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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.

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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 been used at lower doses, in the range of 2–4 g/day, for the treatment 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).

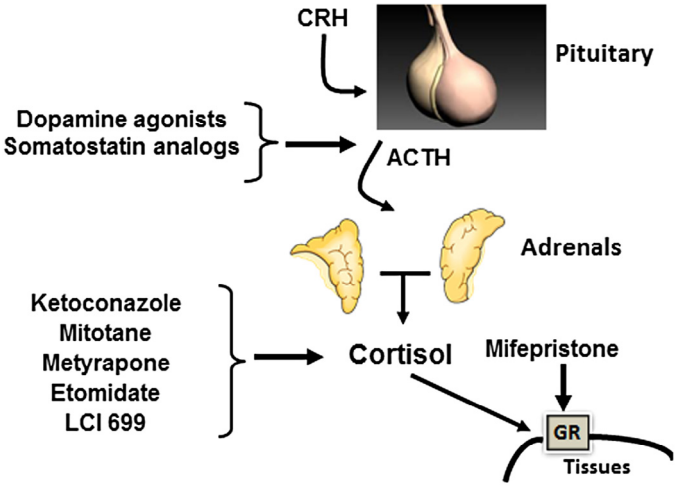

Fig. 1. This schematic outlines the sites of action for the various medications used for the treatment of Cushing's syndrome. Abbreviations used: CRH – corticotropin releasing hormone; ACTH – adrenocorticotropic hormone; GR – glucocorticoid receptor.

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., 2012). One problem has recently been found in that the high levels