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Medical suppression of hypercortisolemia in Cushing's syndrome with particular consideration of etomidate

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Abstract Cushing's syndrome is associated with excessive cortisol secretion by the adrenal gland or ectopic tumours and may result in diabetes, hypertension, and life-threatening infections with high mortality rates especially in the case of surgical resection. Although surgical resection is the treatment of choice, patients may benefit from preceding medical therapy. This may especially be useful as an adjunctive approach in emergency settings, if patients cannot undergo surgery, if surgery or radiotherapy fails, or if the tumour recurs. Medical therapy can be categorized in three different groups—inhibition of steroidogenesis, suppression of adrenocorticotropic hormone, and antagonism of the glucocorticoid receptor. However, the majority of common drugs are not available for parenteral administration, which may evoke a management problem in emergency settings or in patients unable to tolerate oral medication. The carboxylated imidazole etomidate is a well known parenteral induction agent for general anaesthesia. Besides its hypnotic properties, etomidate also has α-adrenergic characteristics and inhibits the enzyme 11-deoxycortisol β-hydroxylase, which catalyzes the final step of the conversion of cholesterol to cortisol. Adverse outcomes have been reported when used for sedation in septic or trauma patients probably by its interference with steroid homeostasis. However, its capability of inhibition of the 11-deoxycortisol β-hydroxylase leads to suppression of cortisol secretion which has been demonstrated to be a useful tool in severe and complicated hypercortisolemia. Within this article, we review the data concerning different pharmacological approaches with particular consideration of etomidate in order to suppress steroidogenesis in patients with Cushing's syndrome.

Keywords Cushing syndrome · Hypercortisolemia · Adrenal suppression · Etomidate

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Introduction

Cushing's syndrome (CS) is marked by glucocorticoid steroid hormone excess. The disease pertains patients of any age with higher prevalence in females [1]. The incidence of CS is 0.7–2.4 per million humans per year [1]. In the majority of cases (70%), CS is caused by an adrenocorticotropic hormone (ACTH) secreting adenoma of the pituitary gland, known as Cushing's disease [2]. 15% of CS are caused by an adenoma of the adrenal gland and the remaining 15% of CS are attributed to an ectopic tumour producing ACTH [3].

The symptoms and clinical signs of CS are well known and have been well described in the literature [4]. However, CS may lead to a life-threatening clanger of blood glucose or blood pressure and is associated with high rates of surgical mortality (5.6%) and morbidity (40%) [5–7]. Therefore, early diagnosis and adequate therapy are inevitable.

Diagnostic options

The characteristic of CS is an inappropriate cortisol secretion insensitive to the normal feedback loop.

Diagnostic tests are based on demonstration of excessive cortisol secretion, loss of circadian rhythm, and abnormal regulation of hypothalamo-pituitary-axis [8]. First line-screening diagnostic methods include urinary free cortisol (≥2 measurements), late night salivary cortisol (≥2 measurements), and a 1 mg overnight dexamethasone suppression test [8]. Dexamethasone-CRH suppression test and the serum midnight cortisol test have been proposed as second-line diagnostics [9].

Once the diagnosis of CS is made, the source of cortisol excess should be located. In these circumstances, the plasma ACTH should be determined as a first step. Plasma ACTH levels of <5 pg/ml are characteristic for an ACTH-independent disease; ACTH levels >15 pg/ml are typically found in ACTH-dependent diseases [10]. Magnetic resonance imaging and computer tomography are most useful for a precise localization of the reasonable tumour [9].

Surgical therapy

The etiology of hypercortisolism is manifold and likewise its therapeutic strategies. Therefore, different strategies have to be considered individually. First-line treatment of Cushing's disease is the surgical resection of the pituitary tumor by transphenoidal approach. This microsurgical approach is still the most widely used technique, because of the excellent view of the surgical field during the operation [2, 11]. Remission rates after operation range from 65 to 90%. The recurrence rates are 5–10% at 5 years and 10–20% at 10 years. Repeated transphenoidal resection may be undertaken if disease persists after initial surgery [12, 13]. The success rate in these cases varies between 50 and 70% in specialized centres [2, 11]. In patients with persistent Cushing's disease, bilateral adrenalectomy can be performed as a final option after at least two attempts of pituitary adenoma resection and persistent severe medical conditions which are not manageable by medical therapy or radiation [11, 13]. Additionally, adrenalectomy is the surgical therapy of choice in patients with cortisol secreting adrenal adenoma. This procedure provides immediate control of hypercortisolism, and the morbidity can be reduced by the use of endoscopic approaches [14]. Thompson et al. could show that 79.4% of patients after bilateral laparoscopic adrenalectomy had unverifiable serum cortisol levels during follow-up; 25.7% of the included patients had serum ACTH levels greater than 300 pg/ml [15]. However, this approach results in lifelong steroid replacement therapy and because of the risk of developing Nelson syndrome, MRI scans and ACTH evaluation have to be performed in periodic intervals [14–16].

Management of patients with adrenal carcinomas requires a multidisciplinary approach, at presentation and at disease relapse. At presentation, the principal considerations are surgical, which is the only curative option [17]. Despite aggressive surgery, 70–85% of patients experience relapse locally or develop metastases. Therefore, it is not surprising that the 5-year survival rate after complete resection is only 16–35%. Incomplete resection of the carcinoma is followed by survival for less than 1 year [17]. Owing to the worse outcome, radiation of the surgical field has been performed in some studies. Whereas initial studies reported a lack of benefit with adjuvant radiation later studies claim high response rates with little toxicity [18, 19]. Finally, for patients in whom surgery is not possible, chemotherapy is often exerted, albeit with modest success (response rates 13–39%) [20, 21].

In patients presented with ectopic ACTH secretion, the source of ectopic ACTH production (e.g. a tumour) should be resected surgically. However, these patients may present two distinct problems: the tumor might not be completely resectable or is not identifiable. If surgery is not feasible or has failed, patients require adrenalectomy or medical therapy [10, 14].

Medical therapy

Although there is general agreement that surgery is the optimal therapy for Cushing's syndrome, drug therapy may have either a primary or an adjunctive role if the patient cannot safely undergo surgery, if acute complications of hypercortisolism occur, if surgery fails, or if the tumour recurs [22, 23]. When medication is the only therapy, a major disadvantage is the need for lifelong therapy, as recurrence usually follows discontinuation of treatment. Drug therapy is also effective in controlling hypercortisolism in patients with ectopic ACTH secretion in whom the primary tumour has not been found or cannot be removed [2, 14, 22]. Different pharmacological agents are available to modulate cortisol production and ameliorate the clinical manifestation of CS. The majority of these drugs are old and some only show marginal results [24, 25]; the efficacy of newer drugs is not known and therefore needs to be evaluated in clinical trials.

The drugs which are used in the treatment of CS are summarized in Table 1 and can be divided into several groups:

- Corticotropin inhibitors
- Adrenal inhibitors
- Adrenal receptor blockers
- Glucocorticoid receptor antagonists

Table 1 Summary of oral drugs in the treatment of Cushing's syndrome

Agent	Daily dose	Side effects
Pasireotide	1,200–1,800 μg	Hyperglycemia, diarrhea, nausea, vomiting, prolongation of QT interval
Aminoglutethimide	0.5–2 g	Sedation, somnolenz, dizziness, rush, cholestasis, bone marrow suppression
Fluconazole	200 mg	Headache, dizziness, nausea, vomitting, diarrhea, fatigue, oliguria, hypokalaemia, paraesthesia, thrombozytopenia, prolonged QT interval, torsades de pointes
Ketoconazole	400–1,200 mg	Hepatic toxity, nausea, vomiting, headache, sedation
Metyrapone	750–6,000 mg	Hypertension, hirsutism, edema, nausea
Mitotane	4–12 g	Ataxia, vertigo, gynecomastia, hypercholesterolemia, nausea
Mifepristone	10–25 mg/kg	Severe hypokalemia, fatigue, vomitting, gynecomastia

Corticotropin inhibitors

Cyproheptadine, PPAR-γ agonists and valproic acid are members of this group. Different reports and small clinical studies failed to show an adequate effect of these agents in the treatment of CS [26–28].

Most of the pituitary adenomas express somatostatin (ssr_5) and dopamine (D_2) receptors [29]. However, the somatostatin analogue octreotide failed to show clinical efficacy, which may be due to the down regulation of somatostatin receptors by glucocorticoids [30]. The available data for a potential role of octreotide in combination with ketoconazole in treating ectopic ACTH producing tumours are unconvincing [31].

The newer somatostatin analogue SOM-230 (pasireotide) showed encouraging data in initial studies. Pasireotide has a high affinity to all somatostatin receptor subtypes and a 40-fold higher affinity to ssr_5 than octreotide [32]. Compared to octreotide, pasireotide leads to an increased suppression of ACTH release [33]. Preliminary results of an open label, single arm phase 2 study of fourteen patients with persistent or recurrent CS treated with pasireotide 600 μg subcutaneously twice daily for a period of fifteen days, showed normalization of serum cortisol levels to baseline in 21%. Half of the patients had serum cortisol levels that were reduced by more than 40% with significant improvement of typical CS symptoms [34].

Adrenal inhibitors

Aminoglutethimide

Aminoglutethimide has been used in adults and children in doses of 500–2,000 mg daily and prevents the conversion of cholesterol to pregnenolone [35]. In patients with CS, application of aminoglutethimide leads to clinical and biochemical remission in up to 42% of cases (50% reduction of morning serum cortisol levels or return to normal cortisol levels) [36]. The suppressive effect of aminoglutethimide can be reversed by the stimulating effect of ACTH [37]. Therefore, aminoglutethimide is not efficacious as a monotherapy [23].

Aminoglutethimide may cause gastrointestinal (nausea, vomiting) and neurological side effects (sedation, lethargy). Hypothyroidism can be found in 5% of treated patients. Cholestasis and bone marrow suppression are also rare side effects [35]. In addition, aminoglutethimide induces different P450 enzymes including CYP1A2 and CYP3A4 which may cause unintentional medication interactions [35].

Ketoconazole

Ketoconazole is the initial drug of choice and inhibits the synthesis of cholesterol by blocking demethylation of lanosterol. Additional mechanisms of action include inhibition of 17α-hydroxylase, 11β-hydroxylase and the cholesterol side chain cleavage [23]. A metaanalysis of patients with CS receiving 400–1,200 mg ketoconazole daily yielded an average remission rate of 70% [23].

Hepatotoxicity is the most common side effect, observed in 12% of cases [23]. Therefore, liver function should be monitored during application of ketoconazole (early markers include serum alkaline phosphatase, ALT, AST, and bilirubin). In addition to hepatic side effects, nausea, vomiting, headache, and sedation might occur [23, 38].

The use of ketoconazole during pregnancy is obsolete, because of its teratogenicity [13]. Similar to aminoglutethimide, ketoconazole interacts with cytochrome P450 enzymes and may cause significant drug interactions [38].

Mitotane

Mitotane is started with a dose of 250–500 mg doses nightly with slow elevation of the doses up to 4–12 g daily. The drug inhibits 11α-hydroxylase, 18-hydroxylase, 3α-hydroxylase, and hydroxysteroid dehydrogenase [24]. Luton et al. [39] found a remission rate of 83% after 8 months in 46 patients with Cushing's disease. In 60% of

these patients, the effect disappeared after the drug was discontinued [39].

Side effects of mitotane therapy include hypercholesterolemia, anorexia, nausea, diarrhoea, decreased memory, and gynecomastia [40]. At higher doses of mitotane, neurological side effects including ataxia, vertigo, confusion, and difficulty with language expression can be observed [24]. Finally, the drug is contraindicated in pregnant women owing to teratogenicity [41].

Adrenal aberrant receptor blockers

In very rare cases of CS, cortisol release is regulated non-physiologically via aberrant receptors independent of ACTH (caused by macronodular hyperplasia). Regulation via β-adrenergic receptors or luteinizing hormone receptors has been described in this context [42, 43]. Pharmacological treatment of these patients consists of β-blockade with propanolol or blockade of luteinizing hormone receptors using gonadotropin releasing hormone antagonists [42, 43].

Glucocorticoid receptor antagonists

Mifepristone has been proven to be effective in the treatment of adrenal cortical carcinoma, ectopic ACTH secretion and Cushing's diseases in investigational, retrospective analyses [11, 44]. The steroid mifepristone binds competitively to the glucocorticoid, progestin and androgen receptor and inhibits the activation of their endogenous ligands. In nonpituitary cases of hypercortisolism, mifepristone is effective at doses of 10–25 mg/kg daily. Severe hypokalemia has been reported in some cases after application of mifepristone in higher doses [11].

Therapy with etomidate

Etomidate belongs to an older group of steroid synthesis inhibitors and has experienced a renewed interest during the last years [23, 45]. Indeed, an increasing number of reports have been published dealing with the effects of etomidate in vitro (Table 2) or with the use of intravenous etomidate to correct severe symptoms of hypercortisolism (Table 3). Etomidate can be used for long-term treatment as well as for emergency settings [3, 46–48]. Particularly in patients with rapidly developing hypercortisolism (e.g. patients with ectopic ACTH-producing tumors) followed by rapidly progressive metabolic disorders, severe hypertension or acute psychotic conditions, a rapid therapy has to be initiated [22, 45]. Etomidate has a rapid onset of action and is particularly useful in patients in emergency settings (e.g. ditched hypertension or acute psychosis which are unable to treat with conventional therapy). Furthermore, etomidate is the only drug in the therapy of hypercortisolism available for parenteral administration which is most valuable in patients who are unable to take oral medication [12, 46, 49]. Finally, etomidate is also used as therapeutic option in patients developing transient liver function disorders after application of ketoconazole [12, 45, 46].

The anesthetic drug etomidate is an imidazole derivate which consits of two isomers; the (+) isomer obtains the hypnotic characteristics of etomidate [50]. Its pharmacokinetics include rapid onset and recovery, minimal respiratory suppression, and hemodynamic stability [51]. At a physiological pH, etomidate is 75% protein bound (mostly to albumin), but only the unbound fraction is metabolically active [52]. Etomidate is degraded to inactive metabolites by hepatic enzymes and plasma esterases [53]. It has α-adrenergic agonist properties which may be the reason for the hemodynamic stability [54]. Furthermore, etomidate inhibits 17α-hydroxylase, 11α-hydroxylase, and 11-deoxycortisol β-hydroxylase which are important enzymes in the steroidogenesis [55].

The main effect of etomidate is hypnosis. An induction dose of etomidate (0.2–0.4 mg/kg) results in apnoea and hypnosis 10–15 s after application [56]. Side effects include pain at the injection side, anaphylactic reactions, minimal change in heart rate, reduction in mean arterial pressure, mild decrease of systolic blood pressure and cardiac index, myoclonus, nausea, and vomiting [57–59]. However, the most critical adverse effect of etomidate is adrenal suppression, occurring approximately 30 min after application of a single dose and may last for about 24 h [60]. In emergency settings, infusion of 2–3 mg/h decreased serum cortisol levels to normal within 24 h [46, 47]. Prolonged application of etomidate in a sub-hypnotic dose (0.03–0.1 mg/kg/h) leads to suppression of cortisol secretion after 48 h without hypnotic or adverse effects [61, 62]. In children continuous infusion of a rate between 0.03 and 0.08 mg/kg/h is recommended [12]. Frequent monitoring of cortisol levels, electrolytes, and glucose levels are necessary in order to prevent adverse effects and hypocortisolemia [49]. Cortisol replacement is recommended when etomidate is applicated for more than 24 h, because cortisol levels decrease dramatically and may induce adrenal insufficiency [61].

Conclusion

In conclusion, hypercortisolism in the context of CS can be presented as a medical emergency with various complications and high mortality rates. Except for emergency settings, surgical resection of the underlying cause is the treatment of choice. Medical treatment is not the first-line therapy (apart from emergency settings), but it offers an

Table 2 Summary of clinical reports dealing with etomidate in the setting of hypercortisolism

Diagnosis	Cases [n]	Age [years]	Gender	Symptoms	Indication for etomidate	Dosage of etomidate	Initial cortisol level [nmol/l]	Normalization of cortisol levels achieved	Specifics	Surgery	Infusion of etomidate [d]	Reference
Ectopic ACTH-secreting tumour	1	56	Male	Hypokalaemia; alkalosis; hypertension; psychosis	Psychotic state of the patient	15–30 mg/h	1,242	Yes	No specification	No specification	14	Gärtner et al. [63]
1 patient with pituitary adenoma; 2 patients with ectopic ACTH-secreting tumours; 3 patients with adenomas of the adrenal gland	6	37–54	5 female; 1 male	No specification	No specification	0.3–0.15 mg/kg/h	220–1,063	Yes	Slight sedation under a dose of 0.03 mg/kg/h; symptoms disappeared unter 0.15 mg/kg/h	No specification	3	Allolio et al. [64]
Pancreascarcinoma with ectopic ACTH-secretion	1	35	Male	Abdominal striae; decreased libido; hypertension; muscle weakness; bipolar disorders	Patient was unable to take oral medication	Initially 2.5 mg/h for 6 days, than 1.2 mg/h for 48 days	1,170	Yes	Cortisol replacement	Exploratory laparotomy	54	Drake et al. [47]
Pituitary adenoma	1	70	Female	Abdominal striae; decreased libido; hypertension; muscle weakness; bipolar disorders	Excessive cortisol production in patient	0.02–0.05 mg/kg/h	705	Yes	No specification	Transphenoidal resection	10	Herrmann et al. [65]
Ectopic ACTH-secreting tumour	1	39	Male	Abdominal striae; osteoporosis; hypertension; muscle weakness	Patient was unable to take oral medication	0.03 mg/kg/h	1,711	Yes	Long term administration of etomidate in a patient who has been inoperable	Exploratory laparotomy	>100	Krakoff et al. [48]
Adenoma of the adrenal gland	1	6	Male	Weight gain; abdominal striae; depression	Transient liver function disorders after oral ketoconazole	Initially 1 mg/h for 16 h, than 2 mg/h for 1 h, followed by 3 mg/h	1,250	Yes	Sedation and intubation cortisol replacement	Bilateral adrenalectomy	12	Greening et al. [46]

Table 2 continued

Diagnosis	Cases [n]	Age [years]	Gender	Symptoms	Indication for etomidate	Dosage of etomidate	Initial cortisol level [nmol/l]	Normalization of cortisol levels achieved	Specifics	Surgery	Infusion of etomidate [d]	Reference
Malignant tumor with ectopic ACTH-secretion	1	74	Male	Metabolic alkolosis; muscle weakness; hypocalcemia; hypertension; hyperglycemia; hepatic dysfunction	Excessive cortisol production in patient with mechanical ventilation	0.06 mg/kg/h	159.5	Yes	Sedation and mechanical ventilation	No surgery (Patient died due to multiple organ dysfunction)	9	Johnson et al. [49]
Carcinoma of the lung with ectopic ACTH-secretion	1	46	Female	Psychosis; abdominal striae; leg edema; abdominal obesity	Psychotic state of the patient	0.02 mg/kg/h	4,200	Yes	Sedation and intubation; cortisol replacement	No surgery (Tumour was inoperable)	4	Bilgin et al.[66]
Adenoma of the adrenal gland	1	6	Male	Obesity; muscle weakness; poor growth; hypertension; precocius puberty	Transient liver function disorders after oral ketoconazole	0.08 mg/kg/h	1,200	Yes	Sedation and intubation; cortisol replacement	Bilateral adrenalectomy	12	Mettauer et al. [12]
Adenoma of the adrenal gland	1	17	Female	Obesity; muscle mass atrophy; cutaneous striae	Transient liver function disorders after oral ketoconazole	Bolus of 10 mg; then 0.045 mg/kg/h continuously	3,201.6	Yes	No sedation or cortisol replacement	Bilateral adrenalectomy	1	Dabbagh et al. [45]
Pheochromocytoma and hyperplasia of the left adrenal gland	1	55	Female	Multiple fungal infections; easily bruised skin; mood changes; hypertension; obesity	Rapid excess of cortisol	No specification	5,900	Yes	Sedation and intubation; cortisol replacement	Bilateral adrenalectomy	5	Lutgers et al. [3]

Table 3 Summary of in vitro analyses dealing with etomidate and adrenal cells

Cell line	Cell density	Concentration of etomidate [M]	Incubation [min]	Effect	Reference
Cells from human adrenal glands (Patients had Cushing's syndrome)	10^5–50^5 cells/ml	10^{-6}–10^{-8}	120	Etomidate at 10^{-8} M reduced cortisol release up to 85%; higher concentrations resulted in complete suppression of cortisol release	Lamberts et al. [67]
Cells from human adrenal glands (Patients had Cushing's syndrome)	30^5 cells/ml	10^{-5}–10^{-11}	120	The ED_{50} for the inhibition of cortisol release was between 10^{-9} and 10^{-8} M; concentrations of 10^{-7} M or higher resulted in complete suppression of cortisol release	Varga et al. [68]

excellent option as an adjuvant therapeutic agent or in order to control hypercortisolism pre- and peri-operatively. Adrenal suppression induced by etomidate can be used safely in sub-hypnotic dosages and presents an excellent short-term control of severe hypercortisolemia when surgery is impossible, other oral medications have failed or in emergency settings.

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