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(54) **MEDICAMENT AND METHOD OF DIAGNOSIS**

(71) Applicant: **UNIVERSITY OF SHEFFIELD**, Sheffield (GB)

(72) Inventor: **John Newell-Price**, Sheffield (GB)

(73) Assignee: **UNIVERSITY OF SHEFFIELD**, Sheffield (GB)

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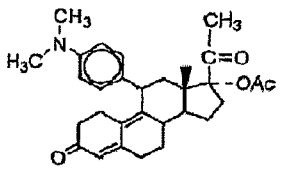
(57) **ABSTRACT**

Disclosed is a diagnostic test to determine suitable therapeutic intervention of subjects suffering from subclinical Cushing's syndrome [SCS] and also agents that antagonise the action of cortisol or inhibit excess cortisol production in the treatment of conditions such as SCS in the presence of an adrenal incidentaloma.

Figure 1



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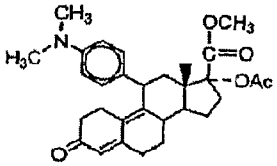

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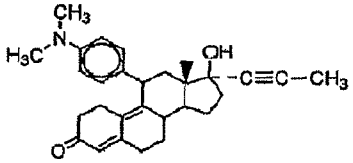
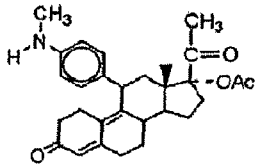
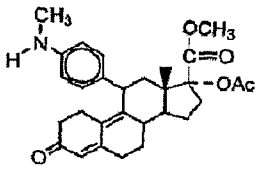


mifepristone



monodemethylated CDB-2914



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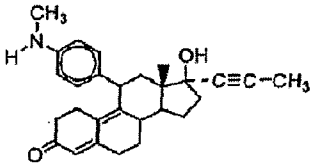

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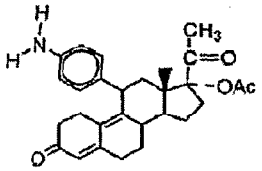

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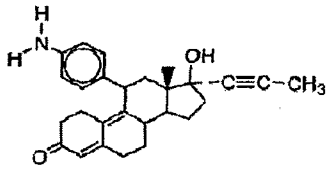
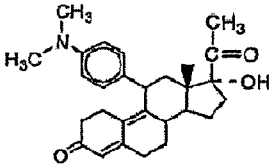
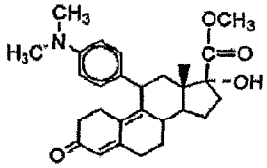


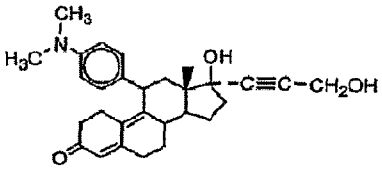
didemethylated mifepristone



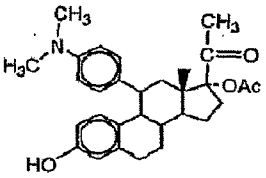
17α-hydroxy CDB-2914



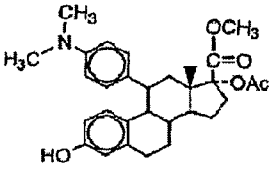
17α-hydroxy CDB-4124



17α-[3'-hydroxy-propynyl] mifepristone



aromatic A-ring CDB-2914



aromatic A-ring CDB-4124

Figure 2

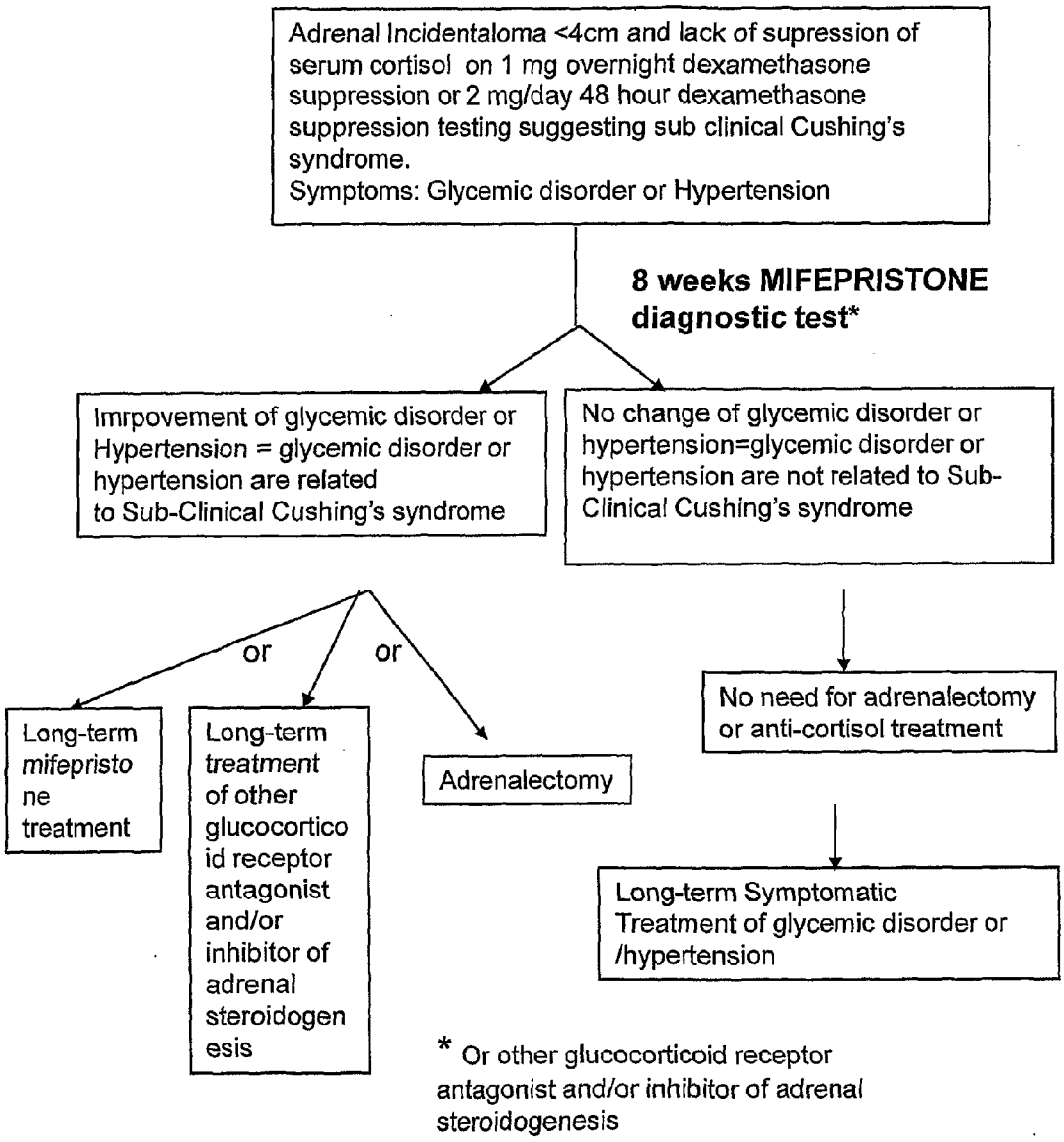
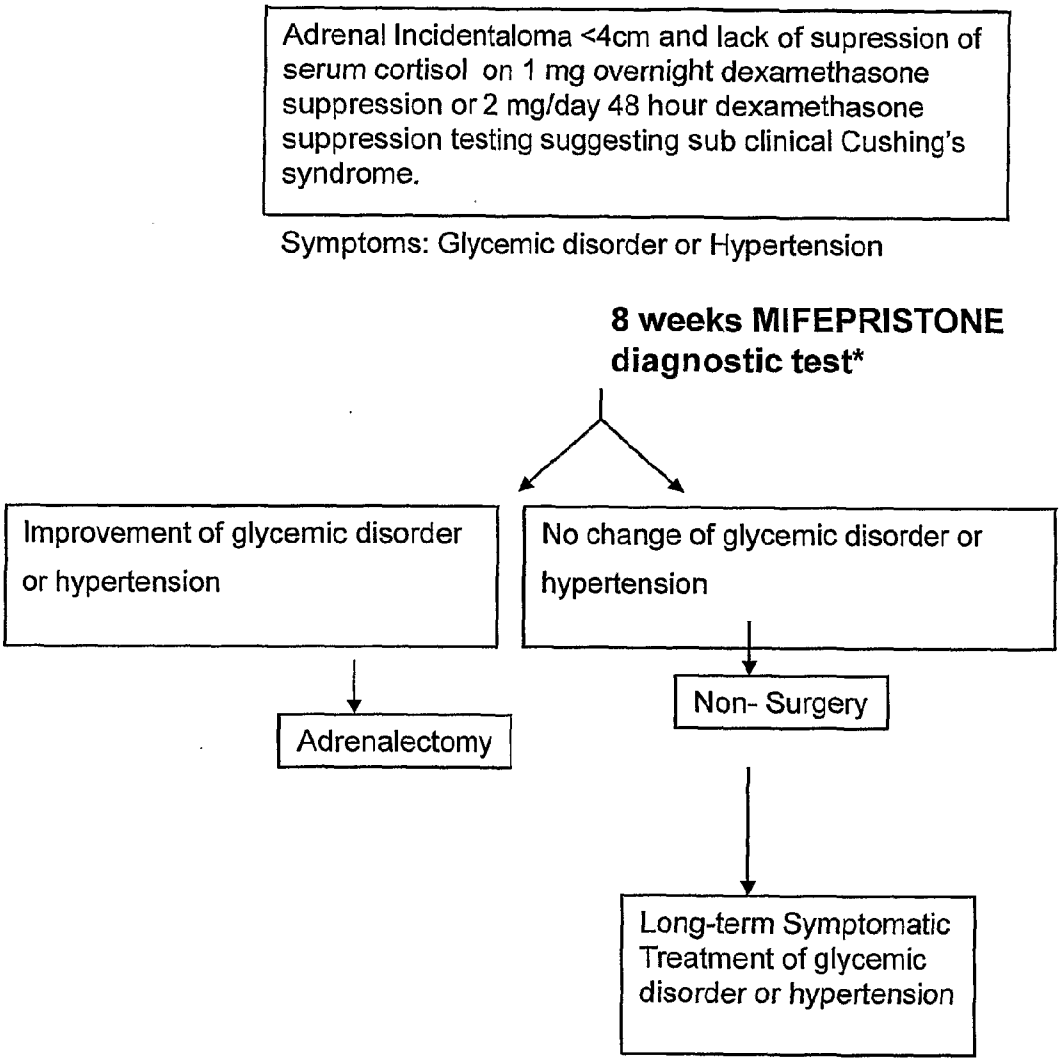


Figure 3



* Or other glucocorticoid receptor antagonist and/or inhibitor of adrenal steroidogenesis

MEDICAMENT AND METHOD OF DIAGNOSIS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This is a continuation of U.S. patent application Ser. No. 13/128,225, filed on May 6, 2011, which is the U.S. National Stage of PCT Application No. PCT/GB2008/003751, filed on Nov. 7, 2008, which was published in English under PCT Article 21(2). The prior applications are incorporated herein by reference in their entirety.

FIELD

[0002] The invention relates to agents that inhibit the production of excess cortisol, or antagonize its effects, in the prevention or treatment of conditions such as subclinical Cushing's syndrome [SCS]; medicaments and pharmaceutical compositions comprising the agents, combinations of agents; and also to a diagnostic test to determine suitable therapeutic intervention of subjects suffering from SCS.

BACKGROUND

[0003] Cortisol, also called the "stress hormone", is secreted by the adrenal glands which are adjacent the kidneys. Cortisol secretion increases when the body is stressed, either physically or psychologically. Cortisol is released from the adrenal gland under the regulation of ACTH derived from the pituitary gland. There is a circadian rhythm to cortisol release with high levels first thing in the morning and very low levels around midnight. ACTH and thus cortisol levels begin to rise between 2-3 am and peak between 7-9 am gradually falling over the day to a nadir between 8 pm and 2 am. Disease conditions associated with excess cortisol secretion include Cushing's syndrome also referred to as hypercortisolism or hyperadrenocorticism and typically results from excess cortisol production due to a pituitary adenoma. Cushing's syndrome has a complex pathology and symptoms include weight gain, telangiectasia, skin thinning, bruising, insomnia, psychiatric disorders or depression, impaired cognition or memory, osteopenia or osteoporosis, obesity, persistent hypertension, insulin resistance which can lead to impaired fasting glucose or impaired glucose tolerance or diabetes mellitus, dyslipidemia, metabolic syndrome, coagulation disorders, proximal muscle weakness, hirsutism, amenorrhea. Untreated Cushing's disease can result in atherosclerosis, heart disease and increased mortality.

[0004] A related disease associated with excess cortisol production is subclinical Cushing's syndrome [SCS]. This condition is commonly associated with adrenal incidentaloma. Incidentaloma's are mostly benign non-secreting tumours discovered by imaging studies performed for unrelated reasons. In approximately 10 to 15% of cases, they produce supraphysiological amounts of cortisol. The levels are insufficient to cause clinical features typically associated with Cushing's syndrome. SCS is common in the general population (~1% or more of those >70y in hospitalized or health-screened populations), and contributes to overall cardiovascular morbidity and mortality. A major problem is that management of SCS is not established. Approximately 90% of patients with SCS have hypertension; over 60% have impaired glucose tolerance or diabetes mellitus, obesity and [illegible] parameters. Carotid intima-media thickness is increased and atherosclerotic plaques are more frequent in patients than in controls.

[0005] In SCS there is the potential to permanently reduce these risks, and to improve bone health, by adrenalectomy. Only a very limited number of individuals with SCS are subjected to adrenalectomy. In those that have undergone this procedure improvements have been found in blood pressure (~10 mmHg drop in systolic BP), lipid profiles, fibrinogen levels, biochemical markers of bone turnover and glycaemic control. However, a problem is deciding whether adrenal surgery will be of benefit for a given patient with SCS, and the basis for selection for such permanent and invasive intervention is not established.

SUMMARY

[0006] There is a need to provide a treatment regime for controlling SCS and a diagnostic test to determine an appropriate treatment regime for a subject suffering from SCS. The response of subjects to the administration of these agents will also allow an objective means to determine if a subject suffering from SCS would benefit from adrenalectomy.

[0007] Glucocorticoid receptor antagonists are known in the art. For example mifepristone (11-[4-(Dimethylamino) phenyl]-17-hydroxy-17-[1-propynyl]-[11β,17β]-estra-4,9-dien-3-one), a derivative of the synthetic progestin norethindrone, is a potent competitive glucocorticoid and progesterone receptor antagonist. Mifepristone is also known as RU486. Mifepristone causes glucocorticoid antagonism by reducing translocation of the receptor to the nucleus and also by antagonising glucocorticoid-dependent transcriptional activity. In man the administration of mifepristone at >200 mg/day blocks central and peripheral glucocorticoid action with resultant activation of the HPA axis. Selective, nonsteroidal glucocorticoid receptor antagonists have been derived from RU486 for instance as described by Morgan et al. (2002) in J. Med. Chem. 45, 2417-2424, as CP-394531, and CP-409069. A further example is RU43044 which is a selective glucocorticoid receptor antagonist. Other nonsteroidal glucocorticoid receptor antagonist compounds are described for example in following patents and patent applications: U.S. Pat. No. 6,380,223, U.S. Pat. No. 6,436,986, U.S. Pat. No. 6,468,975, US2002/0147336, US 2002/0107235, US2004/0014741, US2004/0176595, WO2004/009017, WO 2004/110385, WO2004/111015, US2004/0266758, US2004/0266831, WO2001/16128 WO2006/084917 and WO2008/017658 each of which is incorporated by reference.

[0008] An alternative means to oppose the actions of cortisol is to reduce circulating levels by blocking cortisol synthesis using inhibitors of adrenal steroidogenesis. Cortisol synthesis inhibitory properties have been ascribed to several drugs. For instance, ketoconazole, was initially developed as an anti-fungal therapy. The drug inhibits unselectively the synthesis corticosteroids and at higher doses the synthesis of testosterone. Recently, the use of ketoconazole in cardiovascular and metabolic diseases has been claimed by e.g. U.S. Pat. No. 6,274,582, U.S. Pat. No. 6,642,236. Further examples include aminogluthetimide and metyrapone. Aminogluthetimide blocks the conversion of cholesterol to pregnenolone by inhibiting desmolase which inhibits the synthesis of many steroids including cortisol. Metyrapone blocks cortisol synthesis by inhibition of steroid 11 beta hydroxy-[illegible]

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