Pharmacological Therapy of Cushing's Syndrome: Drugs and Indications

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Abstract: ***Objective*:** To review the main pharmacological properties and clinical applications of the drugs used in the medical therapy of Cushing's syndrome.

***Data Sources*:** Search for articles were performed in the following dababases: MEDLINE, EMBASE, Cochrane Database of systematic Reviews and The Cochrane Central Register of Controlled Trials (CENTRAL). Search terms included Cushing's syndrome and drug therapy.

***Data Synthesis*:** Available data suggest that neuromodulatory compounds affect corticotropin (ACTH) or ACTH-releasing hormone (CRH) synthesis and release. They include serotonin antagonists, dopaminergic agonists, valproic acid, reserpine, somatostatin analogs and thiazolidinediones. These agents have been effective in a limited number of patients with ACTH-dependent Cushing's syndrome. Inhibitors of steroidogenesis reduce cortisol production by blocking one (metyrapone, trilostane) or several (aminoglutethimide, ketoconazole, fluconazole, etomidate) enzymes involved in steroid biosynthesis. Mitotane is a steroidogenesis inhibitor with adrenolitic properties. Mifepriston'e blocks glucocorticoid receptor activation without modifying cortisol synthesis.

***Conclusion*:** Agents that inhibit steroidogenesis are useful in all forms of Cushing's syndrome and are effective in about 70% of patients. Main indications for drug therapy include preparation for surgery, persistence or recurrence after surgery, while awaiting for the effect of radiation therapy, occult ectopic ACTH syndrome, severe hypercortisolism and malignancy related hypercortisolism.

Key Words: Cushing's syndrome, drug therapy, cortisol, corticotropin.

INTRODUCTION

Endogenous Cushing's syndrome results from prolonged exposure to excessive circulating glucocorticoids. Consequences of hypercortisolism include central obesity, plethora, round face, hirsutism, thin skin, myopathy, osteoporosis, increased tissue fragility, poor wound healing, hypertension, diabetes and psychiatric symptoms [1]. Cushing's syndrome can be separated into adrenocorticotropin (ACTH)-dependent and ACTH-independent categories (Table **1**). The term Cushing's disease is used to refer to an ACTH-secreting pituitary adenoma. It is the main cause of endogenous hypercortisolism, representing about 65-75% of patients. A variety of nonpituitary tumors are capable of ectopic secretion of pro-opiomelanocortin (POMC)-derived peptides. Such tumors account for 10-20% of patients with Cushing's syndrome. Only a few cases of ectopic ACTH releasing hormone (CRH)-secreting tumors have been reported [1,2]. Benign or malignant adrenocortical tumors are the most common cause of ACTH-independent Cushing's syndrome (5-20%). Primary pigmented nodular adrenal dysplasia (micronodular adrenal hyperplasia) and macronodular adrenal hyperplasia account for a small percentage of patients with ACTH-independent Cushing's syndrome. Rare causes of ACTH-independent Cushing syndrome include the excess secretion of cortisol by abnormal adrenal expression and function of receptors for various hormones, including gastric inhibitory polypeptide, vasopressin, β-adrenergic agonists, interleukin-1 and luteinizing hormone/human chorionic gonadotropin and serotonin [3,4].

The aims of treatment in patiens with Cushing's syndrome are to reverse the clinical manifestations by reducing cortisol secretion, erradicate any tumor, avoid permanent dependence upon medications and permanent hormone deficiency [1]. The morbidity and mortality associated with Cushing's syndrome and the limitation of current surgery and irradiation therapies highlight the need for the medical therapy. Furthermore, metabolic derangements of the syndrome, and the consequent increase in the risk of surgery, can be efficiently reversed using medical therapy. Drugs may act either by inhibiting ACTH release at pituitary or ectopic level, inhibiting cortisol biosynthesis at adrenal level, or blocking the peripheral glucocorticoid receptors (Fig. **1**). We herein review the main pharmacological properties and clinical applications of the neuromodulators of ACTH release, steroidogenesis inhibitors and glucocorticoid receptor-blocking agents.

Table 1. Main Aetiologies of Endogenous Cushing's Syndrome

ACTH-dependent Cushing's syndrome
ACTH-secreting pituitary adenoma (Cushing's disease)
Other forms of hypothalamic-pituitary dependent Cushing's syndrome (corticotroph hyperplasia, carcinoma)
Ectopic ACTH/CRH syndrome
ACTH-dependent macronodular adrenal hyperplasia
ACTH-independent Cushing's syndrome
Adrenal adenoma
Adrenal carcinoma
Micronodular adrenal hyperplasia (including Carney complex)
ACTH-independent macronodular adrenal hyperplasia
Adrenal hyperplasia due to abnormal hormone receptors

METHODS

All articles related to medical therapy of Cushing's syndrome were searched in MEDLINE from 1964 to 2006. Search was performed by using the term "Cushing Syndrome/drug therapy" as a subheading of the term Cushing Syndrome in the MeSH thesaurus. Another search was performed in EMBASE from 1980 to 2006 with the heading Cushing syndrome and the subheading drug therapy. All clinical trials and systematic reviews related to Cushing's syndrome were also searched at the Cochrane Database of systematic Reviews and The Cochrane Central Register of Controlled Trials (CENTRAL). The selection criteria included all prospective and retrospective studies, all case series, all case reports, and reviews concerning the effects of pharmacological agents on patients with any form or Cushing' syndrome.

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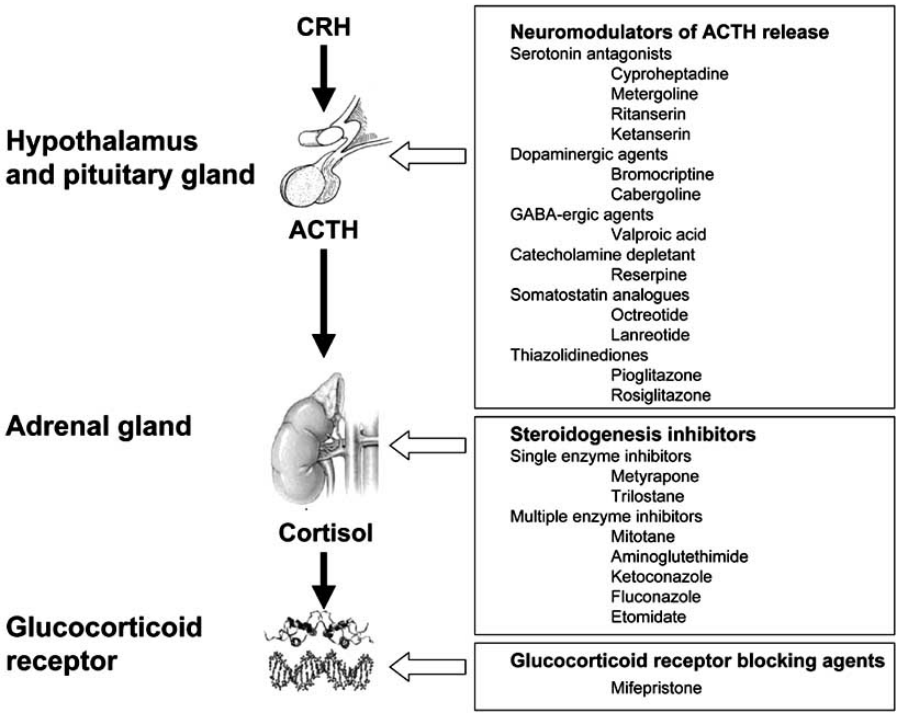


Fig. (1). Pharmacological agents with potential usefulness in the medical treatment of Cushing's syndrome classified according to their site and mechanism of action.

NEUROMODULATORS OF ACTH RELEASE

Serotonin Antagonists

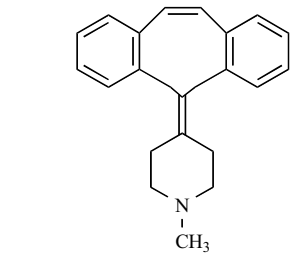
Pharmacological Properties

Cyproheptadine is a nonselective 5-hydroxytryptamine receptor blocking agent that also have histamine, cholinergic and dopamine antagonistic properties (Fig. **2**) [5,6]. Cyproheptadine reduced basal and insulin or metyrapone-stimulated ACTH secretion by suppressing hypothalamic-pituitary-adrenal axis activation [5,7-13]. Furthermore, some studies suggest that cyproheptadine may have a direct pituitary action [10,12].

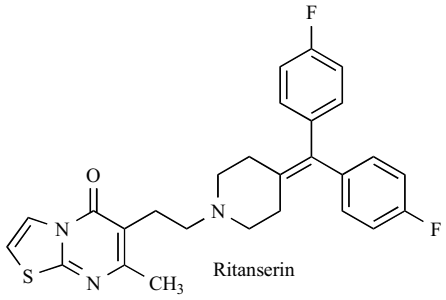
Daily recommended dose of cyproheptadine is 24 mg [6,14]. Ritanserin (Fig. **2**) has been used at daily doses of 10-15 mg and ketanserin at 40-80 mg. Hyperphagia and weight gain are frequent in patients treated with cyproheptadine. Other adverse effects include somnolence, dry mouth and effects derived of histamine H1 antagonism.

Clinical Applications

Several case reports have documented that cyproheptadine treatment induced remission in patients with Cushing's disease after unsuccessful treatment with surgery and/or radiotherapy [7,11,15-20]. Prolonged remission of a case of Cushing's disease following cessation of cyproheptadine therapy has also been reported [21]. In a non-controlled study in 3 patients with Cushing's disease, the administration of cyproheptadine, 24 mg daily, over a period of three to six months was associated with prompt and sustained clinical and laboratory remission [6]. In 2 patients with Cushing's disease, absence of tumor evidence at magnetic resonance imaging, and a hyperpulsatile cortisol secretory pattern, chronic treatment with cyproheptadine resulted in sustained clinical and biochemical improvement and normalization of the median of absolute and relative increments in cortisol peaks [14]. These results suggest that patients with Cushing's disease who are characterized by a hyperpulsatile cortisol secretory pattern and in whom no pituitary lesion can be identified by magnetic resonance imaging, cyproheptadine treatment may be useful.



Cyproheptadine



Ritanserin

Fig. (2). 5-Hydroxytryptamine receptor blocking agents, cyproheptadine and ritanserin.

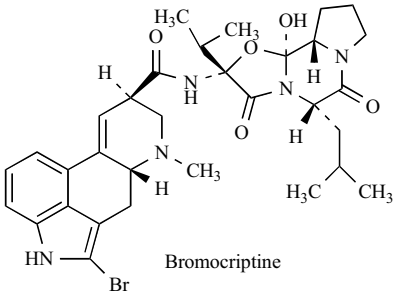
Efectiveness of cyproheptadine treatment has also been reported in some patients with Nelson's syndrome [22]. Some authors have suggested that in patients with Nelson's syndrome or previously treated Cushing's disease, cyproheptadine might decrease ACTH levels in up to 70% of the cases [10,23,24]. However this figure seems to be exaggerated, since some clinical reports have documented a remission of Cushing's disease [7,11,15-19], whereas in others no significant effects were observed [25-30].

Cyproheptadine has been used in childhood to avoid pituitary surgery [17,30] and in Cushing's syndrome during pregnancy [31]. Others selective serotoninergic antagonists, such as metergoline [25,32,33] and ritanserin [34] have been employed in the treatment of a limited number of patients with Cushing's disease. A study using ritanserin or ketanserin in 11 patients with Cushing's disease found that responses were sustained in only 3 patients [35].

Dopaminergic Agents

Pharmacological Properties

Bromocriptine, a lysergic acid derivative, is a dopaminergic agonist with capacity to bind D2 receptors (Fig. **3**). Daily doses of bromocriptine have ranged from 2.5 to 30 mg in patients with Cushing's disease. Responsive patients usually need higher doses than those used in the therapy of prolactinomas. Doses as high as 55 mg/day have been also reported [36]. Nausea, vomiting, dry mouth, nasal congestion, and postural hypotension are the most frequent adverse effects. Dyskinesia, constipation, vasomotor phenomena, eritromelalgia and psychiatric disorders may occur with long-term therapy.



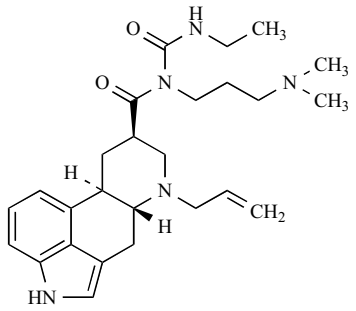


Fig. (3). Dopaminergic receptor agonists, bromocriptine and cabergoline.

Clinical Applications

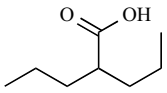
Initial clinical studies suggested that bromocriptine administration were followed by an acute suppression of ACTH secretion in some patients with Cushing' disease or Nelson syndrome [37-39]. Isolated case reports have showed long-term clinical and biochemical remission while on bromocriptine therapy in patients with ACTH-dependent Cushing's syndrome [40-42], while others have showed a lack of effect of this treatment [25,43]. In a small series of patients bromocriptine was effective in 2 patients and ineffective in 4 patients with Cushing's disease [26]. Some authors have reported successful results of bromocriptine treatment in patients with cyclic Cushing's disease [44-47] and reduction of pituitary tumor size [41]. Other reports have showed variable results and only a moderate effectiveness of bromocriptine in the treatment of Cushing's disease [39,48-54]. Therefore it seems possible that some ACTH-secreting pituitary tumors have or may acquire responsiveness to dopaminergic agents [42]. Unfortunately, biochemical response to an acute dose of bromocriptine fails to identify the patients who would benefit from long-term dopaminergic treatment [39,49,51-53].

A placebo-controlled study showed that bromocriptine was not more effective than placebo in the acute reduction of serum cortisol in patients with Cushing' disease [55]. In a three-month non-contolled trial, Invitti *et al*. [56] showed that monthly 50-100 mg injections of a bromocriptine depot preparation did not consistently influence pituitary-adrenal activity, as judged by plasma ACTH, cortisol and urinary free cortisol levels, in a small group of 6 patients with Cushing's disease. Other dopamine agonists do not seem to be more effective, although some authors have suggested that cabergoline (Fig. **3**) may have significant respones rates [57].

Valproic Acid

Pharmacological Properties

Sodium valproate (di-n-propylacetic acid, Fig. **4**), a gamma-aminobutyric acid (GABA)-transaminase inhibitor, increases endogenous concentrations of GABA, a neurotransmitter involved in the glucocorticoid negative feedback mechanisms at hypothalamic level. The mechanism of the inhibition of ACTH secretion by valproate might involve a GABA-induced decrease in the production of CRH or a direct action on the pituitary tumor cells [58].



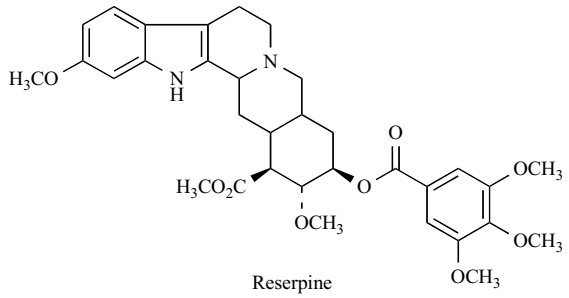


Fig. (4). Two neuromodulators of corticotropin release: valproic acid, a GABA-ergic compound, and reserpine, a drug acting by depleting catecholamine deposits.

Recommended dose of sodium valproate is 200 mg thrice a day [18,59], although daily doses of 1000 mg [60] and 1200 mg [61] have been used. Nausea, vomiting and anorexia are the most frequent side effects. Other reported adverse effects are sedation, ataxia, tremor, rash, hepatotoxicity, alopecia and increase in appetite [18,59].

Clinical Applicatons

Sodium valproate is known to induce a decrease of plasma ACTH in some patients with Nelson's syndrome [58,62], although there is no evidence of the efficacy of the drug in inducing reduction in tumor size [63]. An unique oral dose of 200-400 mg sodium valproate did not induce changes in ACTH and cortisol levels in 11 patients with Cushing's disease and 3 patients with Nelson's syndrome [60].

Medical treatment with sodium valproate induced long-term hypocorticism in a patient with persistent Cushing's disease after transfrontal hypophysectomy [64]. Other case reports of isolated patients with Cushing's disease responsive to sodium valproate have been reported [18,59,64-67]. In a series of 13 patients with

Cushing's disease, only two cases were responsive to sodium valproate treatment [54]. Long-term treatment (3 weeks-9 months) was ineffective in 2 patients with active Cushing's disease and in 1 patient with Nelson's syndrome [60]. In a study performed in 19 patients with Cushing's syndrome, sodium valproate, 600 mg/day for 3 months, did not induce normalization of ACTH or cortisol levels and/or clinical remission [68].

Reserpine

Reserpine acts by depleting cathecolamine and serotonine storages (Fig. **4**). A direct inhibitory effect of reserpine on the secretion of ACTH and β-endorphin from the pituitary of patients with Cushing's disease has been reported [69]. Murayama *et al*. [70] reported that 11 out of 20 patients with Cushing's disease treated with reserpine for a mean of 24 months, daily dose 1-2 mg, in combination with a single course of external pituitary irradiation experienced long term remissions. There were no differences in remission rates in patients classified according to the dose of radiation.

The effects of reserpine treatment, not associated with pituitary irradiation, were also examined in untreated patients with Cushing's disease [71]. Long-term treatment (mean dose 1.7 mg per day, mean duration 15.8 weeks) induced a marked reduction in plasma cortisol, and 24-hour urinary 17-hydroxycorticosteroids and/or free cortisol in 4 of 8 examined patients. Plasma ACTH response to CRH was evidently decreased in one patient evaluated one month after the initiation of reserpine.

Somatostatin Analogues

Pharmacological Properties

The mechanism of action of somatostatin analogues, octreotide and lanreotide (Fig. **5**), in patients with ACTH hypersecretion is not well understood. Tyrrell *et al*. [72] demonstrated that somatostatin

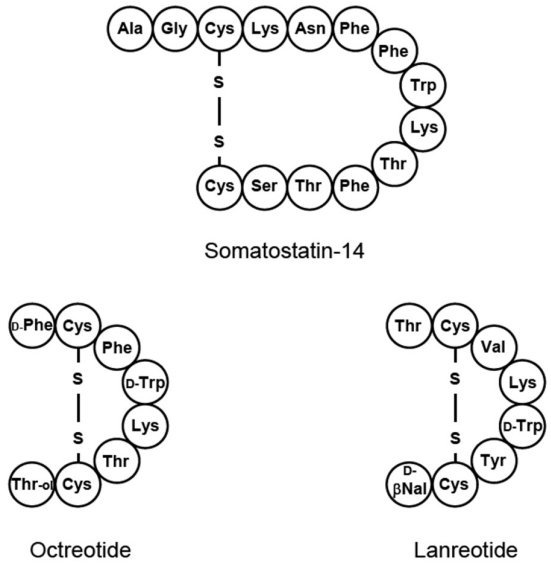


Fig. (5). Aminoacid sequence of native somatostatin (somatostatin-14) and the two clinically available somatostatin analogues, octreotide and lanreotide. D-βNal: D-βNaftylalanine.

infusion in patients with Nelson's syndrome resulted in a sustained, progressive fall in plasma ACTH to 40% to 71% of basal value with a return to initial levels after cessation of the infusion. A fall in plasma ACTH was also observed during the infusion of somatostatin to patients with adrenal insufficiency [73]. A single dose of octreotide was followed by no respone in baseline ACTH concentration in 18 patients with Cushing's disease [74-76]. An absence of effect of octreotide on ACTH responses to CRH has also been reported in 13 patients [75,76]. However, basal and stimulated ACTH secretion has been reported to be inhibited by octreotide in human corticotropic adenoma cell cultures *in vitro* [77]. It has been suggested the presence of somatostatin receptors in human corticotropic adenomas [78,79], although the fact that octreotide has no suppressive effect on ACTH levels of patients with Cushing's disease *in vivo* suggests that cortisol might exert a somatostatin receptor down-regulation *in vivo*.

Studies *in vivo* have shown that somatostatin and its analogue octreotide do not inhibit ACTH secretion in normal subjects [80] and in patients with ACTH secreting pituitary adenomas [74,77]. On the contrary, in patients with ectopic ACTH secretion chronic therapy with octreotide is accompanied by a decrease in ACTH production [81-85]. This action seems to be induced by interaction with somatostatin receptors, mainly subtypes 2 and 5 [86-88]. A recent study has shown that human corticotroph tumors express somatostatin receptors subtypes 1, 2, 4 and 5, and that SOM230 (pasireotide), a new somatostatin analogue with affinity to receptors subtypes 5, 2, 3 and 1, inhibited ACTH secretion in five out of six cultured tumors [89].

Some authors have also suggested a temporary inhibitory effect of somatostatin analogues on adrenal steroidogenesis in patients with Cushing's disease [90]. In GIP-dependent Cushing's syndrome, octreotide temporarily suppressed meal-induced GIP release, thereby suppressing GIP-induced cortisol secretion [91].

Half life of octreotide after subcutaneous injection is short and it has to be administered 3-4 times a day. In patients with Cushing's syndrome the range of used doses has been wide (100-1500 μg/day). Dose has to be modified according to the clinical and hormonal responses. Slow release lanreotide has been used at 30 mg every 21 days [92]. The most commonly found adverse effects of somatostatin analogues are abdominal discomfort, loose stools or diarrhoea, mild malabsortion, flatulence, nausea and pain at the injection site in patients receiving the depot formulations. The development of cholesterol gallstones is the most serious adverse effect of somatostatin analogues [93].

Clinical Applications

Initial clinical studies demonstrated the effectiveness of octreotide in the management of patients with ectopic ACTH secretion [74,81,85,94-96]. A stabilization or even reduction in tumor volume has also been reported [81]. Further studies have confirmed initial results in patients with ectopic ACTH secretion [76,84,90,97,98], although some authors have reported negative results [99,100] or variable responsiveness to octreotide [101]. In summary, a review of patients with the ectopic ACTH syndrome showed that an acute response to octretide has been observed in 24 of 38 patients with the ectopic ACTH syndrome [102]. A prolonged response to octreotide, defined as persistent decrease in serum cortisol, cortisoluria or plasma ACTH of greater than 30% for more than 3 months, has been reported in 10 of 14 cases [82]. It has been suggested that a response to a short trial of octreotide in patients with ACTH-dependent Cushing's syndrome who have no demonstrable pituitary tumor should alert to the possibility of an ectopic ACTH source and might identify patients whose disease may be controllable using octreotide [76].

In patients with Cushing's disease the effectiveness of somatostatin analogues has been debatable [74,75,90]. In two of four patients normalization of ACTH levels was achieved with octreotide treatment [103]. However, most of the investigators did not report significant effects of ACTH secretion [74,76]. Somatostatin analogues seem to inhibit pathological ACTH secretion in Nelson's syndrome. Chronic therapy with octreotide in patients with Nelson's syndrome has been reported to reduce circulanting ACTH levels [74] and tumor size [104] in a few patients.

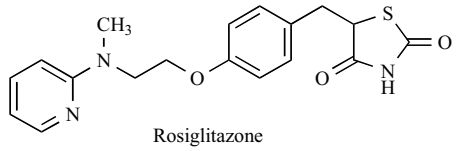
Somatostatin receptor scintigraphy may be useful in patients with ACTH-dependent Cushing's syndrome [105]. The use of radiolabeled somatostatin analogues, such as ^{111}In-pentetreotide, has allowed the location of ACTH-secreting tumors with somatostatin receptors [83,86]. It has been suggested that patients with ectopic ACTH syndrome who exhibit a positive pentetreotide scanning and are responsive to an acute dose of octreotide may be treated with the new sustained release formulations of somatostatin analogues [92].

A patient with metastatic adrenal cortical carcinoma who showed clinical and biochemical improvement after octreotide therapy has been reported [106]. However, these results have not been confirmed by other authors [107].

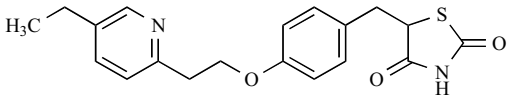
Thiazolidinediones

Pharmacological Properties

Thiazolidinediones are peroxisome proliferator activated receptor (PPAR)-γ agonists. The PPAR-γ is a member of the nuclear receptor superfamily and function as a transcription factor. Activation of PPAR-γ is followed by several biological effects on adipogenesis, carbohydrate and lipid metabolism, inflammation processes and cell proliferation. PPAR-γ agonists, such as rosiglitazone and pioglitazone (Fig. **6**), are a new group of oral antidiabetic agents recently introduced in the therapy of type 2 diabetes. These drugs are insulin sensitizers that reduce insulin resistance, increase glucose uptake in muscle and adipose tissue and decrease hepatic glucose production [108]. Heaney *et al*. [109] demonstrated that PPAR-γ was abundantly expressed in normal ACTH-secreting human anterior pituitary cells and in human ACTH-secreting pituitary tumors. PPAR-γ activation induced cell-cycle arrest and apoptosis and suppressed ACTH secretion in human and murine ACTH tumor cells. In addition, rosiglitazone abolished basal and CRH-induced POMC transcription in mouse corticotroph pituitary tumor cells [109]. A direct effect of rosiglitazone on the steroidogenic enzymes P450c17 and 3β-hydroxysteroid dehydrogenase has been proven by *in vitro* studies [110].



Rosiglitazone



Pioglitazone

Fig. (6). Peroxisome proliferator activated receptor (PPAR)-γ agonists, rosiglitazone and pioglitazone.

Clinical Applications

Hull *et al.* [111] reported on the effect of rosiglitazone administration in two patients with Cushing's disease. The drug induced a significant decrease in early morning cortisol to creatinine ratio without significant clinical improvement during 20-33 days of therapy. No normalization of hormonal values or reduction in tumor size was observed. A reduction of ACTH and cortisol levels and a normalization of urinary free cortisol 30-60 days after the beginning of rosiglitazone administration was observed in 6 out of 14 patients with Cushing' disease [112]. Immunohistochemical analysis of pituitary tumors removed from two responder and two nonresponder patients showed a similar intense immunoreactivity for PPAR-γ in about 50% of cells. Long-term efficacy in some of these patients, as well as escape phenomenon have been reported [113].

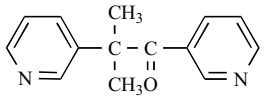
No significant changes in plasma ACTH, serum cortisol, urinary free cortisol and ACTH and cortisol responses to CRH were observed after 30 days of treatment with pioglitazone, 45 mg/day, in five patients with Cushing's disease [114]. Further studies are required to clarify the effectiveness of different doses of thiazolidinediones in patients with Cushing's syndrome.

STEROIDOGENESIS INHIBITORS

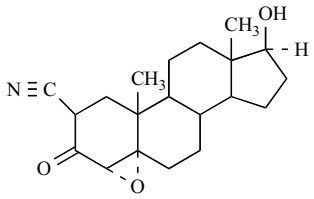
Metyrapone

Pharmacological Properties

Metyrapone, 2-methyl-1,2-bis-[3-piridyl]-1-propanone (Fig. **7**), is a pyridine derivative widely used in the differential diagnosis of Cushing's syndrome and in the assessment of the integrity of the pituitary-adrenal axis [115,116]. Metyrapone acts on cytochrome P450 dependent enzymatic system by blocking 11β-hydroxilase (P450c11β), thus inhibiting conversion of 11-deoxycortisol in cortisol. 11β-hydroxilase blockade also inhibits aldosterone biosynthesis [116]. An inhibition of ACTH secretion by high doses of metyrapone has also been reported [117].



Metyrapone



Trilostane

Fig. (7). Monoenzymatic inhibitors of steroidogenesis, metyrapone (inhibitor of the enzyme 11β-hydroxilase) and trilostane (inhibitor of the enzyme 3β-hydroxysteroid dehydrogenase).

Metyrapone has been used at a daily dose ranging between 500 mg and 6 g in divided doses. The fall in cortisol is rapid, with nadir levels at 2 hours post dose. Doses needed to control hypercortisolemia are higher in patients with ectopic ACTH secretion than in patients with Cushing's disease or adrenal adenomas [118]. Nausea, vomiting, skin rash, ataxia, lethargy, dizziness, vertigo and edema are side effects associated to metyrapone therapy. Incidence of these side effects decreases with daily doses lower than 2 g [119]. Inhibition of 11β-hydroxylase by metyrapone coupled with increased ACTH levels causes increased androgenic and mineralocorticoid precursors. This effect may impair hypertension and hirsutism in women [120]. Combined therapy with ketoconazole may overcome this inconvenience. The increase in 11-deoxycortisol induced by metyrapone is reflected in the urine 17-hydroxycorticosteroids. Urine and serum cortisol should be used to monitor therapy. A strict control of cortisol levels is mandatory under metyrapone treatment, since this drug, as other glucocorticoid synthesis inhibitor, may induce hypoadrenalism. Furthermore, metyrapone is a hepatic enzymatic inductor and may induce hypertensive crisis in some patients [121].

Clinical Applications

The clinical usefulness of this drug has been well characterized by different authors [118,120,122,123]. Metyrapone has been used in the prolonged treatment of patients with Cushing's syndrome due to adrenal tumors [118,124], ectopic ACTH secretion [118,123-

126] and ACTH-secreting pituitary adenomas [118,120,121,127, 128].

In patients with Cushing's disease the clinical features of the disease rapidly improve on metyrapone treatment. Reduction of cortisol levels in these patients may induce an increase in pituitary ACTH secretion [118,120,122,127,128]. In a summary of several studies including 83 patients with Cushing's syndrome, metyrapone, in combination with radiation therapy or other drugs, normalized plasma cortisol in 74% and 17-hydroxycorticosteroids in 75% of the patients [129].

Trilostane

Trilostane, 4α,5-epoxy-17β-hydroxy-3-oxo-5α-androstane-2α-carbonitrile (Fig. **7**), is a competitive inhibitor of the enzyme 3β-hydroxysteroid dehydrogenase [130]. *In vitro*, the drug inhibits conversion of pregnenolone to progesterone. In rats trilostane inhibits corticosterone and aldosterone production and elevates circulating levels of pregnenolone at doses lower than those that produce adrenal hypertrophy or inhibit gonadal steroidogenesis [130]. Daily doses of trilostane in patients with Cushing's syndrome have ranged from 120 to 1440 mg [131,132]. Astenia, abdominal discomfort, diarrhoea, parestesias and increase in salivary secretion have been reported during trilostane treatment. Some authors have reported that trilostane treatment reduced steroid biosynthesis and improved biochemical manifestations of the hypercortisolism in patients with cortisol secreting adrenal tumors and with Cushing's disease [131,133]. However, these results have not been confirmed by others [132,134]. Escape to the effects of trilostane may occur. Although effective in some cases of Cushing's syndrome, the variability of the effect of trilostane may limit its usefulness as a therapeutic agent.

Mitotane

Pharmacological Properties

Mitotane, ortho,para-dichlorodiphenyl dichloroethane (o,p'-DDD, Fig. **8**), is a compound with a chemical structure similar to the insecticide DDT. Administration of mitotane to animals was followed by adrenal gland atrophy, thus calling attention on the endocrine effects of this drug. Mitotane inhibits cholesterol side-chain cleavage enzyme (P450scc) at adrenal mitochondria [135]. It acts also as inhibitor of distinct cytochrome P450 depending enzymes, such as 11β-hydroxylase (P450c11β) and 18-hydroxylase (P450c11AS) and non-cytochrome P450 depending enzymes, such as 3β-hydroxysteroid dehydrogenase (3βHSD) [136]. A particular property mitotane is that it exhibits adrenolitic properties [137,138]. It induces mitochondrial degeneration with atrophy and necrosis of adrenal cortex [139]. The term medical adrenalectomy has been used to designate this effect of the drug [140,141]. Mitotane inhibitory action seems to be more selective in zona fasciculata and zona reticularis and less selective in zona glomerulosa [139]. An effect on ACTH release has also been suggested because patients who exhibit reduction in their hypercortisolism also may have a decrease in plasma ACTH concentrations [138].

Mitotane should be started at 500 mg b.i.d. with progressive increases as needed to obtain an adequate adrenal suppression (2-4 g per day). The onset of action of mitotane is slow and beneficial effects may be delayed between 6 and 8 weeks [137,142]. Its half-life is long and it accumulates in adipose tissue and adrenal glands [143]. The adrenolitic effect of mitotane on biochemical remission can last for long time after the drug is stopped. High doses (8-12 g per day) must be used in Cushing's syndrome due to adrenal carcinoma. To avoid the inconvenience of the delay in the action of mitotane combined therapy with another inhibitor of cortisol synthesis, such as metyrapone, may be used during the first weeks. Urinary free cortisol is the best parameter in monitoring therapy with mitotane. This drug directs extraadrenal metabolism of cortisol to the production of 6β-hydroxycortisol, which is not detected in 17-hydroxycorticosteroids measurement [2,137,138].

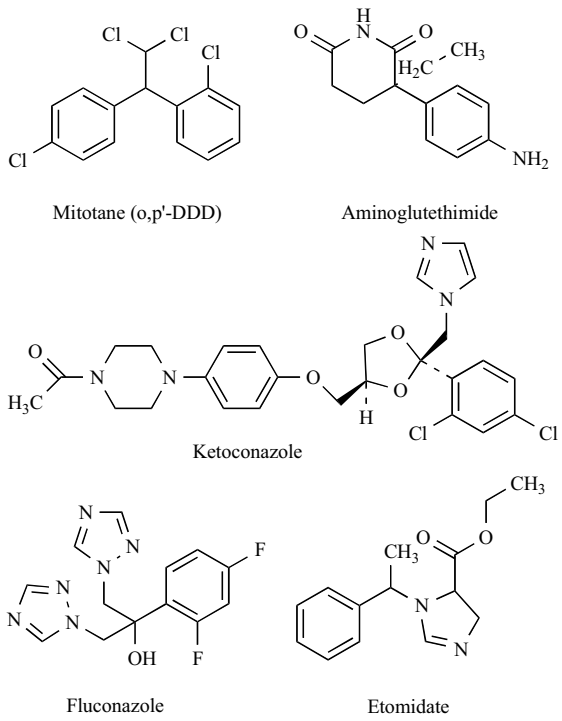


Fig. (8). Multiple enzymatic inhibitors of steroidogenesis: mitotane, aminoglutethimide, ketoconazole, fluconazole and etomidate.

Gastrointestinal and neurological toxicity limits seriously the use of mitotane [137]. Anorexia, nausea, vomiting and diarrhoea are common [142]. Adverse reactions observed less frequently are somnolence, apathy, weakness, ataxia, pruritus, leukopenia, arthralgia, depression and exantema. At higher doses, neurological findings are common and include abnormal gait, dizziness, vertigo, confusion and problems with language expression. Mitotane is an enzymatic inductor. This drug produces an increrase in cholesterol synthesis and an elevation of serum levels of total and LDL-cholesterol even when used at low doses [137,144]. Treatment with simvastatin reversed the hyperlipidemia [145]. Increased urate excretion may give rise to hypouricemia [146]. Mitotane increases serum levels of thyroxin-binding globulin, cortisol-binding globulin and sex hormone-binding globulin. The drug or some of its metabolits may have estrogenic actions and some patients may develop gynaecomastia [137].

Some of the adverse reactions to mitotane may be in relation to drug-induced hypoadrenalism. Mitotane accelerates the clearance of some steroids, such as dexamethasone and fludrocortisone, but not cortisol or prednisolone. If dexamethasone is used, doses higher than usual replacement dose are necessary.

Clinical Applications

Mitotane has been used as medical therapy after surgical treatment in adrenal carcinoma and in inoperable adrenal carcinomas [140,147,148]. In patients with Cushing's syndrome produced by adrenal carcinoma, mitotane induced a reduction in cortisol levels in up to 75% of patients, and a transient decrease in tumour volume in 30% of the patients [140,142]. However, these effects have not been obtained by others [149] and a retrospective analysis of 105 patients showed no benefit of mitotane on patient survival [142].

The effectiveness of mitotane in decreasing cortisol hypersecretion has been demonstrated in patients with Cushing's disease [43,126,139,150]. Low doses of mitotane (up to 4 g/day) has been used concurrently with or after pituitary irradiation in patients with Cushing's disease with remission in 29 out of 36 patients [138]. Remission of the disease was obtained in 38 of 46 patients with Cushing's disease given mitotane alone and in all 16 patients who received this drug combined with irradiation [137]. Nevertheless, 60% of these patients subsequently relapsed and needed additional courses of drug or radiation therapy. Given the effectiveness of this treatment, combined therapy with mitotane and pituitary radiation has been recommended [2]. Long term remission with mitotane therapy has been reported in a patient with intractable Cushing's disease [151]. The incidence of Nelson's syndrome after mitotane medical adrenalectomy appears to be lower than that reported after surgical adrenalectomy. Less frequently, mitotane has been used in the treatment of ectopic ACTH syndrome [152].

Aminoglutethimide

Pharmacological Properties

Aminoglutethimide (Fig. **8**), first used as an anticonvulsant drug, blocks several cytochrome P450 mediated steroid hydroxylation steps, including those required for conversion of cholesterol to pregnenolone and for the aromatization of androgens to estrogens. It blocks adrenal synthesis of cortisol, aldosterone and androgens, and the production of estrogens in extraglandular tissues. Adrenal glands appear full of lipid drops in a similar way to that found in the lipoidic form of the congenital adrenal hyperplasia [119]. Other effects of aminoglutethimide on adrenal steroidogenesis include inhibition of other cytochrome P450 enzymes, such as 21-hydroxilase, 17α-hydroxilase, 11β-hydroxilase, C17,20 liase and 18-hydroxilase [153].

Recommended daily doses range from 0.5 to 2 g [154-159]. The agent is begun at a dose of 500 mg daily, in divided doses, and can be increased by 250 to 500 mg every three to four days. Adverse reactions include drowsiness, nausea, vomiting, anorexia, letargy, sedation, depression, somnolence, headache and blurred vision [154]. A transient morbiliform rash is common in the first two weeks of therapy. Slurred speech and ataxia have been also reported [119]. Aminoglutethimide reduces iodine uptake capacity by the thyroid gland, thus a 5% of the patients may exhibit sings of hypothyroidism. This drug accelerates metabolism of dexamethasone, although not that of cortisol [153].

Clinical Applications

Aminoglutethimide was used in the 1960s to inhibit cortisol secretion in patients with adrenal carcinoma [159] and with ACTH-dependent Cushing's syndrome [160]. This drug provided palliation from the signs and symptoms of hypercorticism in 13 of 21 patients with metastatic adrenocortical carcinoma and four of six patients with ectopic ACTH production due to metastatic carcinomas. Six patients with adrenal adenomas showed clinical and biochemical improvement, and 14 out of 33 patients with bilateral adrenal hyperplasia of pituitary origin improved [154]. Some case reports showed biochemical control of hypercortisolism by aminoglutethimide in patients with ectopic ACTH secretion [161], with failure to obtain clinical improvement [124]. In some cases reduction in cortisol levels produced an adrenal insufficiency requiring replacement therapy with exogenous glucocorticoids [119,154,162]. It seems to be less efficient in Cushing's disease compared to other causes of Cushing's syndrome. This may be due to an increase in ACTH overcoming the enzymatic blockade, or by hepatic enzyme induction increasing the drug's own metabolism [155].

Ketoconazole

Pharmacological Properties

Ketoconazole, an imidazole derivative (Fig. **8**), inhibits ergosterol biosynthesis in fungi and cholesterol synthesis in mammal cells [163]. It reduces adrenal and gonadal androgen biosynthesis both *in vitro* and *in vivo* [164], and also cortisol synthesis [165, 166]. Ketoconazole inhibits predominantly C17,20 lyase activity, which accounts for the inhibitory effect of testosterone production in man [164,165]. Blockade of the cholesterol side chain cleavage (P450scc), 11β-hydroxylase (P450c11β) and 17α-hydroxylase (P450c17) activities gives rise to a decrease in cortisol production. An inhibition of 18-hydroxylase activity has also been reported [167].

The effects of ketoconazole on ACTH secretion is a matter of debate. Some authors [168] have reported an enhanced response of ACTH to ovine CRH after the administration of ketoconazole. However, a lack of compensatory increase in ACTH levels in spite of significant decreases in cortisol production has also been reported [169-172]. It has been suggested that ketoconazole might exert a possible glucocorticoid agonistic action at pituitary level, preventing the expected rise in ACTH secretion in patients with Cushing's disease [172]. *In vitro* studies in rat anterior pituitary fragments and in primary cultures of rat anterior pituitary cells have demonstrated that ketoconazole inhibits CRH-stimulated ACTH release in a dose-dependent manner [173,174].

A wide range of doses, 200 to 1200 mg per day, in divided doses, has been used in patients with Cushing's syndrome. Achlorhydria and antiacid treatments reduce absorption of ketoconazole. Ketoconazole is usually well tolerated. The main side effects are gastrointestinal, and pruritus, occurring in 5-10% of the patients. Less frequently it has been reported the presence of headache, irritability, somnolence, dizziness, fever, photofobia, edema and rash [169]. In rare cases anaphylaxis has been reported after the first dose. Hypoadrenalism and adrenal crisis have been reported [175]. Inhibition of androgen synthesis may cause erectile dysfunction, decreased libido and gynaecomastia [164,169]. Reversible alterations in hepatic tests is detected in about 10-15% of the patients [176]. Severe symptomatic hepatic damage is a rare side effect [169], although some cases of hepatotoxicity with fatal outcome have been reported [177].

Clinical Applications

In normal subjects ketoconazole reduced cortisol responses to ACTH [165]. Numerous clinical studies, both short-term [178-180] and long-term [169,170,172,181], have shown that ketoconazole administration to patients with Cushing's syndrome is followed by a rapid reduction of serum and urinary cortisol levels, and by an improvement in clinical symptoms.

Beneficial effects of ketoconazole have been clearly demonstrated in patients with Cushing's disease [43,169-172,176,178,179, 181-185], adrenal tumours [169,172,186,187] and adrenal hyperplasia [167]. In patients with Cushing's disease, ketoconazole normalized plasma cortisol in 69% and urinary cortisol or 17-hydroxycorticosteroids in 81% of cases [129]. Variable results have been obtained in patients with ectopic ACTH secretion [169,178-180,184,188-192]. In a series of 15 patients with ectopic ACTH syndrome, ketoconazole, 400-1200 mg/day, improved hypokalemia, metabolic alkalosis, diabetes and hypertension in the majority of patients. However complete hormonal response was only achieved in seven patients with a median duration of response of 25 days [190].

Ketoconazole reduced hyperandrogenism and normalized cortisol levels in a case of Cushing's syndrome due to virilizing adrenocortical carcinoma with predominance of the C17,20 pathway [193]. Regression of metastatic adrenal carcinoma during palliative ketoconazole therapy has also been reported [187]. Recently, a patient with recurrence of Cushing's syndrome due to metastatic adrenal carcinoma has been reported to normalize her cortisol levels under therapy with fluconazole (Fig. **8**), an antifungal azole-derivative, at doses between 200 and 400 mg/day [194].

The beginning of ketoconazole action is slower than that of metyrapone. However, ketoconazole do not increase androgen concentration, being more acceptable in peripubertal children and women, in particular in patients with severe hirsutism [170,172]. Advantageous effects usually persist long term with ketoconazole in monotherapy, although escape has been reported in patients with Cushing's disease treated for long periods [171,179].

Reduction in cortisol production may give rise to an increase in ACTH secretion in patients with Cushing's disease but not in patients with ectopic ACTH secretion [184]. However, ACTH levels do not appear to override steroidogenic blockade by the drug in Cushing's syndrome. A reduction in plasma cholesterol levels has also been reported in patients with Cushing's syndrome receiving ketoconazole [169]. Hypoadrenalism may occur with ketoconazole therapy, hence some authors recommend routine corticosteroid replacement therapy [192].

Etomidate

Pharmacological Properties

Etomidate (Fig. **8**), a hypnotic with no analgesic activity, is used for induction of general anesthesia with minimal hemodynamic perturbation and little respiratory depression. Etomidate is an imidazole derivative that decreases cortisol and aldosterone levels and their responses to ACTH [195]. It produces a concentration-dependent blockade of two mitochondrial cytochrome P450 dependent enzymes, cholesterol-side-chain cleavage enzyme, and 11β-hydroxylase [195-199].

Clinical Applications

Etomidate has been used for short-term control of hypercortisolemia in severely ill patients with Cushing's syndrome [200-202] and ectopic ACTH syndrome [203,204]. It is a useful drug when a rapid control of cortisol levels in patients with severe hypercortisolaemia and life-threatening complications is needed. A preparation of propylene glycol containing etomidate can be used safely for a prolonged period to reduce hypercortisolemia in patients unable to take oral medications [203]. Nonhypnotic low dose infusion of 0.1-0.3 mg/kg/h has been used in patients with severe Cushing's syndrome. This drug may be an effective strategy for the control of severe hypercortisolemia, especially in patients with resistance to ketoconazole and metyrapone and life-threatening deterioration. Sedative effects and the need for intravenous administration limit the usefulness of this compound [205].

GLUCOCORTICOID RECEPTOR-BLOCKING AGENTS

Mifepristone

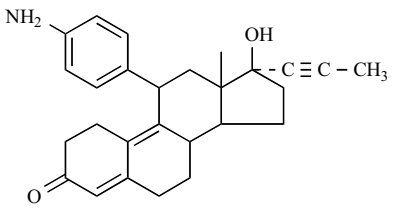
Pharmacological Properties

Mifepristone (RU-486), 17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one (Fig. **9**), is a synthetic steroid molecule with high affinity to the glucocorticoid and progesterone receptor, where it acts as a competitive antagonist [206,207]. Mifepristone seems to inhibit both the glucocorticoid receptor activation and the gene transcription phenomenon. An agonistic action on glucocorticoid receptor has also been reported, but it was inadequate to prevent adrenal insufficiency [208].

Mifepristone has been used at doses ranging 5-25 mg/kg/day [209-211]. The long half-life of the drug poses problems with titration of dose within a therapeutic range. Addisonian crisis has been reported in patients treated with this drug [209]. Mifepristone causes ACTH disinhibition and exacerbation of hypercortisolism [211].

Clinical Applications

In patients with Cushing's syndrome, mifepristone therapy improved clinical symptoms of hypercortisolism [209,212]. In Cushing's disease administration of mifepristone improves glucocorticoid-dependent biochemical parameters and induces a strong and long lasting ACTH and cortisol rise [212], what is an inconvenience to evaluate therapeutic effectiveness. The lack of a biomarker of glucocorticoid receptor activity is another difficulty in monitoring therapy. In patients with Cushing' disease prolonged administration of mifepristone caused activation of the pituitary-adrenal axis with a rise in urinary and plasma cortisol levels that would overcome the peripheral effects of the drug [212]. Long-term effectiveness and dramatic clinical improvement have been reported in a patient with severe Cushing's disease treated with pituitary irradiation after unsuccessful transsphenoidal surgery who received high dose mifepristone for 18 months [211]. Mifepristone has been recommended for rapid reversal of symptoms in patients with acute and severe complications, such as hypercortisolemic psychosis [210]. It has also been recommended in inoperable patients with ectopic ACTH secretion or adrenal carcinoma who have failed to respond to other treatments [207].



Mifepristone (RU-486)

Fig. (9). Mifepristone, a glucocorticoid receptor antagonist.

COMBINED TREATMENTS

Combined therapy has been used in some patients with the intention to reduce dose of each drug and diminish the incidence of adverse effects. Drugs tend to act synergistically and it is seldom necessary to use maximum doses of drugs in combination. Several authors [119,124,125] have used combined therapy of aminoglutethimide plus metyarpone, thus producing an enzymatic blockade of cortisol biosynthesis at different levels. Normalization of plasma or urinary cortisol was achieved in 67-100% of cases. Replacement glucocorticoid therapy is needed to avoid adrenal insufficiency. Hydrocortisone is the drug of choice, since aminoglutethimide accelerates dexamethasone metabolism. Aminoglutethimide in combination with mitotane has been used in a patient with ectopic ACTH secretion [152].

Combined treatment with 1.200 mg/day of sodium valproate and 15 mg/day of bromocriptine, two modulators of ACTH release, induced a complete remission in a patient with Cushing's disease with failure to respond to each drug in monotherapy [61]. However the association of cyproheptadine and bromocriptine did not result in effective reduction of ACTH levels in patients with Cushing's disease after bilateral adrenalectomy [24].

A patient with the ectopic ACTH syndrome due to a lung carcinoma was successfully managed with lanreotide, a long-acting somatostatin analogue, 90 mg per month, together with the long-acting dopamine agonist cabergoline, 7 mg per week [213]. In this patients the presence of somatostatin receptor subtype 5 and dopamine D2 receptor expression was demonstrated in a tumor sample.

Association of valproate and metyrapone combines a centrally acting drug with an inhibitor of cortisol biosynthesis. Glaser *et al*. [67] demonstrated the effectiveness of this combination in patients with Cushing's disease. In 6 patients with Cushing's the addition of sodium valproate to metyrapone produced a further reduction in plasma and urinary cortisol [214].

Effectiveness of combined therapy with ketoconazole and octreotide has also been reported in patients with ACTH-dependent

Cushing's syndrome, even in patients with poor response to each drug in monotherapy [215]. This regimen has allow a reduction in ketoconazole dose without loss of therapeutic effectiveness, what is of special significance in patients who develop hepatic intolerance to ketoconazole. It has also been suggested that ketoconazole treatment would potentiate the inhibitory action of octreotide on ACTH secretion [215].

INDICATIONS FOR MEDICAL THERAPY IN CUSHING'S SYNDROME

Definitive cure of Cushing's syndrome only can be attained by surgery or radiotherapy. Therefore these procedures are the treatments of choice in patients with ACTH-dependent or independent hypercortisolism [1,129,169,216-218]. Nevertheless, drug therapy plays a main role in the management of patients with Cushing's syndrome. Medical therapy for definitive treatment of noncurable Cushing's disease or for palliative treatment of malignancy-related hypercortisolism has been estimated to be necessary in 33% of patients with Cushing's syndrome [129]. However, temporary pharmacological treatment may be necessary in almost all patients at any time throughout the natural history of their disease.

Indications of pharmacological therapy in these patients are summarised in Table **2**. Drug therapy allows attaining a normocortisolemic state, and the correction of metabolic abnormalities, before surgery is performed in patients in whom surgical procedure has been chose as first line therapy [219]. When surgery is contraindicated, drugs are used as palliative therapy in patients with Cushing's syndrome of any etiology with the aim of avoiding the deleterious consequences of prolonged exposure to cortisol excess.

Table 2. Indications for Medical Therapy in Patients with Cushing's Syndrome

Preparation for surgery
Contraindications for surgery
Persistence or relapse after surgery
In combination with radiation therapy
Ocult ectopic ACTH syndrome
Severe hypercortisolism
Palliative treatment of malignancy-related hypercortisolism

In patients in whom surgery has failed, medical therapy is often essential to reduce the hypercortisolism and its consequences. It should be atempted before bilateral adrenalectomy is considered. In patients with ACTH-secreting pituitary adenomas treated by pituitary irradiation drug therapy is an effective way to control cortisol hypersecretion while awaiting the long-term effect of radiotherapy. In patients with an occult source of ectopic ACTH secretion medical therapy is notably useful while investigations for location of the origin of ACTH production are performed. In cases of severe hypercortisolism with serious physical or psychological symptoms rapid and effective reduction of cortisol levels are required. In the occasional patients in whom an accurate diagnosis cannot be established with certainty medical therapy may also be indicated in order to maintain normocortisolemia.

Advantages of medical therapy in these circumstances include correction of hyperglycaemia and hypokaliemia, improvement in myopathic symptoms, neuropsychiatric derangements and capilar fragility [129]. Adrenal insufficiency is a danger inherent to all forms of medical therapy of Cushing's syndrome. Cortisol secretion must be monitored in all patients under hypocortisolemic drug therapy. Cortisol production rate by isotopic dilution [220] is the most accurate method to measure endogenous cortisol secretion, however it is unfeasible in the clinical setting in most centres. A cortisol profile with repeated samples throughout the day can detect transient hypoadrenalism [221]. It is a useful procedure, but not without practical difficulty. Urinary free cortisol levels is the simplest way to estimate the effectiveness of therapy.

THERAPEUTIC STRATEGIES

Cushing's Disease

Pituitary adenomectomy by transsphenoidal approach is the treatment of choice in most patients with Cushing's disease [1,222-224]. Remission of hypercortisolism after operation is achieved in 70-80% of patients, depending on the tumour volume and surgical experience. Relapse of the disease may occur in 5-20% of these patients. Therefore, when hypercortisolism persists or relapses after initial surgery, radiation therapy [1,126,225,226] o a second surgical operation [227] is indicated. While awaiting for the effect of radiotherapy pharmacological treatment must be employed (Fig. **10**).

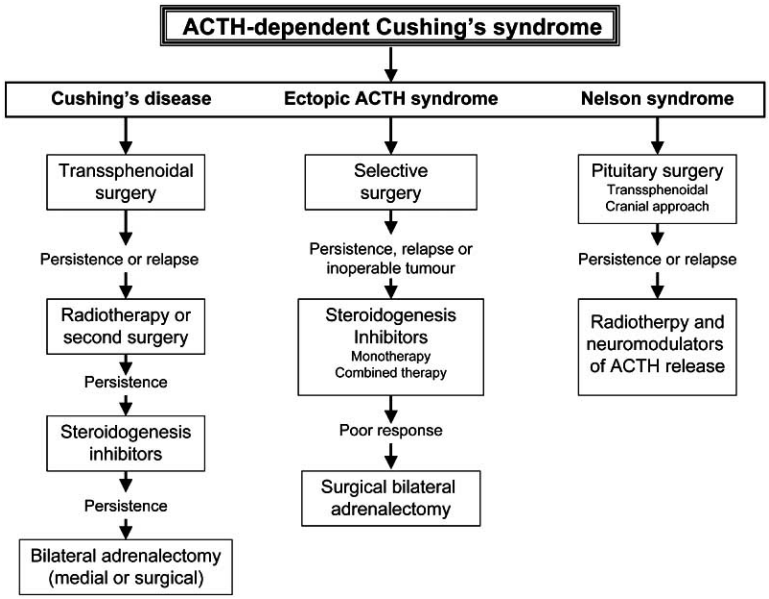


Fig. (10). Simplified algorithm for the treatment of ACTH-dependent Cushing's syndrome.

There is no drug with ability to attain a sustained and effective blockade of ACTH secretion or effects in these patients. Long-tem studies have shown no favourable results with centrally acting drugs. Inhibitors of cortisol production are, therefore, to be used in these patients (Table **3**). The choice of drug varies according to the opinion or experience of the authors. Some recommend mitotane [137,138,151], while others prefer ketoconazole [169,172,195,225], metyrapone [118,120,122] or combination of these compounds [119,124].

Table 3. Percentages of Normalization of Corticosteroid Values in Patients with Cushing's Disease Treated by Inhibitors of Cortisol Biosynthesis

Drug	Percentage of normalization
Mitotane	47-73
Ketoconazole	70-84
Metyrapone	50-75
Metyarpone plus radiotherapy	85
Aminoglutethimide	46
Aminoglutethimide plus radiotherapy	50
Metyrapone plus aminoglutethimide	67-100

*Data from Miller & Crapo [129], Misbin *et al*. [154], and Engelhardt & Weber [217].

In patients with Cushing's disease who are not cured by transsphenoidal surgery or pituitary irradiation surgical bilateral adrenalectomy or medical adrenalectomy with mitotane is indicated for final definitive cure. Those who do not have a complete response with mitotane or who cannot be treated by adrenalectomy can be given adrenal enzyme inhibitors to ameliorate hypercortisolism.

Ectopic ACTH Secretion

Removal of the ectopic source of ACTH is the optimal management in patients with ectopic ACTH syndrome [228]. Medical interventions have been employed in attempts to control the hypercortisolsim associated with inoperable ectopic ACTH production or after unsuccessful surgery. ^{111}In-pentetreotide scintigraphy is usefull to identify patients with neuroendocrine tumors that exhibit somatostatin receptors. In these cases a trial with somatostatin analogues is warranted. Intraoperative ^{111}In-pentetreotide scintigraphy with a hand-held gamma detector probe has recently been proposed to increase the intraoperative detection rate of small tumors and their metastases [229].

Ketoconazole [169,171,178-180,184,185,188-192], mitotane [152], metyrapone [118,123-125,152,230] and aminoglutethimide [125] in monotherapy or in combination [124,125] are the most useful drugs in these patients. The use of mitotane is limited by its slow onset of action. Plasma ACTH levels usually do not rise in response to decreasing cortisol concentrations, alghouth significant elevations have been reported [125]. Replacement therapy with glucocorticoids should be added in case of drug induced hypoadrenalism. Combination therapy with ketoconazole and octreotide is promising. Its usefulness has been demonstrated even in patients with poor response to each drug taken singularly [215]. In patients uncontrollable with medical therapy surgical adrenalectomy is indicated.

Nelson's Syndrome

Pituitary irradiation is the best procedure to prevent the development of Nelson's syndrome in patients undergoing either medical or surgical adrenalectomy. Protection is not complete, since some adrenalectomized patients develop Nelson's syndrome despite prior irradiation [231,232]. All adrenalectomized patients should be followed indefinitely with periodic measurement of plasma ACTH and imaging of the pituitary gland. When a patient with Nelson's syndrome develops a large tumor, it is often locally invasive and difficult to manage. Pituitary surgery, either by the transsphenoidal or cranial approach, is the treatment of choice. Large tumors have the propensity to recur [226]. Radiotherapy should be employed postoperatively in all patients with residual tumor [233]. Proton beam radiation seems to be more successful than conventional radiation. To avoid damage to the optic pathways stereotactic gamma knife [234] or linear accelerator photon knife radiosurgery [235] have been advised, but there are few reported results.

Until now there is no effective drug therapy for Nelson's syndrome (Fig. **10**). Cyproheptadine was effective in few cases [22]. Sodium valproate therapy did not show effectiveness in the long-term [236,237]. Acute administration of bromocriptine lowered plasma ACTH concentrations acutely in patients with Nelson's syndrome [238]. In some cases, long-term octreotide treatment has been reported to be effective with normalization of ACTH levels and no tumor extension [74]. Interestingly, ketoconazole decreased ACTH secretion *in vitro* in pituitary adenoma cells from patients with Nelson's syndrome [239].

ACTH-Independent Cushing's Syndrome

Adrenal adenoma is treated by surgery, usually unilateral adrenalectomy, with an excellent outcome. Surgery is also the first line treatment for adrenal cortical carcinoma, although it rarely is curative since many patients have metastases at the time of diagnosis. High doses of mitotane are the drug of choice in metastatic or persistent disease after surgery [135,140,240,241]. This therapy is palliative in some cases, but it can avoid recurrences in patients who lack detectable disease after surgery [242]. In patients with intolerance to mitotane, ketoconazole, metyrapone or aminoglutethimide can be used (Fig. **11**). In patients with functional metastatic adrenocortical carcinoma who have failed to respond to adrenal blocking agents and cytotoxic chemotherapy a trial with octreotide may be justified [106].

Most cases of macro- or micronodular adrenal hyperplasia are treated by bilateral adrenalectomy [243-245]. Steroidogenesis inhibitors may be used if needed to control hypercortisolism. The demostration that the presence and activation of adrenal aberrant receptors may be responsible for chronic hypercortisolism has been provided in some cases in which remission of the disease was observed under specific receptor blockade (Fig. **11**) [246,247].

Cushing's Syndrome in Pregnancy

Untreated Cushing's syndrome during pregnancy is associated with significant maternal and fetal morbidity. Adrenal tumor is the main cause of Cushing's syndrome during pregnancy [248-250]. Surgical adrenalectomy has been successfully used in pregnant women with Cushing's syndrome [248]. This procedure may reduce the incidence of fetal death, neonatal and maternal complications [251]. Pituitary surgery is also recommended in women with Cushing's disease [252].

Medical therapy is indicated late in the third trimester and pending definitive therapy [249]. Aminoglutethimide [253] and metyrapone [254] have been used. Both drugs cross the placental barrier and may inhibit cortisol biosynthesis in the fetus; furthermore, fetal virilization precludes the use of aminoglutethimide [253]. Metyrapone seems to be the drug of choice in cases of nonsurgical treatment during pregnancy. It is well tolerated and is not known to be teratogenic [254,255], but its efficacy is unclear [248,256] and it has been associated to hypertension and progression to preeclampsia. Metyrapone induced increase in 11-deoxycorticosterone may enhance sodium retention and increase vascular contractility [121]. This drug has been used to control the hypercortisolism in a woman who developed pregnancy-induced Cushing's syndrome [257]. A partial blockade of 11β-hydroxylase in an offspring with elevated 11-deoxycortisol, but normal cortisol levels, has been re-

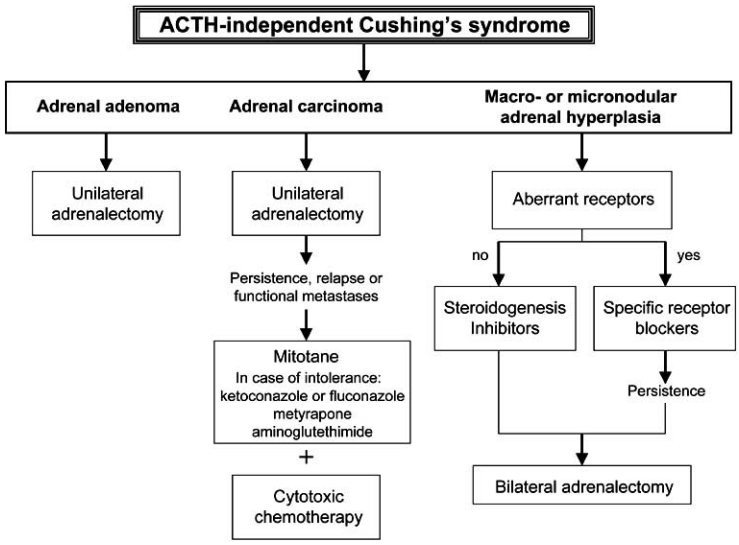


Fig. (11). Simplified algorithm for the treatment of ACTH-independent Cushing's syndrome.

ported [258]. Corticosteroid replacement in infants has not been necessary in the reported cases.

Ketoconazole has been used in few cases without adverse effects [259]. However, this drug is teratogenic in the rat and should not be used in pregnancy. Mitotane should not be given to pregnant women because it crosses the placenta and is teratogenic [260]. Mitotane is also contraindicated in women desiring fertility within 2-5 years since its effects may persist after discontinuation due to gradual release form adipose tissue [260].

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