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(54) **CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS**

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A61K 31/496	(2006.01)
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See application file for complete search history.

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(57) **ABSTRACT**

Applicant provides methods of treating diseases including Cushing's syndrome and hormone-sensitive cancers by concomitant administration of a glucocorticoid receptor antagonist (GRA) and steroidogenesis inhibitors, and by concomitant administration of a GRA and CYP3A inhibitors. Applicant provides methods of treating diseases including Cushing's syndrome and hormone-sensitive cancers by concomitant administration of mifepristone and ketoconazole. Subjects treated with CYP3A inhibitors or steroidogenesis inhibitors may suffer from toxicity or other serious adverse reactions; concomitant administration of other drugs would be expected to increase the risk of such toxicity and adverse reactions. Applicant has surprisingly found that GRAs may be administered to subjects receiving CYP3A inhibitors or steroidogenesis inhibitors such as ketoconazole without increasing risk adverse reactions; for example, Applicant has found that mifepristone may be concomitantly administered with ketoconazole (a CYP3A inhibitor and a steroidogenesis inhibitor), providing safe concomitant administration of the GRA and ketoconazole. In embodiments, the GRA dose may be reduced.

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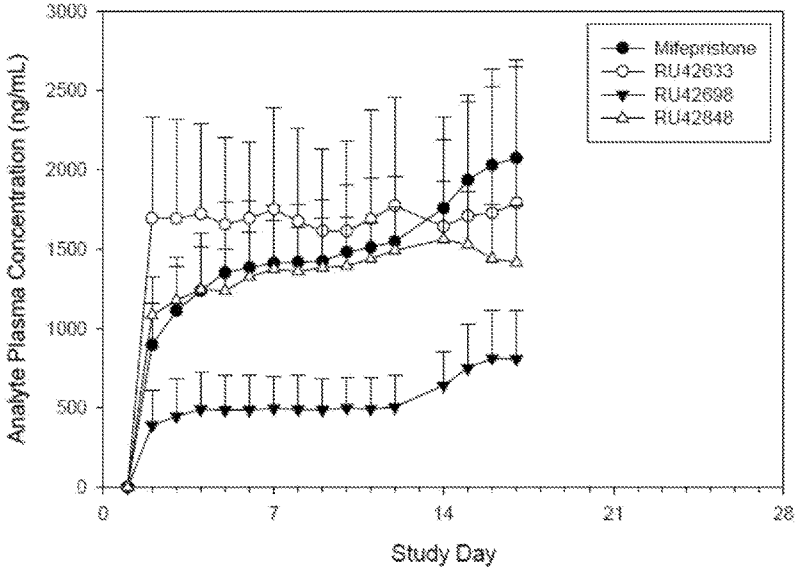

FIG. 1

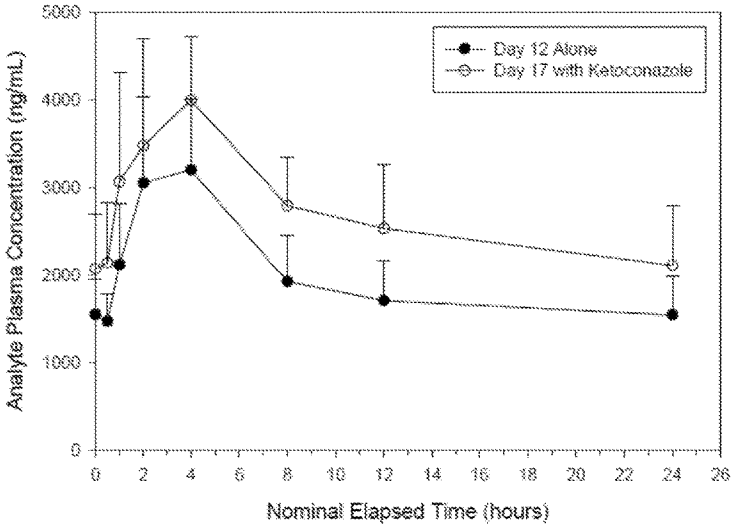

FIG. 2

CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of, and priority to, U.S. Provisional Application Ser. No. 62/465,772, filed Mar. 1, 2017, and U.S. Provisional Application Ser. No. 62/466,867, filed Mar. 3, 2017, the entire contents of both of which applications are hereby incorporated by reference in their entireties.

BACKGROUND

Steroid molecules, such as steroid hormones, play an important role in bodily functions and in bodily responses to infectious and other diseases, and to the environment. Many steroid molecules are synthesized in the body, or are produced from molecules consumed in the diet. Steroid molecules which act as hormones in the body include estrogen, progesterone, testosterone, and cortisol. Some steroid molecules have medicinal effects. Inhibition of steroid synthesis or metabolism can be useful in the treatment of some disorders.

Cortisol, a steroid molecule, plays an important role in many bodily functions. Cortisol exerts effects by binding to cortisol receptors, which are present in most tissues in the body. However, dysregulation of cortisol may have adverse effects on a subject. For example, Cushing's syndrome, caused by excess levels of cortisol, is characterized by symptoms including elevated blood pressure, elevated blood glucose, increased weight, increased mid-section perimeter, other pre-diabetic symptom, a "moon-face" facial appearance, immune suppression, thin skin, acne, depression, hirsutism, and other symptoms. Clinical manifestations of Cushing's syndrome include abnormalities in glucose control, requirement for anti-diabetic medication, abnormalities in insulin level, abnormal psychiatric symptoms, cushingoid appearance, acne, hirsutism, and increased or excessive body weight, and other symptoms.

One effective treatment of cortisol dysregulation is to block the binding of cortisol to cortisol receptors, or to block the effect of cortisol binding to cortisol receptors. Mifepristone binds to cortisol receptors, and acts to block such binding and to block the effect of cortisol on tissues. Mifepristone is 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4,9-dien-3-one).

Another effective treatment of cortisol dysregulation is to reduce the synthesis of cortisol, e.g., by reducing or blocking steroid synthesis. A "steroidogenesis inhibitor" is a compound which reduces or blocks the synthesis of steroid molecules (including, e.g., cortisol) when administered to a subject. Steroidogenesis inhibitors include, for example, ketoconazole, metyrapone, etomidate, and other drugs.

Many enzymes are involved in steroid synthesis and in steroid metabolism, including cytochrome P450 enzymes, encoded by CYP genes. Inhibiting steroid synthesis may lower the levels of steroids, including, e.g., cortisol, in the blood. For example, CYP3A enzymes play important roles in the synthesis of steroid hormones such as cortisol.

However, many drugs inhibit the levels or actions of CYP3A gene products (termed "inhibit CYP3A"). The following drugs inhibit CYP3A: ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole, among many drugs which inhibit CYP3A. For example, the following drugs strongly inhibit CYP3A (i.e., increase AUC (area under the concentration-time curve) by 10-fold or greater of sensitive index substrates), either alone or in combination with other drugs: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir, ritonavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, saquinavir, telaprevir, tipranavir, troleandomycin, and voriconazole.

Ketoconazole is an exemplary and an important steroidogenesis inhibitor and is a strong CYP3A inhibitor. Ketoconazole (chemical name: 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl] methoxy]phenyl]piperazine) is administered for the treatment of fungal infections; it also affects steroid metabolism by inhibiting steroidogenesis, and has anti-glucocorticoid and anti-androgen effects due to its interference with enzymatic conversion of cholesterol to hormones such as cortisol and testosterone. Ketoconazole has effects on liver enzymes and the gastrointestinal (GI) tract, among other effects (Fleseriu and Castinetti, *Pituitary* 19:643-653 (2016)).

Ketoconazole inhibits steroid synthesis and is thus useful in the treatment Cushing's syndrome; in the treatment of prostate cancer and other androgen-sensitive cancers; to reduce estrogen or progesterone production (e.g., in patients with hormone-sensitive cancers such as breast cancer and ovarian cancer); and in other treatments.

A drug such as ketoconazole is typically metabolized and excreted by a subject over time following administration. An effective dose is determined based on the expected amounts of metabolism and excretion of the drug. Changes in the amounts or rates of metabolism and/or excretion of a drug will affect the dose required, and may make an otherwise safe dose, if metabolism or excretion changes, into either a less, or ineffective dose, or a more effective or even toxic dose.

However, although sometimes clinically useful, ketoconazole may have adverse, including seriously toxic, effects (Fleseriu and Castinetti, *Pituitary* 19:643-653 (2016)). The U.S. Food and Drug Administration issued a Drug Safety Communication (Jul. 26, 2013 Safety Announcement regarding Nizoral® (ketoconazole)) warning of potentially fatal liver damage associated with oral ketoconazole treatment and warning of the risk of adrenal insufficiency, also a potentially fatal disorder. The Safety Announcement warned: "Nizoral tablets can cause liver injury, which may potentially result in liver transplantation or death." The Safety Announcement further stated: "Nizoral tablets may interact with other drugs a patient is taking and can result in serious and potentially life-threatening outcomes, such as heart rhythm problems." Thus, ketoconazole can be quite toxic if administered in excessive amounts, or if it is administered to sensitive individuals, particularly when administered systemically (as opposed, e.g., to topically). This toxicity can lead to liver damage (sometimes requiring liver transplantation). Other CYP3A inhibitors, including, e.g., itraconazole, ritonavir, and other CYP3A inhibitors as discussed herein, may have similar effects and may require similar warnings.

The simultaneous, or nearly simultaneous (e.g., concomitant) presence of two drugs in a subject may alter the effects

dose of a drug is often strongly affected by taking the amount and rate of its degradation in, and elimination from, the body (e.g., by liver or kidney action). However, the presence of a second drug in the body, which is also being acted upon by the liver and kidney, can have significant effects on the amount and rate of degradation of the first drug, and can increase the amount of the first drug that remains in the body at a given time beyond the amount that would have been present at that time in the absence of the second drug. Thus, the presence of a second drug can often increase the effective dose of the first drug. Where the first drug has toxic side effects, such an increase in effective dose of the first drug may lead to dangerous toxicity that would not have been expected were the second drug not present.

Concomitant administration of different drugs often leads to adverse effects since the metabolism and/or excretion of each drug may reduce or interfere with the metabolism and/or excretion of the other drug(s), thus increasing the effective concentrations of those drugs as compared to the effective concentrations of those drugs when administered alone. Thus, concomitant administration of drugs is often expected to increase the risk of toxic effects of one or both of the co-administered drugs. Some drugs, such as ketoconazole, present risk of liver damage (including severe cases including liver failure and even requiring liver transplants) and other toxic effects when administered alone; the risk of such toxic effects is believed to be increased when other drugs are concomitantly administered. Where a drug, such as ketoconazole, is known to present a high risk of toxic effects, clinicians will typically avoid its concomitant administration with other drugs.

However, patients often require treatment with multiple drugs, so that the potential toxicity of drugs such as ketoconazole present disadvantages that can have deleterious consequences for the patient who requires ketoconazole treatment, or may require foregoing the use of ketoconazole or of some other drug which may have otherwise been required for successful treatment.

Accordingly, improved methods of treatment allowing the administration of other drugs along with CYP3A inhibitors (such as, e.g., ketoconazole) and along with steroidogenesis inhibitors (such as, e.g., ketoconazole) are desired.

SUMMARY

Applicant discloses herein that CYP3A inhibitors such as, e.g., ketoconazole, may be concomitantly administered with glucocorticoid receptor modulators (GRMs) such as the GR antagonik (GRA) mifepristone. Such concomitant administration of a CYP3A inhibitor such as ketoconazole and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow the reduction in the amount of a GRM, or of a CYP3A inhibitor, administered to the subject; such reduction may reduce the risk of toxic effects of the CYP3A inhibitor concomitantly administered with the GRM. In embodiments, the CYP3A inhibitor is a strong CYP3A inhibitor. Such concomitant administration of a CYP3A inhibitor such as ketoconazole and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, may allow the reduction in the amount of GRM administered to the subject, and may allow the reduction in the amount of a CYP3A inhibitor administered to the subject;

Applicant discloses herein that steroidogenesis inhibitors may be concomitantly administered with glucocorticoid receptor modulators (GRMs) such as the GR antagonist (GRA) mifepristone. Such concomitant administration of a steroidogenesis inhibitor and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow concomitant administration of a GRA and a steroidogenesis inhibitor, may allow the reduction of the amount of GRM administered to the subject, or may allow the reduction in the amount of a steroidogenesis inhibitor administered to the subject; such reductions may reduce the risk of toxic effects of the steroidogenesis inhibitor. Such concomitant administration of a steroidogenesis inhibitor and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow the reduction in the amount of GRM or of a steroidogenesis inhibitor administered to the subject; such reduction may improve treatment of the subject and may reduce the risk of toxic effects of the steroidogenesis inhibitor.

For example, Applicant has surprisingly discovered that mifepristone may be administered to patients concomitantly receiving ketoconazole. For example ketoconazole may be administered to patients previously, or concomitantly, also receiving mifepristone so that the patient concomitantly receives ketoconazole and mifepristone. Such concomitant administration of ketoconazole and mifepristone is typically safe for the patient, provides the therapeutic benefits of both drugs to the patient, and may allow the reduction in the amount of mifepristone administered to the subject; such reduction may provide an effective dose of mifepristone that is a lower dose, yet still provides similar plasma mifepristone levels as, and may be as effective as, the dose of mifepristone administered in the absence of ketoconazole. Such concomitant administration of ketoconazole and mifepristone provides the therapeutic benefits of both drugs to the patient, may allow a reduction in the amount of mifepristone administered to the patient, and may allow the reduction in the amount of ketoconazole administered to the patient; such reduction may reduce the risk of toxic effects of ketoconazole, and may improve the treatment of the patient.

Applicant's surprising discovery is believed to apply to patients suffering from a disease or disorder and receiving a CYP3A inhibitor, including a strong CYP3A inhibitor such as ketoconazole; such patients suffering from a disease or disorder may be safely administered a GRM, such as mifepristone, concomitantly with the administration of a CYP3A inhibitor such as ketoconazole. Such concomitant administration is believed to be safe for the patient. For example, concomitant administration of ketoconazole and mifepristone surprisingly does not increase the risk of ketoconazole toxicity in the patient, and is believed to be safe for the patient. In particular, Applicant discloses herein that Cushing's syndrome patients receiving ketoconazole may be safely administered mifepristone concomitantly with the administration of ketoconazole. Such concomitant administration of ketoconazole and mifepristone to a patient suffering from Cushing's syndrome is believed to be safe for the patient suffering from Cushing's syndrome, which is characterized by hypercortisolism. Patients suffering from Cushing's syndrome, such as those suffering from endogenous Cushing's syndrome, may suffer hyperglycemia secondary to hypercortisolism. Concomitant administration of a GRA

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