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Drugs and HPA axis

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Abstract This paper outlines the interferences of the most widely used drugs with hypothalamo-pituitary-adrenal function and the related laboratory parameters, with the purpose of providing practical help to clinicians during testing for hypo- or hypercortisolemic states.

Keywords Drugs · HPA axis · Cortisol · ACTH · Urinary free cortisol

Introduction

Clinicians should always be aware of potential interactions between drugs and the hypothalamo-pituitary-adrenal (HPA) axis as these may modify parameters used for clinical assessment of its functional status. Accurate investigation of present and past drug history is therefore necessary to avoid misdiagnosis and inappropriate treatments. This treatise will review drug-induced changes in hormone measurements used for the diagnostic work-up for hypo- or hypercortisolemic states, starting with synthetic glucocorticoids and drugs used for treatment of Cushing's syndrome, then proceeding on to interferences of other pharmacological agents with parameters of HPA function in basal conditions and upon dynamic testing.

Synthetic glucocorticoids

Synthetic glucocorticoids exert a multitude of effects on almost every organ system and rank among the most widely used drugs. They are employed in a variety of non-endocrine diseases (e.g., rheumatic, renal, allergic, asthmatic, ocular, skin, gastrointestinal, infectious, hepatic disorders), in addition to their use as replacement therapy for adrenal insufficiency. Two kinds of side effects should be kept in mind during the use of glucocorticoids: one resulting from continued use of supraphysiological doses, i.e. iatrogenic Cushing's syndrome, and the other secondary to drug withdrawal, i.e. HPA suppression.

Iatrogenic Cushing's syndrome, the most common form of hypercortisolism, is an unique disorder in which clinical features and biochemical changes typical of endogenous hypercortisolism, coexist with suppression of the HPA axis. Development of Cushingoid features is closely related to the dose and potency of the administered steroid as well as to the length of treatment, whereas the route of drug administration does not seem to be of primary importance. Indeed, even the development of iatrogenic Cushing's syndrome due to topical ocular steroids has been reported [1, 2]. Another interesting example of iatrogenic Cushing's syndrome are HIV-infected patients on inhaled corticosteroids, such as fluticasone, and protease-inhibiting antiretroviral drugs, such as ritonavir [3]. This association inhibits steroid hepatic metabolism and increases steroid bioavailability, thereby causing Cushingoid features and secondary adrenal insufficiency. Iatrogenic Cushing's syndrome has also been reported in a few patients treated with inhaled glucocorticoids and drugs such as itraconazole and clarithromycin, which inhibit hepatic cytochrome P450 3A (CYP3A), thus increasing glucocorticoid bioavailability [4–6]. Continuous cutaneous application of glucocorticoid preparations (e.g., ointments) on injured skin may also cause the development of iatrogenic Cushing's syndrome [7–9]. In the abovementioned circumstances, measurement of serum and urinary cortisol will yield variably increased levels in patients

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administered cortisone, hydrocortisone, prednisone and prednisolone as these drugs cross-react in most cortisol assays. Conversely, cortisol levels will be low in patients on dexamethasone, which does not interfere with cortisol measurements. Both basal and stimulated ACTH plasma levels are invariably low on glucocorticoid therapy.

Abrupt cessation of prolonged treatment with suppressive doses of glucocorticoids may precipitate secondary adrenal insufficiency. Some risk factors for HPA axis suppression are well recognized, such as pharmacokinetics, biological potency and half-life, in addition to affinity of the steroid for the glucocorticoid receptor [10]. Parenteral glucocorticoid therapy is more likely to suppress the HPA axis than topical administration, such as inhaled or intra-articular steroids. A recent report even described secondary adrenal insufficiency in infants after protracted topical steroids for diaper rash [11]. On the whole, it is usually accepted that adrenal atrophy with attendant insufficiency develops in patients who received the equivalent of 30 mg/day hydrocortisone, 7.5 mg/day prednisolone or 0.75 mg/day dexamethasone or more, per os, for at least three weeks. In these cases, the laboratory shows low levels of serum and urinary cortisol and low plasma ACTH concentrations.

Drugs used for treatment of Cushing's syndrome

Medical therapy is usually employed to correct endogenous hypercortisolism after surgery has failed and can be targeted to the hypothalamus/pituitary, the adrenal glands or the glucocorticoid receptor. All agents that modulate corticotropin-releasing factor (CRH) or ACTH release (Table 1) may affect parameters of HPA activity although their efficacy in Cushing's disease is mostly anecdotal. In addition to drugs affecting neurotransmission, which will be discussed in detail below, a spate of new drugs has recently been proposed for treatment of ACTH-dependent Cushing's syndrome, including PPAR-γ agonists and recently developed somatostatin analogues. So far, no report on the possible changes in HPA function in patients administered these compounds for diabetes, acromegaly, gastrointestinal tumors etc. has been published. Ketoconazole, the mainstay of medical therapy in Cushing's syndrome, and the other steroid synthesis inhibitors (Table 1) are employed also in other clinical conditions, e.g. mycoses, anesthesia and malignant neoplasms, and may lead to low serum cortisol and androgen levels. Administration of ketoconazole, however, does not seem to be accompanied by a compensatory increase of plasma ACTH, as occurs with other steroid synthesis inhibitors, allegedly due to a concomitant restraint of ACTH release [12]. Of note, the anesthetic etomidate has been implicated in stress-associated hypocortisolemia in critically ill patients [13, 14]. Mifepristone (RU-486), a potent antagonist of glucocorticoid and progesterone receptors, thwarts the negative glucocorticoid feedback thus increasing ACTH/cortisol secretion in healthy [15] and ill subjects [16–18]. Somatostatin analogues decrease plasma ACTH and serum cortisol levels in some patient with ACTH-secreting pituitary or ectopic tumors but not in normal subjects [19].

Baseline plasma ACTH and serum or salivary cortisol

Most studies on changes in HPA parameters refer to basal plasma ACTH and serum cortisol levels, while far fewer are the reports on hormonal values under dynamic conditions, i.e. provocative or inhibitory maneuvers. Measurement of plasma ACTH is a means to discriminate pituitary from adrenal hypo- and hyperfunction. Conversely, estimation of morning cortisol is used mainly for the diagnosis of adrenocortical insufficiency while late-night serum or salivary cortisol is employed in the diagnostic work-up of Cushing's syndrome.

Many drugs interfere with basal HPA activity and therefore affect the results of ACTH and cortisol measurement, with neurotransmitter-modulating drugs as the most frequent culprits. The effects of these compounds depend on the dose administered, the length of treatment and the underlying disorder as changes observed in healthy

Table 1 Drugs used for treatment of Cushing's syndrome

CRH/ACTH inhibitors
Serotonin antagonists: cyproheptadine, ketanserin, ritanserin, metergoline
Dopaminergic agonists: bromocriptine, cabergoline
Catecholamine depletors: reserpine
GABAergic agents: valproic acid
Somatostatin analogues: octreotide, lanreotide, pasireotide
Peroxisome proliferator-activated receptor (PPAR-γ) agonists: pioglitazone, rosiglitazone
Steroid synthesis inhibitors
Single enzyme inhibitors: metyrapone, trilostane
Multiple enzyme inhibitors: mitotane, aminoglutethimide, ketoconazole, fluconazole, etomidate
Glucocorticoid receptor antagonists
Mifepristone (RU486)

subjects may differ from those observed in patients with psychiatric or other disorders. Clinicians should also take note of patients' behavioral habits, such as smoking or alcohol intake, with the excess of the latter as a well-known cause of clinical and/or biochemical pseudoCushing. Further, cigarette smoking appears to be associated with abrupt increases in cortisol levels whereas a cortisol decline is observed upon ceasing to smoke [20]. Measurement of basal ACTH and/or cortisol secretion is usually the first step of the diagnostic work-up and careful case history is therefore mandatory.

Serotonergic agonists and antagonists

Serotonin receptor agonists, commonly used as appetite suppressors, anxiolytic and antidepressants, mostly stimulate HPA axis, as has been observed with fenfluramine at high doses (i.e. above 30 mg/die p.o.) [21, 22], azapirones [23–26], sertraline [27] and flesinoxan [28]. These effects appear dose-dependent, as shown for the selective serotonin reuptake inhibitor (SSRI) citalopram [29, 30], and subject to tachyphylaxis [31]. No increase in basal ACTH and cortisol levels has been reported with another SSRI, fluoxetine, administered to normal volunteers [32, 33]. Of note, the serotonin-mediated activation on HPA function is blunted in chronic fatigue syndrome, a condition which may mimic adrenal insufficiency [34]. Ecstasy (i.e., 3,4-methylenedioxymethamphetamine or MDMA) [35], its less toxic derivative 3,4-methylenedioxyethamphetamine (MDE) [36] and meta-chlorophenylpiperazine (*m*-CPP) [37] induce a marked rise in serum cortisol concentrations, possibly due to their effect on serotonin neurons. As for serotonin antagonists, in addition to those mentioned previously (see Table 1), atypical antidepressants trazodone [38] and etoperidone [39] have been shown to inhibit HPA activity in normal volunteers.

Dopaminergic agonists and antagonists

Both dopaminergic agonists, e.g., apomorphine [40], lergotrile [41], and antagonists, e.g. metoclopramide [42–44], fluphenazine [45], have been reported to enhance plasma ACTH and serum cortisol concentrations in normal subjects as well as in various clinical conditions, including schizophrenia and prolactin-secreting tumors. In healthy women, however, the ACTH and cortisol increase induced by metoclopramide appears restricted to the mid-luteal phase as no changes were observed during the early and late follicular phase [46]. A similar observation has been reported in one study with methylphenidate [47] although not confirmed by another [48]. Interestingly, dopaminergic agonists bromocriptine and cabergoline may decrease ACTH/cortisol secretion in patients with Cushing's disease. Acute levodopa administration, used in tandem with the peripheral DOPA decarboxylase inhibitor benserazide, appears to lower serum cortisol levels in patients with Parkinson's disease [49] while haloperidol, a well-known antipsychotic, does not affect HPA activity in healthy subjects [50]. Lastly, the alkaloid cocaine, which is known to inhibit dopamine uptake, can also increase cortisol values in healthy individuals [51].

Adrenergic agonists and antagonists

The alpha 2 receptor agonist clonidine has been shown to reduce cortisol levels in several studies, including those on obese and hypertensive individuals [52–54]. Likewise, an ACTH and cortisol decrease has been observed during clonidine testing in children with short stature [55]. Conversely, alpha 2 receptor antagonists such as yohimbine and idazoxan appear to increase cortisol levels [56]. The antidepressant reboxetine, a selective noradrenaline reuptake inhibitor, also significantly stimulates HPA activity [57] with more pronounced effects in males compared with females [58]. Amphetamine, a central sympathomimetic amine, induces a short-lasting rise in cortisol levels in normal subjects [59] whereas a paradoxical suppression can be observed in depressed patients [60].

Opiate agonists and antagonists

Complete and partial agonists or mixed opiate agonist-antagonists, such as the antidiarrheal loperamide [61], the analgesics morphine, methadone, pentazocine and nalorphine [62], buprenorphine [63], codeine [64], and the recreational drug heroin [65] significantly suppress basal serum cortisol levels. This has been documented in normal subjects, patients with anorexia [66], Addison's disease [67], pituitary disease (acromegaly, prolactinoma, pituitary dwarfism) [68], obesity [69], polycystic ovary syndrome [70] or psychiatric ailments [71]. Conversely, spiradoline, a recently developed kappa receptor agonist, stimulates cortisol secretion dose-dependently, in keeping with different actions of opioid receptor subtypes on the HPA axis [72]. As expected, opioid antagonists naloxone [73], naltrexone [74] and nalmefene [75] increase both plasma ACTH and serum cortisol concentrations in healthy individuals as well as in patients with bulimia [76], acromegaly [77], obesity [78], alcohol abuse [79] or mood disorders [80]. A less pronounced increase compared with normal subjects has been observed in patients with Nelson's syndrome [81], Alzheimer's [82] or Parkinson's disease [83], whereas patients with polycystic ovary syndrome exhibit a more marked increase after naloxone administration [84]. Of note, the ACTH and cortisol increase induced by naltrexone is particularly marked in alcohol-dependent subjects [85].

GABAergic agonists

Valproic acid, the anticonvulsant GABAergic agonist, does not affect ACTH/cortisol secretion in the short term [86] but has been found to decrease basal ACTH/cortisol secretion during protracted administration in epileptic patients [87, 88] and, due to this action, has been used with variable effects in Cushing's disease and Nelson's syndrome [89]. Of note, valproic acid has also been shown to inhibit steroid biosynthesis by acting upon 3β-hydroxydehydrogenase [90], an effect that has been linked to the increased incidence of polycystic ovary syndrome in patients on chronic treatment [91]. The central GABAergic system appears to be involved in the HPA suppressive effect of benzodiazepines, e.g., temazepam [92], alprazolam [93], thus interruption of these psychoactive drugs is recommended prior to testing HPA function. Clinicians should also be aware that secondary adrenal failure may develop in patients on long-term treatment with benzodiazepines, as recently reported with flunitrazepam [94].

Cholinergic agents

The cholinesterase inhibitor physostigmine, used to counteract poisoning by anticholinergic drugs or plants, is associated with an increase in plasma ACTH and serum cortisol concentrations in healthy subjects [95, 96] and in patients with Alzheimer's disease [97, 98] or major depression [99]. Elderly subjects and men appear more sensitive to this effect compared with younger subjects and women [100, 101].

Miscellaneous psychotropic drugs

Antipsychotic drugs such as olanzapine and quetiapine, which antagonize serotonin, dopamine and histamine receptors, appear to reduce HPA activity in healthy subjects [50]. In contrast, tricyclic antidepressants such as desimipramine [102], imipramine [103] and clomipramine [104, 105] enhance ACTH and cortisol release in a dose-dependent manner. Mirtazapine, a recently developed antidepressant which antagonizes serotonin, histamine and alpha 2 adrenergic receptors, reduces cortisol levels in healthy subjects [106] as well as in anorexic [107] and depressed patients [108].

Immunomodulatory and hormonal drugs

Cytokines, such as interferons (IFN), interleukins (IL) and tumor necrosis factor (TNF), stimulate HPA axis and, indeed, immunotherapy for cancer or chronic hepatitis increase ACTH and cortisol levels [109]. This can be seen after acute or chronic administration of IFN-alpha [110], IFN-beta [111], IFN-gamma [112], TNF-alpha [113] and IL-1 alpha and beta [114], IL-2 [115] and IL-6 [116]. However, not all cytokines exert the same effect, as IL-3 administration may blunt the IL-2-induced cortisol increase [117].

Among hormonal compounds, growth hormone (GH) and thyroid hormones may interfere with HPA function. During recombinant human (rh) GH replacement therapy, morning serum cortisol levels significantly declined in adult GH-deficient patients with preserved HPA activity [118]. Patients with thyrotoxicosis display higher plasma ACTH concentrations and free cortisol index (serum cortisol/CBG) values compared with euthyroid subjects [119]. Furthermore, long-lasting severe thyrotoxicosis is associated with a reversible attenuation of the adrenal response to an acute challenge [120]. Medroxyprogesterone acetate (MPA) and megestrol, synthetic progestational agents used in the treatment of endometriosis, hirsutism and metastatic breast cancer, interact with the glucocorticoid receptor, and their long-term administration may result in Cushingoid features and suppression of ACTH and cortisol secretion. This has been shown to occur in healthy subjects [121, 122] as well as cancer [123–125] and AIDS patients [125, 126]. In this context it is worth recalling that estrogens increase cortisol-binding globulin synthesis thereby leading to a variable elevation of serum cortisol [127]. This effect is more apparent with oral estrogen preparations and might be insignificant with transdermal patches [128]. Conversely, long-term administration of the selective estrogen receptor modulator raloxifene is reported to decrease cortisol levels and increase ACTH levels in postmenopausal women [129]. Interestingly, the cholecystokinin 8-like peptide ceruletide, used for paralytic ileus and pancreatic malfunction, stimulates ACTH and cortisol secretion [130] as does the antidepressant herb mixture *Hypericum perforatum* (St. John's Wort) [131]. Lastly, desmopressin, the long-acting analogue of arginin vasopressin, elicits the release of ACTH and cortisol in patients with Cushing's disease but not in the majority of normal, obese and depressed subjects [132].

Urinary free cortisol, midnight cortisol and dynamic tests of adrenal function

In the absence of specific studies, it can be assumed that the effects of different drugs, as reported in the previous chapters, also apply to the estimation of urinary free cortisol, midnight serum cortisol and to the dynamic exploration of the HPA function.

Urinary free cortisol

Urinary free cortisol (UFC) is widely used to screen for Cushing's syndrome using radioimmunoassays (RIA) or

the more specific high performance liquid chromatography (HPLC) and false results may be caused by drugs that interfere with the assay or with HPA function. Synthetic steroids variably cross-react with antibodies used in cortisol RIA assays and may lead to over- or underestimation of UFC measurements [133, 134] and some, such as prednisolone [135], may coelute with cortisol even on HPLC. Falsely elevated values due to coelution have been reported also for carbamazepine [135, 136] and digoxin [135] but this problem can apparently be overcome with HPLC coupled to tandem mass spectrometry (HPLC-MS/MS) [137]. Fenofibrate, a lipid-lowering agent, also interferes with cortisol measurement at HPLC and a double HPLC-MS/MS is required for precise measurement [138]. As regards direct drug effects on UFC excretion, an increase in UFC has been observed in subjects on fenfluramine (180 mg/daily) [139] or chronic use of the narcotic γ-hydroxybutyric acid [140] while a reduction is apparent in patients taking benzodiazepines [141, 142] or mirtazapine [106, 143]. Unlike serum cortisol, UFC measurements seem unaffected by estrogen replacement [144] or oral contraceptive administration [145].

Licorice administration may mimic mineralocorticoid excess (hypertension and hypokalemia) and is associated with an increase in UFC due to inhibition of 11β-hydroxysteroid dehydrogenase type 2, the isoenzyme which converts cortisol to cortisone [146]. In contrast, rhGH replacement therapy was associated with significant reduction in UFC levels in adult patients with GH deficiency [118], likely through inhibition of 11β-hydroxysteroid dehydrogenase type 1, which converts cortisone to cortisol [147].

Dexamethasone suppression tests

Dexamethasone suppression test is of decisive importance for the diagnosis and differential diagnosis of Cushing's syndrome and relies on the sensitivity of the hypothalamo-pituitary unit to the negative feedback from exogenous glucocorticoids. Dexamethasone, a synthetic long-acting glucocorticoid, is metabolized primarily by cytochrome P450 3A4 (CYP3A4), which is responsible for the metabolism of a large number of xenobiotics. Agents that increase hepatic CYP3A4 activity, such as carbamazepine [148], phenytoin [149], rifampicin [150], barbiturates [151, 152] and, recently, St. John's Wort [153, 154] accelerate dexamethasone clearance and hence cause false positive results (lack of inhibition). Of note, false positive results occur mostly with the low dose dexamethasone suppression tests (1 mg or 2 mg overnight) whereas the suppressibility by high dose dexamethasone appears to be maintained in patients with Cushing's disease [155]. Other drugs which may lead to falsely high post-dexamethasone cortisol values are cholinergic agents such as physostigmine and the muscarinic agonist arecoline [156, 157], serotonergic agonists, e.g., buspirone [158], citalopram [159], the GABAergic γ-hydroxybutyric acid [140] and the lithium-tricyclic antidepressant association [160]. Of note, this effect by lithium could mask recovery of cortisol suppressibility by low doses of dexamethsasone, an index of favorable outcome in depressed patients treated with antidepressants [161].

As mentioned previously, estrogen administration leads to increased serum cortisol levels and these may be increased to the Cushingoid range even after dexamethasone [127, 162, 163]. Salivary cortisol is recommended if estrogens cannot be withdrawn [164].

Midnight serum or salivary cortisol

Midnight serum cortisol, another mainstay of the diagnosis of Cushing's syndrome, is increased during antidepressant treatment with mirtazapine [165], clomipramine [166], desimipramine [167], moclobemide (an inhibitor of monoamine oxidase A) [168], the antipsychotic olanzapine [169] and the SSRI inhibitor fluvoxamine [167]. Late-night cortisol is also increased by the antimineralocorticoid canrenoate [170]. Conversely, nocturnal cortisol secretion is reduced by the tricyclic antidepressant trimipramine [171–173] as well as in heroin addicts [174].

ACTH stimulation test

The ACTH stimulation test is used to assess adrenocortical reserve in primary and secondary adrenal insufficiency and the cortisol response may be abnormally reduced in patients on paroxetine and sertraline, two SSRI inhibitors [175]. Likewise, low cortisol responses to ACTH have been registered in subjects on MPA or megestrol [176–178] as well as in patients with organic GH deficiency on rhGH therapy although not in children with idiopathic isolated GH deficiency [179]. The same trend of response may be documented in patients requiring antifungal steroid synthesis inhibitors such as ketoconazole [180] or high-dose fluconazole [181]. Conversely, the β-adrenergic antagonist propanolol seems to enhance the cortisol elevation induced by ACTH [182] as well as by CRH [183].

Corticotropin-releasing hormone stimulation test

The CRH test is employed in the differential diagnosis of Cushing's syndrome (distinction between ACTH-dependent and independent forms and, within the former, between Cushing's disease and ectopic ACTH secretion) and to disclose adrenal insufficiency secondary to ACTH deficiency.

Cortisol concentrations after CRH stimulation are higher in patients on citalopram [184], propanolol [182, 185], canrenoate [186] or metoclopramide [187]. Interferon alpha likewise enhances the ACTH and cortisol response to CRH in cancer patients [188]. Conversely, opiates such as morphine attenuate the CRH-induced ACTH and cortisol release [189, 190], as do imipramine [191] and temazepam [192]. Interestingly, in patients with Cushing's disease, the CRH response is unaffected by temazepam [192].

Conclusions

A number of drugs can impair the laboratory assessment of HPA function either influencing ACTH/cortisol secretion, and hence their peripheral concentrations, or interfering with hormonal assays. Careful drug history should always be obtained whenever HPA activity has to be evaluated.

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