prescription drug use" (page 2 of "Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications Guidance for Industry"). This same U.S. FDA report names multiple "strong CYP3A" inhibitors (increasing AUC of sensitive CYP3A substrates by more than 5-fold), including many (e.g., ketoconazole, itraconazole, ritonavir, boceprevir, cobicistat, conivaptan, telaprevir, troleandomycin, and variconazole, among others) which increase AUC of sensitive CYP3A substrates by more than 10-fold. Thus, large plasma level increases of greater than 5-fold or greater than 10-fold would be expected for CYP3A substrates, such as mifepristone, when concomitantly administered with a strong CYP3A inhibitor such as, e.g., ketoconazole, itraconazole, ritonavir, or others.

[0015] The use of ketoconazole, itraconazole, or of some other drug along with, e.g. mifepristone, may be thought to be required for successful treatment of a patient. However, since concomitant administration of a CYP3A substrate (such as, e.g., mifepristone or other glucocorticoid receptor modulator) with a CYP3A inhibitor (such as ketoconazole, itraconazole, or others) would be expected to raise the levels of the CYP3A substrate to unsafe levels, or could expose the patient to dangerous or toxic effects of one or the other drug, a physician may forego the concomitant use of ketoconazole, itraconazole, or other drug which may have otherwise been thought to be required for successful treatment.

[0016] However, patients may require treatment with multiple drugs, despite the possible disadvantages that can have deleterious consequences for the patient.

[0017] Accordingly, improved methods of treatment allowing the administration of other drugs along with CYP3A inhibitors (such as, e.g., ketoconazole, itraconazole, and others) and along with steroidogenesis inhibitors (such as, e.g., ketoconazole, itraconazole, and others) are desired.

SUMMARY

[0017a] In one aspect of the present disclosure, there is provided use of mifepristone in the manufacture of a medicament for the treatment of hyperglycemia secondary to hypercortisolism in a patient characterized as having endogenous Cushing's syndrome, wherein a reduced mifepristone dose is to be administered when the patient is receiving concomitant administration of a strong CYP3A inhibitor, wherein said reduced mifepristone dose is greater than 300 milligrams (mg) per day and is at least 25% less than the mifepristone dose for control of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome

in the absence of said strong CYP3A inhibitor, wherein said strong CYP3A inhibitor is selected from ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

[0018] Applicant discloses herein that CYP3A inhibitors such as, e.g., ketoconazole, itraconazole, and others, may be concomitantly administered with glucocorticoid receptor modulators (GRMs) such as the GR antagonist (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

CLAIMS

1. Use of mifepristone in the manufacture of a medicament for the treatment of hyperglycemia secondary to hypercortisolism in a patient characterized as having endogenous Cushing's syndrome, wherein a reduced mifepristone dose is to be administered when the patient is receiving concomitant administration of a strong CYP3A inhibitor, wherein said reduced mifepristone dose is greater than 300 milligrams (mg) per day and is at least 25% less than the mifepristone dose for control of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome in the absence of said strong CYP3A inhibitor, wherein said strong CYP3A inhibitor is selected from ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

2. The use of claim 1, wherein said use comprises the use of a once-daily dose of said mifepristone.

3. The use of claim 1 or 2, wherein said use comprises the use of a dose of said mifepristone for oral administration.

4. The use of any of claims 1 - 3, wherein said reduced mifepristone dose is 300 mg/day less than the mifepristone dose for use in the treatment of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome in the absence of said CYP3A inhibitor.

5. The use of any of claims 1 - 3, wherein said reduced mifepristone dose is 600 mg/day less than the mifepristone dose for use in the treatment of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome in the absence of said CYP3A inhibitor.

6. The use of any of claims 1 - 3, wherein said reduced mifepristone dose is 600 mg/day and said mifepristone dose for use in the treatment of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome in the absence of said CYP3A inhibitor is 900 mg/day.

7. The use of any of claims 1 - 3, wherein said reduced mifepristone dose is 900 mg/day and said mifepristone dose for use in the treatment of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome in the absence of said CYP3A inhibitor is 1200 mg/day.

8. The use of any of claims 1 - 3, wherein said reduced mifepristone dose is 600 mg/day and said mifepristone dose for use in the treatment of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome in the absence of said CYP3A inhibitor is 1200 mg/day.

9. The use of any of claims 1 - 8, wherein the CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, posaconazole, and voriconazole.

10. The use of any of claims 1 - 8, wherein the CYP3A inhibitor is selected from the group consisting of nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, and paritaprevir.

11. The use of any of claims 1 - 8, wherein the CYP3A inhibitor is selected from the group consisting of ritonavir, nelfmavir, indinavir, boceprevir, lopinavir, saquinavir, telaprevir, tipranivir, and paritaprevir.

12. The use of any of claims 1 – 8, wherein the CYP3A inhibitor is selected from the group consisting of nefazodone, clarithromycin, conivaptan, cobicistat, and troleandomycin.

13. The use of claim 7, wherein said reduced mifepristone dose is a second mifepristone reduced dose of 900 mg/day following administration of a first reduced mifepristone dose of 600 mg/day, wherein both reduced doses are for use in the treatment of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, wherein the mifepristone dose for said use in the absence of said CYP3A inhibitor is 1200 mg/day.