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(54) METHODS FOR TREATING DELIRIUM GLUCOCORTICOID RECEPTOR- SPECIFIC ANTAGONISTS

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(57) **ABSTRACT**

This invention generally pertains to the field of psychiatry. In particular, this invention pertains to the discovery that agents which inhibit the binding of cortisol to its receptors can be used in methods for treating delirium. Mifepristone, a potent specific glucocorticoid receptor antagonist, can be used in these methods. The invention also provides a kit for treating delirium in a human including a glucocorticoid receptor antagonist and instructional material teaching the indications, dosage and schedule of administration of the glucocorticoid receptor antagonist.

METHODS FOR TREATING DELIRIUM GLUCOCORTICOID RECEPTOR- SPECIFIC ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of provisional application No. 60/288,619, filed May 4, 2001.

FIELD OF THE INVENTION

[0002] This invention generally pertains to the field of psychiatry. In particular, this invention pertains to the discovery that agents that inhibit the binding of cortisol to the glucocorticoid receptor can be used in methods of treating delirium.

INTRODUCTION

[0003] Delirium is a disturbance in consciousness that typically results from an underlying physical condition. Patients suffering from delirium display changes in cognition (such as memory deficits, disorientation, and language or perceptual disturbances) that develop over a short period of time and tend to fluctuate during the course of the day.

[0004] The neurophysiological causes of delirium are not known in detail. The predominant neurochemical hypothesis for the origin of delirium focuses on underactivity of cholinergic neurotransmission in particular domains of the brain (see Trzepacz, *Dement Geriatr Cogn Disord* 10:330-334 (1999)). However, abnormalities in other neurotransmitters—such as serotonin, dopamine, gamma-aminobutryic acid, and glutamate—may also be involved in the development of delirium under particular conditions (see Flacker & Lipsitz, *J Gerontol A Biol Sci Med Sci* 54:B239-46 (1999)).

[0005] Cortisol, a glucocorticoid hormone secreted in response to ACTH (corticotropin), shows circadian rhythm variation, and further, is an important element in responsiveness to many physical and psychological stresses. It has been proposed that, with age, the cortisol regulatory system becomes hyperactivated in some individuals, resulting in hypercortisolemia. It has additionally been postulated that high levels of cortisol are neurotoxic, particularly in the hippocampus, a brain structure that is thought to be central to the processing and temporary storage of complex information and memory (see, e.g., Sapolsky et al., *Ann. NY Acad. Sci.* 746:294-304, 1994; Silva, *Annu. Rev. Genet.* 31:527-546, 1997; de Leon et al., *J. Clin. Endocrinol & Metab.* 82:3251, 1997).

[0006] The brain and CNS actions of cortisol and other glucocorticoids are not limited to neurotoxicity, however. In addition to influencing cerebral blood flow, oxygen consumption, and cerebral excitability, glucocorticoids have extensive effects on neurotransmitter function (see DeKloet et al., *Handbook Neurochem* 8:47-91 (1985)). These effects include inhibition of binding to central muscarinic cholinergic receptors, as well as modulation of serotonin turnover, hypothalamic dopamine balance, and suppression of beta-endorphin levels in the brain. The ability of glucocorticoids to perturb neurotransmitters involved in the pathogenesis of delirium suggests that disturbance of glucocorticoid regulation might play a role in delirium. However, while pathologically elevated glucocorticoid levels (due to adrenal dysfunction or ingestion of synthetic hormones) have been connected with the induction of delirium (see Stroudemire et al., *Gen Hosp Psychiatry* 18:196-202 (1996)), the relationship between physiological glucocorticoid levels and delirium remains unclear (for review see Flacker & Lipsitz, *J Gerontol A Biol Sci Med Sci* 54:B23946 (1999)). Assessments of hypothalamic-pituitary-adrenal axis function in delirious patients by dexamethasone-suppression testing have been conflicting (see Koponen et al., *Nord Psykiatr Tidsskr* 43:203-207 (1987); McKeith, *Br J Psychiatry* 145:389-393 (1984); O'Keefe & Devline, *Neuropsychobiology* 30:153-156 (1994)). Furthermore, while some studies measuring glucocorticoid levels directly have found an association between delirium and persistent hypercortisolism (Gustafson et al., *Cerebrovasc Dis* 3:33-38 (1993)), other studies have failed to link the incidence of delirium with elevated cortisol levels (van der Mast et al., in Filippini ed., *Recent Advances in Tryptophan Research*, New York: Plenum Press, 93-96 (1996); McIntosh et al., *Psychoneuroendocrinology* 10:303-313 (1985)).

[0007] There has been no evidence prior to this invention, however, that a glucocorticoid receptor antagonist can be an effective treatment for delirium, especially in patients having cortisol levels that fall within a normal range. Many of the actions of cortisol are mediated by binding to the type I (mineralocorticoid) receptor, which is preferentially occupied, relative to the type II (glucocorticoid) receptor, at physiological cortisol levels. As cortisol levels increase, more glucocorticoid receptors are occupied and activated. Because cortisol plays an essential role in metabolism, inhibition of all cortisolmediated activities, however, would be fatal. Therefore, antagonists that specifically prevent type II glucocorticoid receptor functions, but do not antagonize type I mineralocorticoid receptor functions are of particular use in this invention. Mifepristone (RU486) and similar antagonists are examples of this category of receptor antagonists.

[0008] The present inventors have determined that glucocorticoid receptor antagonists such as RU486 are effective agents for the specific treatment of delirium in patients with normal or decreased cortisol levels. The present invention therefore fulfills the need for an effective treatment for the symptoms of delirium by providing methods of administering glucocorticoid receptor antagonists to treat patients diagnosed with delirium.

SUMMARY OF THE INVENTION

[0009] The invention provides a method of ameliorating the symptoms of delirium in a patient who has normal or decreased cortisol levels. The method comprises administration of a therapeutically effective amount of a glucocorticoid receptor antagonist to the patient.

[0010] In one embodiment of the invention, the method of treating delirium uses a glucocorticoid receptor antagonist comprising a steroidal skeleton with at least one phenyl-containing moiety in the 11-beta position of the steroidal skeleton. The phenyl-containing moiety in the 11-beta position of the steroidal skeleton can be a dimethylaminophenyl moiety. In alternative embodiments, the glucocorticoid receptor antagonist comprises mifepristone, or, the glucocorticoid receptor antagonist is selected from the group consisting of RU009 and RU044.

[0011] In other embodiments, the glucocorticoid receptor antagonist is administered in a daily amount of between about 0.5 to about 20 mg per kilogram of body weight per day; between about 1 to about 10 mg per kilogram of body weight per day; or between about 1 to about 4 mg per kilogram of body weight per day. The administration can be once per day. In alternative embodiments, the mode of glucocorticoid receptor antagonist administration is oral, or by a transdermal application, by a nebulized suspension, or by an aerosol spray.

[0012] The invention also provides a kit for the treatment of delirium in a human, the kit comprising a glucocorticoid receptor antagonist; and, an instructional material teaching the indications, dosage and schedule of administration of the glucocorticoid receptor antagonist. In alternative embodiments, the instructional material indicates that the glucocorticoid receptor antagonist can be administered in a daily amount of about 0.5 to about 20 mg per kilogram of body weight per day, of about 1 to about 10 mg per kilogram of body weight per day, or about 1 to about 4 mg per kilogram of body weight per day. The instructional material can indicate that cortisol contributes to delirium symptoms in patients with delirium, and that the glucocorticoid receptor antagonist can be used to treat delirium. In one embodiment, the glucocorticoid receptor antagonist in the kit is mifepristone. The mifepristone can in tablet form.

[0013] A further understanding of the nature and advantages of the present invention is realized by reference to the remaining portions of the specification and claims.

[0014] All publications, patents and patent applications cited herein are hereby expressly incorporated by reference for all purposes.

DEFINITIONS

[0015] The term "treating" refers to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, the methods of the invention successfully treat a patient's delirium by decreasing the incidence of disturbances in consciousness or cognition.

[0016] The term "delirium" refers to a psychiatric condition in its broadest sense, as defined in American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, D.C., 2000 ("DSM-IV-TR"). The DSM-IV-TR defines "delirium" as a disturbance of consciousness, developing over a short period of time, accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing delirium.

[0017] The term "cortisol" refers to a family of compositions also referred to as hydrocortisone, and any synthetic or natural analogues thereof.

[0018] 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.

[0019] The term "mifepristone" refers to a family of compositions also referred to as RU486, or RU38.486, or 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or 11-beta-(4dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(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: 11B-[p-(Dimethylamino)phenyl]-17B-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one;/11B-(4-dimethyl-aminophenyl)-17B-hydroxy-17A-(prop-1-ynyl)-estra4,9-dien-3-one; 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1)-estra4,9-diene-17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1)-E; (11B,17B)-11-[4-dimethylamino)-phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; and 11B-[4-(N,N-dimethylamino)phenyl]-17A-(prop-1-ynyl)-D-4,9-estradiene-17B-ol-3-one.

[0020] 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. A "specific glucocorticoid receptor antagonist" also refers to any composition or compound which inhibits any biological response associated with the binding of a GR to an agonist. 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.

[0021] A patient "not otherwise in need of treatment with a glucocorticoid receptor antagonist" is a patient who is not suffering from a condition which is known in the art to be effectively treatable with glucocorticoid receptor antagonists. Conditions known in the art to be effectively treatable with glucocorticoid receptor antagonists include Cushing's disease, drug withdrawal, psychosis, dementia, stress disorders, and psychotic major depression.

DETAILED DESCRIPTION OF THE INVENTION

[0022] This invention pertains to the surprising discovery that agents that can inhibit glucocorticoid-induced biological responses are effective for treating delirium. In treating delirium, the methods of the invention can preferably relieve the symptoms of delirium or lead to complete resolution of the underlying disorder itself. In one embodiment, the methods of the invention use agents that act as GR antagonists, blocking the interaction of cortisol with GR, to treat or ameliorate delirium or symptoms associated with delirium. The methods of the invention are effective in ameliorating the symptoms of a delirium patient afflicted with either normal, increased or decreased levels of cortisol or other glucocorticoids, natural or synthetic.

[0023] 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 transduction pathways.

[0024] The biologic effects of cortisol, including pathologies or dysfunctions caused by hypercortisolemia, can be modulated 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 delirium.

[0025] Delirium typically manifests itself with a variety of symptoms, including memory impairment, disorientation, perceptual disturbances, disturbances in the sleep-wake cycle, and disturbed psychomotor behavior. Thus, a variety of means of diagnosing delirium and assessing the success of treatment, i.e., the success and extent the symptoms of delirium are lessened by the methods of the invention, can be used, and a few exemplary means are set forth herein. These means can include classical, subjective psychological evaluations and neuropsychiatric examinations as described below.

[0026] 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 delirium 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.

[0027] 1. Diagnosis of Delirium

[0028] Delirium is characterized by disturbances of consciousness and changes in cognition that develop over a relatively short period of time. The disturbance in consciousness is often manifested by a reduced clarity of awareness of the environment. The patient displays reduced ability to focus, sustain or shift attention (DSM-IV-TR diagnostic Criterion A). Accompanying the disturbance in consciousness, delirium patients display a disturbance in cognition (e.g., memory impairment, disorientation, language difficulties) or perceptual disturbances (e.g., misinterpretations, illusions, or hallucinations) (Criterion B). To be considered delirium, these disturbances in consciousness, cognition, or perception should develop over a short period of time and tend to fluctuate during the course of the day (Criterion C).

[0029] The glucocorticoid receptor antagonists of the present invention are effective in treating delirium arising from any of several possible etiologies. Delirium may arise from a number of general medical conditions, including central nervous system disorders (e.g., trauma, stroke, encephalopathies), metabolic disorders (e.g., renal or hepatic insufficiency, fluid or electrolyte imbalances), cardiopulmonary disorders (e.g., congestive heart failure, myocardial infarction, shock), and systemic illnesses or effects (e.g., infections, sensory deprivation, and postoperative states). Glucocorticoid receptor antagonists are also effective to treat Substance-Induced Delirium (e.g., delirium induced by substance intoxication or withdrawal, medication side effects, and toxin exposure). Delirium may arise from multiple simultaneous etiologies (e.g., a combination of a general medical condition and substance intoxication) and such delirium, as well as delirium of unknown or unclassified origin, may be treated with the glucocorticoid receptor antagonists of the present invention.

[0030] A diagnosis of delirium is distinct from a diagnosis of dementia or psychosis. Although memory impairment is common in both delirium and dementia, a patient with dementia alone is alert and usually does not display the disturbance in consciousness that is characteristic of delirium. Dementia patients typically lack the waxing and waning of symptoms over a 24-hour period that characterizes delirium. Likewise, while delusions, hallucinations and agitation may be a feature of both delirium and psychosis, psychotic patients suffer from a basic disturbance in thought content. In contrast, delirious patients primarily suffer from disturbances in perception and orientation, rather than internal thought content. Psychotic symptoms, if present, tend to be fragmented rather than systematic. Delirium is also distinguished from dementia, psychosis, stress disorders, and mood disorders by the characteristic waxing and waning of symptoms, by signature EEG abnormalities described herein, and by the presence of a precipitating factor such as a general medical condition or substance intoxication.

[0031] Delirium may be diagnosed and evaluated with any one of several objective, standardized test instruments known in the art, although skilled clinicians may readily diagnose delirium through unstructured clinical interactions. Standardized test instruments are constructed by experienced clinical researchers based on DSM diagnostic criteria, and are typically validated through statistical studies and comparisons of various patient populations. Generally, standardized instruments assess both manifest psychological or physiological symptoms as well as internal thought processes. The presence and severity of delirium may be determined by assessing disturbances in arousal, level of consciousness, cognitive function (e.g., memory, attention, orientation, disturbances in thinking) and psychomotor activity. Standardized test instruments for the diagnosis of delirium are usually administered by a professional health care practitioner, and may comprise interactive examination as well as observation of patient behavior.

[0032] Standardized test instruments for assessing delirium include the Delirium Rating Scale (for review see Trzepacz, *Psychosomatics* 40:193-204 (1999)), the Memorial Delirium Assessment Scale (Breitbart et al., *J Pain Symptom Manage* 13:128-137 (1997)), the Delirium Severity Scale (Bettin et al., *Am J Geriatr Psychiatry* 6:296-307 (1998)), and the Delirium Symptom Interview (Albert et al., *J Geriatr Psychiatry Neurol* 5:14-21 (1992)). Cutoff scores yielding the most statistically valid division of patients into delirium and non-delirium populations are calculated based

on optimal positive and negative predictive power, and have been established and reported for each test (e.g., a score of 13 or greater on the Memorial Delirium Assessment Scale or a score of 10 or greater on the Delirium Rating Scale) and may be used to select patients for therapy.

[0033] Delirium may also be diagnosed and rated by the use of electroencephalography (EEG) (for review see Jacobson & Jerrier, *Semin Clin Neuropsychiatry*, 5:86-92 (2000)). Electroencephalograms of delirium patients are marked by a characteristic slowing or dropout of the posterior dominant rhythm, generalized theta or delta slow-wave activity, poor organization of the background rhythm, and loss of reactivity of the EEG to eye opening and closing. Delirium patients may also be diagnosed by quantitative EEG (QEEG), in which they display increased absolute and relative slow-wave (theta and delta) power, reduced ratio of fast-to-slow band power, reduced mean frequency, and reduced occipital peak frequency. Accordingly, EEG or QEEG may be used to select patients for treatment with glucocorticoid receptor antagonists, or to monitor the effectiveness of glucocorticoid receptor antagonist therapy.

[0034] 2. General Laboratory Procedures

[0035] 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 delirium, 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.

[0036] a. Determining Blood Cortisol Levels

[0037] Varying levels of blood cortisol have been associated with delirium, although the invention may also be practiced upon patients with apparently normal levels of blood cortisol. Thus, monitoring blood cortisol and determining baseline cortisol levels are useful laboratory tests to aid in the diagnosis, treatment and prognosis of a delirium patient. A wide variety of laboratory tests exist that can be used to determine whether an individual is normal, hypo- or hypercortisolemic. Delirium patients 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.

[0038] 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* 143:442446, 1986), can also provide diagnostic, prognostic or other information to be used adjunctively in the methods of the invention.

[0039] 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.

[0040] b. Determination of Blood/Urine Mifepristone Levels

[0041] 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 delirium, an illustrative example of determining blood and urine mifepristone levels is set forth in the Example below.

[0042] c. Other Laboratory Procedures

[0043] Because the presentation of delirium may be complex, a number of additional laboratory tests can be used adjunctively in the methods of the invention to assist in diagnosis, treatment efficacy, prognosis, toxicity and the like. For example, as increased hypercortisolemia has also been associated with delirium, diagnosis and treatment assessment can be augmented by monitoring and measuring glucocorticoid-sensitive variables, including but limited to fasting blood sugar, blood sugar after oral glucose administration, plasma concentrations thyroid stimulating hormone (TSH), corticosteroid-binding globulin, luteinizing hormone (LH), testosterone-estradiol-binding globulin, and/or total and free testosterone.

[0044] 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.

[0045] 3. Glucocorticoid Receptor Antagonists to Treat Delirium

[0046] The invention provides for methods of treating delirium 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.

[0047] a. Steroidal Anti-Glucocorticoids as GR Antagonists.

[0048] Steroidal glucocorticoid antagonists are administered for the treatment of delirium in various embodiments of the invention. Steroidal antiglucocorticoids can be

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