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Review

Current approaches to the pharmacological management of Cushing's disease

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ABSTRACT

If treatment of Cushing's disease (CD) by surgery is not successful, medical therapy is often required. Long-term use of metyrapone is limited by hirsutism and hypertension and escape because of increased ACTH levels. Although ketoconazole can normalize cortisol levels in 50%, liver toxicity limits its use. Mitotane, an adrenolytic agent, has had minimal use for benign disease. Etomidate is useful when rapid reduction in cortisol levels is needed. Cabergoline can normalize cortisol levels in CD in about one-third of patients and is well tolerated. Pasireotide can normalize cortisol levels in CD in about 25% but causes worsening of glucose tolerance in most patients. Mifepristone, a blocker of cortisol receptors, improves clinical aspects of CD in most patients but cortisol and ACTH measurements do not reflect clinical activity and adrenal insufficiency, hypokalemia, and endometrial hyperplasia can occur. Combinations of drugs can be tried in patients resistant to monotherapy.

Contents

1. Introduction

Cushing's syndrome is associated with a two- to fivefold increase in mortality (Clayton et al., 2011; Dekkers et al., 2013). Curative treatment results in a reduction in that mortality to normal but substantial morbidity persists (Clayton et al., 2011; Feelders et al.,

Abbreviations: CD, Cushing's disease; CS, Cushing's syndrome; ACTH, adrenocorticotropic hormone; UFC, urinary free cortisol; MRI, magnetic resonance imaging.

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2012). Transsphenoidal surgery is generally considered to be the initial preferred treatment for patients with Cushing's disease with cure rates in the 80–90% range in the hands of experienced pituitary surgeons (Biller et al., 2008; Clayton et al., 2011; Feelders et al., 2012; Lambert et al., 2013; Patil et al., 2008). The following case illustrates the problem, however, in the patient who is not cured by surgery.

1.1. Case description

This 30 year old woman initially presented with a 3 year history of increasing facial hair, facial rounding, abdominal obesity, hypertension, diabetes, and oligomenorrhea. She had no muscle weakness or pigmented striae. Initial laboratory testing showed a basal 8 AM cortisol level of 30.2 μg/dL with an ACTH level 77 pg/mL (normal 5–27 pg/mL). An overnight 1 mg dexamethasone suppression test showed an 8 AM cortisol level of 17.7 μg/dL. Her 24 h urinary free cortisol (UFC) was 305 μg (normal 4.0–50 μg). Her hemoglobin A1c was 8.4%. An MRI showed a 7 mm hypodense area consistent with a pituitary adenoma. Unfortunately, insurance issues dictated that she have transsphenoidal surgery at a hospital with an inexperienced pituitary surgeon. The pathology report read "Cellular debris with tiny fragment of adenoma." Postoperatively, she felt the same with no improvement and still required large doses of insulin. Postoperative laboratory testing showed an 8 AM cortisol level of 18 μg/dL with an ACTH level of 47 pg/mL (6–50 pg/mL) and a 24 h UFC of 398 μg (4.0–50 μg).

Thus, this patient has had unsuccessful pituitary surgery. Options now include repeat surgery by an experienced pituitary surgeon (Ram et al., 1994), irradiation (usually stereotactic) (Starke et al., 2010), or medical therapy (Bertagna and Guignat, 2013; Feelders and Hofland, 2013). If irradiation is chosen as the primary treatment, it takes years for this to be effective (Starke et al., 2010) and medical therapy would be required to bring the hypercortisolemic state under control so as to improve her morbidity and mortality. The various types of medical therapy for hypercortisolism will be briefly reviewed here.

2. Medical therapy

2.1. General nature of medical therapy

The medical therapy for hypercortisolism dates back to 1975, when Krieger and colleagues first reported the successful use of cyproheptadine, an anti-serotonin agent, for the treatment of Cushing's disease, based on the concept of increased hypothalamic serontoninergic activity as being contributory to the development of the condition (Krieger et al., 1975). Although subsequent studies showed much lower response rates and further trials were not done, the potential for successful medical treatment had now been demonstrated and this stimulated the development of many other medications over the years. Drug therapy has been directed at the pituitary to decrease ACTH secretion by corticotroph tumors, at the adrenal to block multiple steps involved in cortisol synthesis, and at the cortisol receptor to block cortisol action (Fig. 1). These additional agents will be discussed in approximate order of their historical use, focusing on the results of relatively large series and not discussing the results from individual case reports and small series.

2.2. Mitotane

Mitotane (o,p′-DDD) is an adrenolytic agent that also inhibits 11β hydroxylase and cholesterol side chain cleavage and has been used as the mainstay for the treatment of adrenal cancer. However, it has

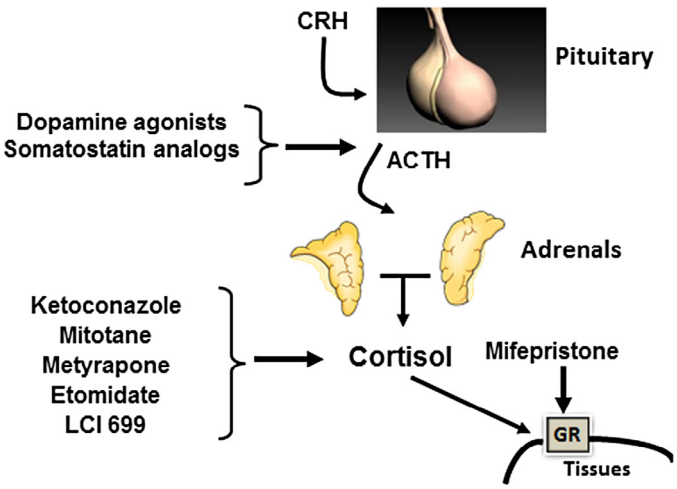

Fig. 1. This schematic outlines the sites of action for the various medications used for the treatment of Cushing's syndrome. Abbreviations used: CRH – corticotropin releasing hormone; ACTH – adrenocorticotropic hormone; GR – glucocorticoid receptor.

ment of Cushing's disease. In 1979, Luton et al. reported the results of treatment with mitotane alone in 46 patients (16 patients previously irradiated) with Cushing's disease, finding that 38 achieved remission of disease with a course of treatment. However, 60% relapsed and needed additional courses of drug or irradiation and 63% ultimately did not need adrenalectomy with 40/62 off medication (Luton et al., 1979). A new series reported from the same institution included 49 patients treated *de novo* and 27 after surgery (Baudry et al., 2012). Of the 67 treated chronically 48 (72%) obtained a normal UFC after a median of 6.7 months, 10 (15%) withdrew due to lack of efficacy after a median of 7.9 months and 19 (28%) withdrew due to intolerance (10 with normal UFC). Thus, 38/67 (57%) had long term normal UFC; 17/24 with normal UFC who stopped treatment later had a recurrence. Overall, 7/76 (11%) of patients attained permanent remission off treatment. Dose-related adverse gastrointestinal and neurologic symptoms are common and limit its use; abnormal liver function tests and gynecomastia are also common adverse effects. A pituitary adenoma appeared during follow-up in 12/48 with no visible tumor on initial MRI scans (Baudry et al., 2012). Furthermore, as a potent inducer of CYP3A4, drug interactions also may limit its use (van Erp et al., 2011).

2.3. Metyrapone

Metyrapone blocks the 11-hydroxylase enzyme that converts 11-deoxycortisol to cortisol. It had been used for years diagnostically for the evaluation of hypoadrenalism and in small series of patients with Cushing's syndrome. A large series reported in 1991 showed that with short-term treatment of 2–3 months, cortisol normalized in 40/53 (75%) patients (Verhelst et al., 1991). However, with long-term treatment three patients were controlled for 9, 60, and 173 months and then went into remission. However, treatment became ineffective in three other patients after 7–17 months. They noted that the decrease in negative feedback of cortisol resulted in increased ACTH levels which then overcame the block causing increased cortisol levels again. In addition, the increased ACTH stimulated other pathways resulting in increased androgen production with hirsutism in women and hypertension from the increased 11-deoxycortisol levels. In a more recent series, 23 patients were treated for 4 months preoperatively, with cortisol levels being normalized in 6 (26%) and controlled in 7 (30%) (Valassi et al.,

of 11-deoxycortisol that occur with metyrapone treatment cross-react in the standard immunoassay for cortisol, so that treatment must be monitored using a method not affected by such interference, such as liquid chromatography with tandem mass spectrometry (Monaghan et al., 2011).

2.4. Ketoconazole

Ketoconazole is an imidazole derivative that has been the mainstay of medical treatment for Cushing's syndrome for many years. It blocks several steps in cortisol synthesis, including side chain cleavage, 17-hydroxylase, 17,20 lyase, 11β-hydroxylase, and aldosterone synthase (Feelders and Hofland, 2013). Early studies suggested a normalization rate of UFC of over 90% (Sonino et al., 1991; Tabarin et al., 1991). A recent series reported data on 200 patients (78% females, 106 microadenomas, 36 macroadenomas, 58 with no tumor visible) treated with ketoconazole in doses ranging from 200 to 1200 mg/day, most receiving 600 and 800 mg/day (Castinetti et al., 2014). Of 39 patients treated prior to surgery for 4 months, 19 pts (48.7%) achieved a normal UFC. In 158 patients treated postoperatively or primarily (surgery contraindicated), 78 (49.3%) achieved normal UFC, 37 (23.4%) had a >50% decrease in UFC and 43 (27.2%) had an unchanged UFC. The drug was stopped in 26.8% due to lack of efficacy and in 25.6% due to adverse effects. In this series, liver enzyme elevations were found as follows: <5× increase in 30 (15.8%), a 5–10× increase in 4 and a 40× increase in 1. These increases occurred within 4 weeks of starting or with dose increments and all increases returned to normal with drug withdrawal. Other side effects of ketoconazole include rash, gastrointestinal symptoms and hypogonadism in men. Ketoconazole is a strong CYP3A4 inhibitor (substrates include amiodarone, carbamazepine, amitriptyline, SSRIs, benzodiazepines, calcium channel blockers, statins, colchicine) and therefore may affect dosing of these and other drugs.

In 2013, the U.S. Food and Drug Administration (FDA) specified a "black box warning" regarding liver toxicity with ketoconazole use; ketoconazole had never had U.S. FDA approval for use in Cushing's syndrome (U.S. FDA, 2013). The European Medicines Agency recommended against prescribing ketoconazole in 2013 as well (European Medicines Agency, 2013). Ketoconazole is no longer available for use in many countries at present.

2.5. Etomidate

Etomidate is another imidazole that inhibits 11β-hydroxylase, aldosterone synthase, and side chain cleavage. It was originally used as an anesthetic agent but was found to cause adrenal insufficiency. Subsequently, it has been used for the treatment of severe hypercortisolemia in the critically ill patient, usually preoperatively to improve surgical risk (infection, wound dehiscence, hypercoagulability, hypertension, hyperglycemia). It must be given IV – in the intensive care unit (ICU) in subhypnotic doses of 0.04–0.05 mg/kg/h. It has a rapid onset of action, cortisol levels falling in 12–24 h. There is a need to monitor serum cortisol and potassium levels closely. It is often used in a "block and replace" strategy with higher doses and concomitant IV hydrocortisone (0.5–1 mg/h). Thus, it has a very limited but specific use (Preda et al., 2012).

2.6. Thiazolidinediones

Great excitement followed the discovery of peroxisome proliferator-activated receptors-γ (PPAR-γ) in human normal and tumorous corticotroph cells and that PPAR-γ ligands inhibited corticotroph tumor cell proliferation and ACTH secretion. Unfortunately, multiple clinical trials of these agents, rosiglitazone and sient responses in a small number of patients and such use has been abandoned.

2.7. Cabergoline

Dopamine D2 receptors have been found in 80% of corticotroph tumors (Pivonello et al., 2004). In studies of these tumors with D2 receptors, 100% had significant inhibition of ACTH secretion *in vitro* with cabergoline and 60% of the patients harboring these tumors had significant reduction of cortisol levels and 40% had normalization of cortisol levels with 1–3 mg cabergoline per week *in vivo*. Therefore, 80% × 40% = 32% of all patients (since measurement of D2 receptors not routine) can expect control of hypercortisolism with cabergoline (Pivonello et al., 2004). In five series totaling 83 patients, 31 (37%) achieved normal cortisol levels (Godbout et al., 2010; Illouz et al., 2006; Lila et al., 2010; Pivonello et al., 2009; Vilar et al., 2010).

2.8. Pasireotide

Corticotroph adenomas express substantial amounts of somatostatin receptor subtype 5 in addition to subtypes 1, 2, and 3 (Hofland and Lamberts, 2003). Unlike octreotide and lanreotide, pasireotide has substantial action at subtype 5 (Hofland and Lamberts, 2003). In a recent prospective, randomized study of 162 patients with Cushing's disease, pasireotide given in daily subcutaneous injections was able to normalize UFC at 12 months in 19.1% of patients, although many more had falls in UFC that did not reach normal (Colao et al., 2012). Patients had substantial improvements in body weight, blood pressure, and quality of life. However, a worsening of glucose tolerance occurred in 73%. Of 67 patients normoglycemic at baseline, 14 (21%) remained normal, 29 (43%) became pre-diabetic and 23 (34%) became diabetic during treatment. In a study in healthy volunteers, it was found that pasireotide reduced incretin (glucagon-like peptide 1 [GLP-1] and glucose insulinotropic peptide [GIP]) and insulin secretion, without affecting insulin sensitivity (Henry et al., 2013). In another study, treatment with the incretin-based antihyperglycemic agents liraglutide and vildagliptin significantly reduced pasireotide-induced hyperglycemia (Breitschaft et al., 2014). Therefore, these would be reasonable medications to initiate in patients being treated with pasireotide.

2.9. Mifepristone

Mifepristone was initially developed as a progesterone receptor antagonist and has been used widely as an abortifacient (RU486). Mifepristone is also a glucocorticoid receptor antagonist with greater affinity for the receptor than either cortisol or dexamethasone. Between 1985 and 2010, 66 Cushing's syndrome patients treated with mifepristone had been reported (Castinetti et al., 2010) prior to the large, multicenter SEISMIC trial, in which mifepristone was used in 43 patients with Cushing's disease, 4 with ectopic ACTH syndrome and 3 with adrenal cancer (Fleseriu et al., 2012). Because of its mechanism of action, during treatment cortisol and ACTH levels rise rather than fall, and treatment dosing is based on improvement in clinical outcomes (glucose tolerance, blood pressure, weight, waist circumference, quality of life) as well as adverse effects. Fifteen of 25 (60%) had a ≥25% fall in glucose area under the curve during oral glucose tolerance tests (Fleseriu et al., 2012). However, similar to pasireotide, there were also substantial improvements in weight and quality of life. Blood pressure improvement was variable because in many patients the high cortisol levels overwhelmed the type 2 11-beta-hydroxysteroid dehydrogenase activity (which normally converts cortisol to cortisone) at the mineralocorticoid receptor, thereby activating the mineralocorticoid receptor with worsening salt re-

Table 1
Drugs used to treat Cushing's syndrome[a].

Drug	Cushing's disease only?	Percent of patients achieving normal urinary free cortisol	Adverse effects
Metyrapone	N	26%	Nausea, hirsutism, ↑BP
Mitotane	N	57%	GI, neurologic
Ketoconazole	N	49%	↑Liver function tests, liver failure
Etomidate	N	100%	IV only, ICU needed, sedation
Cabergoline	Y	37%	Nausea
Mifepristone	N	NA[b]	Adrenal insufficiency, hypokalemia, menorrhagia
Pasireotide	Y	26%	Hyperglycemia, other somatostatin receptor ligand adverse effects
LCI699	N	80%	Hypokalemia

[a] Note – only mifepristone and pasireotide are approved by the U.S. Food and Drug Administration for the treatment of Cushing's syndrome.
[b] Because of glucocorticoid receptor blockade, UFC increases rather than decreases with effective therapy and therefore UFC cannot be used to judge efficacy.

Subsequent experience has shown that early addition of a mineralocorticoid blocker, such as spironolactone or eplerenone (preferred in men as it does not cause blockade of the androgen receptor), is beneficial in this regard (Fleseriu et al., 2013). Another adverse effect was endometrial hyperplasia which is a specific progesterone receptor modulator-associated endometrial change (PAEC) consisting of a thickened endometrium that is not thought to be a premalignant state (Fleseriu et al., 2012, 2013). However, this can be associated with severe menorrhagia. Monitoring of treatment can be difficult because of the lack of biochemical parameters to follow and overdosing causing adrenal insufficiency can occur. If severe adrenal insufficiency occurs, large doses of dexamethasone (10 mg) may be necessary because of the receptor blockade (Fleseriu et al., 2013).

2.10. LCI699

LCI699 is an 11β-hydroxylase and aldosterone synthase inhibitor that is now completing phase 2 studies. In a 22 week study, LCI699 normalized UFC in 15 of 19 patients (78%) (Bertagna et al., 2014). Phase 3 trials are just now beginning. Because of the build-up of the 11-deoxycortisol levels with this drug, cortisol levels also have to be measured with liquid chromatography–tandem mass spectrometry (Trainer, 2014).

2.11. Combination therapy

Because many of these agents act by different mechanisms, it could be expected that using them in combination might be more effective that using them singly. However, because of the relative rarity of these patients, such combination therapy studies have only been done in small numbers of patients and in an uncontrolled manner. Two-drug treatment regimens were reported in two studies. Valassi et al. (2012) used metyrapone alone in 23 patients, ketoconazole alone in 17 patients and a combination of ketoconazole and metyrapone in 22 patients but how patients were chosen for each type of treatment was not clear. Control of Cushing's syndrome was achieved in 30%, 45% and 25% of those treated with metyrapone alone, ketoconazole alone and with the combination, respectively (Valassi et al., 2012). In a study of the combination of cabergoline with ketoconazole, Vilar et al. (2010) reported that 3 of 12 patients with persistent Cushing's disease following surgery were controlled with cabergoline alone and that an additional 6 patients were controlled when ketoconazole was added to cabergoline.

Three drug regimens were reported in two studies. Feelders et al. (2010) reported substantial benefit by the sequential addition of cabergoline to pasireotide and then ketoconazole if normalization of UFC was not achieved with the first two drugs. Normalization of UFC was achieved with pasireotide alone in 5/17 (29%), and the addition of cabergoline caused a normalization in an additional 4 were obtained in six of the eight remaining patients (Feelders et al., 2010). In another study, 7 of 11 patients with severe, Cushing's disease treated with therapy combining mitotane (3.0–5.0 g/24 h), metyrapone (3.0–4.5 g/24 h), and ketoconazole (400–1200 mg/24 h) concomitantly achieved normalization of UFC; substantial falls in UFC in the other 4 were found as well (Kamenicky et al., 2011).

3. Conclusions

Ketoconazole and cabergoline have had varying degrees of success in patients with Cushing's disease, although the recent "black box" warning regarding ketoconazole hepatotoxicity makes that drug less desirable and less available (Table 1). Other earlier therapies, such as metyrapone and mitotane, are less successful but mitotane still seems to be popular in France. Mifepristone offers high success clinically and metabolically but can be difficult to use because of difficulty in titrating dose and adverse effects of adrenal insufficiency and menorrhagia. Pasireotide will be helpful in a small percentage of patients with Cushing's disease but has a major adverse effect of hyperglycemia. LCI 699 may end up being a better metyrapone but studies are still very preliminary. Combination therapy may have a role in difficult to manage cases.

Some particular situations may influence the choice of treatment. For example, the pregnant patient cannot be treated with mifepristone or mitotane and safety aspects of pasireotide in this condition have not been established; therefore, only cabergoline, metyrapone and ketoconazole would be indicated but none of these have extensive experience recorded in pregnancy. The uncommon patient with a large pituitary adenoma might best be treated with agents with direct pituitary effects, such as cabergoline and pasireotide. The rare patients with very severe hypercortisolism who are too ill for surgery can have an initial short-term treatment with etomidate or longer term treatment with the combination of mitotane, metyrapone or ketoconazole described earlier.

Now, 39 years following Dorothy Krieger's first report of the medical therapy of Cushing's disease, we have many choices for the medical therapy of patients with Cushing's syndrome. It is now possible to tailor treatment to the individual patient.

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