PATENT APPLICATION

OPTIMIZING MIFEPRISTONE LEVELS FOR CUSHING'S PATIENTS

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Entity: Small

OPTIMIZING MIFEPRISTONE LEVELS FOR CUSHING'S PATIENTS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/150,757, filed April 21, 2015, which is incorporated in its entirety herein for all purposes.

BACKGROUND OF THE INVENTION

[0002] It has been reported previously that administration of the same dose of mifepristone can produce widely varying blood serum levels in different patients. The varied blood serum levels can result in some patients not receiving an efficacious dose of mifepristone. For patients suffering from a mental disorder, the blood serum levels need to be maintained at about 1300 ng/mL. For patients suffering from Cushing's syndrome, it was surprisingly discovered that blood serum levels need to be maintained at a level of at least about 1631 ng/mL for a therapeutic response. Thus, a method for ensuring that the blood serum levels of mifepristone remain in an efficacious and safe range is needed for patients suffering from Cushing's syndrome.

BRIEF SUMMARY OF THE INVENTION

[0003] In one embodiment, the present invention provides a method for improving efficacy of mifepristone treatment in a patient suffering from Cushing's syndrome. The method includes treating the patient with seven or more daily doses of mifepristone over a period of seven or more days; testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1631 ng/mL; and adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1631 ng/mL. The patient of the present invention is not already suffering from a condition indicated for treatment with mifepristone. Thus, the method thereby improves the efficacy of mifepristone treatment for patients suffering from Cushing's syndrome for the patient suffering from Cushing's syndrome.

DETAILED DESCRIPTION OF THE INVENTION

I. INTRODUCTION

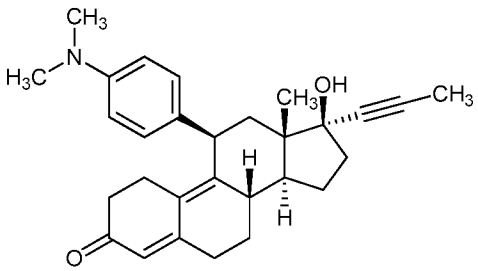
[0004] Administration of the same dose of mifepristone can produce widely varying mifepristone blood serum levels in different patients. For the same dose, the blood serum levels can differ by as much as 800% from one patient to another. For those patients with lower blood serum levels, the effectiveness of mifepristone treatment can suffer significantly. The present invention provides a method for optimizing the blood serum levels of mifepristone so that the blood serum levels remain in an efficacious range and the patient receives the necessary treatment.

[0005] The method of the present invention optimizes blood serum levels of mifepristone in a patient suffering from Cushing's syndrome by first treating the patient with mifepristone. The treatment can be for any appropriate period of time, such as seven or more daily doses over a period of seven or more days. Following treatment for an appropriate period of time, the serum levels of the patient are tested to determine whether the blood levels of mifepristone are greater than 1631 ng/mL. The daily dose of the patient is then adjusted in order to achieve mifepristone blood levels of greater than 1631 ng/mL.

[0006] Previous methods of optimizing mifepristone levels are known for patients suffering from mental disorders. But the earlier methods describe a minimum mifepristone blood level of only 1300 ng/mL. While patients with Cushing's syndrome are known to have higher cortisol levels, it is surprising that higher mifepristone blood level of 1631 ng/mL would be necessary to achieve optimal efficacy in treating Cushing's syndrome.

II. DEFINITIONS

[0007] "Mifepristone" refers to a compound having the following structure:



[0008] The term mifepristone also refers to a family of compositions also known as: RU486 or RU38.486; 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one); 11-beta-(4dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(1-propynyl)-estra-4,9-dien-3-one); 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)-estra-4,9-dien-3-one; 17B-hydroxy-11B- (4-dimethylaminophenyl-1)-17A-(propynyl-1)-estra-4,9-diene-3-one; 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. Salts, hydrates and prodrug forms of mifepristone are also useful in the formulations of the present invention.

[0009] Mifepristone and its analogs bind to the glucocorticoid receptor (GR), typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to the GR. As such, mifepristone has been used to treat conditions associated with elevated cortisol levels including, for example, hyperadrenocorticism, also known as Cushing's syndrome (Chrousos, pp 273-284, In: Baulieu, ed. *The Antiprogestin Steroid RU 486 and Human Fertility Control. Plenum Press*, New York (1989), Sartor (1996) *Clin. Obstetrics and Gynecol.* **39**:506-510). Patients with some forms of psychiatric illnesses can be responsive to treatments which block the effect of cortisol, as by administering GR antagonists (Van Look (1995) *Human Reproduction Update* **1**:19-34). In one study, a patient with depression associated with Cushing's Syndrome was responsive to a high dose, up to 1400 mg per day, of mifepristone (Nieman (1985) *J. Clin Endocrinol. Metab.* **61**:536). Due to its antiprogestogenic activity, mifepristone has also been employed in emergency contraception, medical abortion, and treatment of uterine fibroids and meningioma (Healy (2009) *Australian Prescriber* **32**:152-154).

[0010] "Patient" refers to animals such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. The patient can have a condition known to be treated by glucocorticoid antagonists such as mifepristone. Such conditions include, but are not limited to, psychiatric illnesses and hormonal disorders. In certain embodiments, the patient is a human. The patient can be male or female.

[0011] "Cushing's syndrome" refers to an endocrine disease with an estimated incidence of approximately 10-15 per 1 million persons (Meier and Biller (1997) *Endocrinol Metab Clin North Am* **26**:741-762), and is associated with an increased blood concentration of cortisol (hypercortisolism) over a long period of time. Cushing's syndrome is classified as either ACTH dependent or non ACTH dependent. ACTH dependent Cushing's syndrome is characterized by a chronic ACTH hypersecretion which stimulates the growth of the adrenal glands and the hypersecretion of corticosteroids. The most common underlying cause of ACTH dependent Cushing's syndrome is excessive production of ACTH by pituitary adenomas known as Cushing's disease. Cushing's syndrome resulting from the production of ACTH in another location than the pituitary gland is known as ectopic Cushing's syndrome. Examples of ectopic sites include thymoma, medullary carcinoma of the thyroid, pheochromocytoma, islet cell tumors of the pancreas and small cell carcinoma of the lung. ACTH independent Cushing's syndromes are caused by adrenal tumors that can be either adenomas or carcinomas. Both adrenal adenomas and carcinomas are characterized by chronic cortisol hypersecretion.

[0012] "Optimizing" refers to the process of testing mifepristone blood levels and adjusting the dosage of mifepristone administered to the patient in need in order to achieve mifepristone blood levels above 1631 ng/mL.

[0013] "Treat", "treating" and "treatment" collectively refer 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; or, in some situations, preventing the onset of dementia. 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.

[0014] "Testing" refers to determining the mifepristone blood levels in a patient. The testing can be performed by any suitable instrument, such as a plasma sampling collection device capable of detecting mifepristone serum levels.

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