticoid receptors are present in two forms: a ligand-binding GR-alpha of 777 amino acids; and, a GR-beta isoform that differs in only the last fifteen amino acids. The two types of GR have high affinity for their specific ligands, and are considered to function through the same signal transduction pathways.

The biological effects of cortisol, including pathologies or dysfunctions caused by hypercortisolemia, can be modu-

lated and controlled at the GR level using receptor antagonists. Several different classes of agents are able to act as GR antagonists, i.e., to block the physiologic effects of GR-agonist binding (the natural agonist is cortisol). These antagonists include compositions, which, by binding to GR, block the ability of an agonist to effectively bind to and/or activate the GR. One family of known GR antagonists, mifepristone and related compounds, are effective and potent anti-glucocorticoid agents in humans (Bertagna, *J. Clin. Endocrinol. Metab.* 59:25, 1984). Mifepristone binds to the GR with high affinity, with a K of dissociation $<10^{-9}$ M (Cadepond, *Annu. Rev. Med.* 48:129, 1997). Thus, in one embodiment of the invention, mifepristone and related compounds are used to treat gastroesophageal reflux disease in a subject.

As the methods of the invention include use of any means to inhibit the biological effects of an agonist-bound GR, illustrative compounds and compositions which can be used to treat gastroesophageal reflux disease in a subject are also set forth. Routine procedures that can be used to identify further compounds and compositions able to block the biological response caused by a GR-agonist interaction for use in practicing the methods of the invention are also described. As the invention provides for administering these compounds and compositions as pharmaceuticals, routine means to determine GR antagonist drug regimens and formulations to practice the methods of the invention are set forth below.

II. Diagnosis of Gastroesophageal Reflux Disease in a Subject

Gastroesophageal reflux disease (GERD) is characterized by heartburn and regurgitation, which may also include dysphagia. The heartburn characteristic of GERD is most frequently described as a sub-sternal burning that occurs after meals and often worsens when lying down. Other symptoms that may be associated with GERD include, but are not limited to atypical chest pain, hoarseness, nausea, cough, odynophagia and asthma.

Diagnosis may be made from the presentation of the characteristic GERD symptoms alone, but sometimes further tests are needed to confirm the diagnosis of GERD. In cases wher further diagnosis is warranted, the further diagnosis is typically made by treating patients with medications that suppress the production of acid by the stomach. Acid suppressing medications include proton pump inhibitors such as Prilosec (omeprazole), Prevacid (lansoprazole), Aciphex (rabeprazole), Protonix (pantoprazole), and Nexium (esomeprazole), and histamine blockers such as Zantac (ranitidine), Tagamet (cimetidine), and Pepcid (famotidine). If the heartburn then is diminished to a large extent, a diagnosis of GERD may be confirmed.

In some cases further diagnostic measures may be carried out. For example, if doubts remain about the diagnosis the after the above tests are completed, or if complications are a concern. The gold standard for diagnosing GERD is esophageal acid testing.

Patients with the symptoms or complications of GERD have reflux of more acid, and the acid remains longer in the esophagus when compared to healthy individuals. Thus, diagnosis of GERD can be confirmed or extended by performing a 24-hour esophageal pH test. A pH monitor is placed in the esophagus above the lower esophageal sphincter, and the pH is recorded at regular intervals over a 24-hour test period. Combined with a diary of symptoms kept by the patient, this method permits GERD to be diagnosed and correlated with the lowering of esophageal pH that occurs with reflux.

A method for prolonged measurement (48 hours) of acid exposure in the esophagus may also be conducted. The method utilizes a small, wireless capsule that is attached to the esophagus just above the LES. The capsule measures the acid refluxing into the esophagus and transmits this information to a receiver that is worn at the waist. At the completion of the test, the information from the receiver is downloaded into a computer and analyzed. The capsule falls off of the esophagus after 3-5 days and is passed in the stool.

III. General Laboratory Procedures

When practicing the methods of the invention, a number of general laboratory tests can be used to assist in the diagnosis, progress and prognosis of the patient with gastroesophageal reflux disease, including monitoring of parameters such as blood cortisol, drug metabolism, brain structure and function and the like. These procedures can be helpful because all patients metabolize and react to drugs uniquely. In addition, such monitoring may be important because each GR antagonist has different pharmacokinetics. Different patients and disease conditions may require different dosage regimens and formulations. Such procedures and means to determine dosage regimens and formulations are well described in the scientific and patent literature. A few illustrative examples are set forth below.

a. Determining Blood Cortisol Levels

The invention may be practiced upon patients with apparently normal levels of blood cortisol. However, since the treatment for gastroesophageal reflux disease comprises administration of a glucocorticoid receptor antagonist, monitoring blood cortisol and determining baseline cortisol levels are useful laboratory tests to aid in the diagnosis, treatment and prognosis of a gastroesophageal reflux disease patient. A wide variety of laboratory tests exist that can be used to determine whether an individual is normal, hypo- or hypercortisolemic. Patients with gastroesophageal reflux disease typically have normal levels of cortisol that are often less than 25 μg/dl in the morning, and frequently about 15 μg/dl or less in the afternoon, although the values often fall at the high end of the normal range, which is generally considered to be 5-15 μg/dl in the afternoon.

Immunoassays such as radioimmunoassays are commonly used because they are accurate, easy to do and relatively cheap. Because levels of circulating cortisol are an indicator of adrenocortical function, a variety of stimulation and suppression tests, such as ACTH Stimulation, ACTH Reserve, or dexamethasone suppression (see, e.g., Greenwald, *Am. J. Psychiatry* 143:442-446, 1986), can also provide diagnostic, prognostic or other information to be used adjunctively in the methods of the invention.

One such assay available in kit form is the radioimmunoassay available as "Double Antibody Cortisol Kit" (Diagnostic Products Corporation, Los Angeles, Calif.), (*Acta Psychiatr. Scand.* 70:239-247, 1984). This test is a competitive radioimmunoassay in which ^{125}I-labeled cortisol competes with cortisol from an clinical sample for antibody sites. In this test, due to the specificity of the antibody and lack of any significant protein effect, serum and plasma samples require neither preextraction nor predilution. This assay is described in further detail in Example 2, below.

b. Determination of Blood/Urine Mifepristone Levels

Because a patient's metabolism, clearance rate, toxicity levels, etc. differs with variations in underlying primary or

secondary disease conditions, drug history, age, general medical condition and the like, it may be necessary to measure blood and urine levels of GR antagonist. Means for such monitoring are well described in the scientific and patent literature. As in one embodiment of the invention mifepristone is administered to treat gastroesophageal reflux disease, an illustrative example of determining blood and urine mifepristone levels is set forth in the Example below.

c. Other Laboratory Procedures

Laboratory tests monitoring and measuring GR antagonist metabolite generation, plasma concentrations and clearance rates, including urine concentration of antagonist and metabolites, may also be useful in practicing the methods of the invention. For example, mifepristone has two hydrophilic, N-monomethylated and N-dimethylated, metabolites. Plasma and urine concentrations of these metabolites (in addition to RU486) can be determined using, for example, thin layer chromatography, as described in Kawai *Pharmacol. and Experimental Therapeutics* 241:401-406, 1987.

IV. Glucocorticoid Receptor Antagonists to Treat Gastroesophageal Reflux Disease in a Subject

The invention provides for methods for treating gastroesophageal reflux disease in a subject utilizing any composition or compound that can block a biological response associated with the binding of cortisol or a cortisol analogue to a GR. Antagonists of GR activity utilized in the methods of the invention are well described in the scientific and patent literature. A few illustrative examples are set forth below.

A. Steroidal Anti-Glucocorticoids as GR Antagonists.

Steroidal glucocorticoid antagonists are administered to treat gastroesophageal reflux disease in various embodiments of the invention. Steroidal antiglucocorticoids can be obtained by modification of the basic structure of glucocorticoid agonists, i.e., varied forms of the steroid backbone. The structure of cortisol can be modified in a variety of ways. The two most commonly known classes of structural modifications of the cortisol steroid backbone to create glucocorticoid antagonists include modifications of the 11-beta hydroxy group and modification of the 17-beta side chain (see, e.g., Lefebvre, *J. Steroid Biochem.* 33:557-563, 1989).

Examples of steroidal GR antagonists include androgen-type steroid compounds as described in U.S. Pat. No. 5,929,058, and the compounds disclosed in U.S. Pat. Nos. 4,296,206; 4,386,085; 4,447,424; 4,477,445; 4,519,946; 4,540,686; 4,547,493; 4,634,695; 4,634,696; 4,753,932; 4,774,236; 4,808,710; 4,814,327; 4,829,060; 4,861,763; 4,912,097; 4,921,638; 4,943,566; 4,954,490; 4,978,657; 5,006,518; 5,043,332; 5,064,822; 5,073,548; 5,089,488; 5,089,635; 5,093,507; 5,095,010; 5,095,129; 5,132,299; 5,166,146; 5,166,199; 5,173,405; 5,276,023; 5,380,839; 5,348,729; 5,426,102; 5,439,913; 5,616,458, 5,696,127, and 6,303,591. Such steroidal GR antagonists include cortexolone, dexamethasone-oxetanone, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9-estradien-3-one (RU009), and 17β-hydroxy-17α-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one (RU044).

Other examples of steroidal antiglucocorticoids are disclosed in Van Kampen et al. (2002) Eur. J. Pharmacol. 457(2-3):207, WO 03/043640, EP 0 683 172 B1, and EP 0 763 541 B1, each of which is incorporated herein by reference. EP 0 763 541 B1 and Hoyberg et al., *Int'l J. of Neuro-psychopharmacology,* 5:Supp. 1, S148 (2002); disclose the compound (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (ORG 34517) which in one embodiment, is administered in an amount effective to treat gastroesophageal reflux disease in a subject.

1. Removal or Substitution of the 11-beta Hydroxy Group

Glucocorticoid antagonists with modified steroidal backbones comprising removal or substitution of the 11-beta hydroxy group are administered in one embodiment of the invention. This class includes natural antiglucocorticoids, including cortexolone, progesterone and testosterone derivatives, and synthetic compositions, such as mifepristone (Lefebvre, et al. supra). Preferred embodiments of the invention include all 11-beta-aryl steroid backbone derivatives because these compounds are devoid of progesterone receptor (PR) binding activity (Agarwal, FEBS 217:221-226, 1987). Another preferred embodiment comprises an 11-beta phenyl-aminodimethyl steroid backbone derivative, i.e., mifepristone, which is both an effective anti-glucocorticoid and anti-progesterone agent. These compositions act as reversibly-binding steroid receptor antagonists. For example, when bound to a 11-beta phenyl-aminodimethyl steroid, the steroid receptor is maintained in a conformation that cannot bind its natural ligand, such as cortisol in the case of GR (Cadepond, 1997, supra).

Synthetic 11-beta phenyl-aminodimethyl steroids include mifepristone, also known as RU486, or 17-beta-hydrox-11-beta-(4-dimethyl-aminophenyl)17-alpha-(1-propynyl)estra-4,9-dien-3-one). Mifepristone has been shown to be a powerful antagonist of both the progesterone and glucocorticoid (GR) receptors. Another 11-beta phenyl-aminodimethyl steroids shown to have GR antagonist effects includes RU009 (RU39.009), 11-beta-(4-dimethyl-aminoethoxyphenyl)-17-alpha-(propynyl-17-beta-hydroxy-4,9-estradien-3-one) (see Bocquel, J. Steroid Biochem. Molec. Biol. 45:205-215, 1993). Another GR antagonist related to RU486 is RU044 (RU43.044) 17-beta-hydrox-17-alpha-19-(4-methyl-phenyl)-androsta-4,9(11)-dien-3-one) (Bocquel, 1993, supra). See also Teutsch, Steroids 38:651-665, 1981; U.S. Pat. Nos. 4,386,085 and 4,912,097.

One embodiment includes compositions containing the basic glucocorticoid steroid structure which are irreversible anti-glucocorticoids. Such compounds include alpha-keto-methanesulfonate derivatives of cortisol, including cortisol-21-mesylate (4-pregnene-11-beta, 17-alpha, 21-triol-3, 20-dione-21-methane-sulfonate and dexamethasone-21-mesylate (16-methyl-9alpha-fluoro-1,4-pregnadiene-11 beta, 17-alpha, 21-triol-3, 20-dione-21-methane-sulfonte). See Simons, *J. Steroid Biochem.* 24:25-32, 1986; Mercier, *J. Steroid Biochem.* 25:11-20, 1986; U.S. Pat. No. 4,296,206.

2. Modification of the 17-beta Side Chain Group

Steroidal antiglucocorticoids which can be obtained by various structural modifications of the 17-beta side chain are also used in the methods of the invention. This class includes synthetic antiglucocorticoids such as dexamethasone-oxetanone, various 17, 21-acetonide derivatives and 17-beta-carboxamide derivatives of dexamethasone (Lefebvre, 1989, supra; Rousseau, *Nature* 279:158-160, 1979).

3. Other Steroid Backbone Modifications

GR antagonists used in the various embodiments of the invention include any steroid backbone modification which effects a biological response resulting from a GR-agonist interaction. Steroid backbone antagonists can be any natural or synthetic variation of cortisol, such as adrenal steroids missing the C-19 methyl group, such as 19-nordeoxycorticosterone and 19-norprogesterone (Wynne, Endocrinology 107:1278-1280, 1980).

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