Pharmacological Management of Cushing's Syndrome: An Update

ABSTRACT

The treatment of choice for Cushing's syndrome remains surgical. The role for medical therapy is twofold. Firstly it is used to control hypercortisolaemia prior to surgery to optimize patient's preoperative state and secondly, it is used where surgery has failed and radiotherapy has not taken effect. The main drugs used inhibit steroidogenesis and include metyrapone, ketoconazole, and mitotane. Drugs targeting the hypothalamic-pituitary axis have been investigated but their roles in clinical practice remain limited although PPAR-γ agonist and somatostatin analogue som-230 (pasireotide) need further investigation. The only drug acting at the periphery targeting the glucocorticoid receptor remains Mifepristone (RU486). The management of Cushing syndrome may well involve combination therapy acting at different pathways of hypercortisolaemia but monitoring of therapy will remain a challenge. **(Arq Bras Endocrinol Metab 2007;51/8:1339-1348)**

Keywords: Cushing's syndrome; Drug therapy; Steroidogenesis inhibitor; Hypothalamic-pituitary modulator

RESUMO

Manejo Farmacológico da Síndrome de Cushing: Uma Atualização. O tratamento de escolha para a síndrome de Cushing ainda é a cirurgia. O papel da terapia medicamentosa é duplo: ele é usado para controlar o hipercortisolismo antes da cirurgia e otimizar o estado pré-operatório do paciente e, adicionalmente, quando ocorre falha cirúrgica e a radioterapia ainda não se mostrou efetiva. Os principais medicamentos são empregados para inibir a esteroidogênese e incluem: metirapona, cetoconazol e mitotano. Medicamentos visando o eixo hipotálamo-hipofisário têm sido investigados, mas seu papel na prática clínica permanece limitado, embora o agonista PPAR-γ e análogo de somatostatina, som-230 (pasireotídeo), requeira estudos adicionais. A única droga que age perifericamente no receptor glicocorticóide é a mifepristona (RU486). O manejo da síndrome de Cushing deve envolver uma combinação terapêutica atuando em diferentes vias da hipercortisolemia, mas o monitoramento dessa terapia ainda permanece um desafio. **(Arq Bras Endocrinol Metab 2007;51/8:1339-1348)**

Descritores: Síndrome de Cushing; Terapia médica; Inibidores da esteroidogênese; Moduladores hipotálamo-hipofisários

atualização

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CUSHING'S IS A RARE DISEASE and therefore of minimal interest to the pharmaceutical industry and hence for many years there were few developments. However in recent times there has been renewed interest in whether agents marketed for other conditions may have a role to play in the medical management of Cushing's syndrome. This review will endeavour to assess the place of the 'new' agents alongside the longer established agents.

The definitive management for Cushing's syndrome is surgical excision of the underlying cause of the hypercortisolaemia, with the exception of ACTH-independent bilateral macronodular hyperplasia where pharmacological treatment directed against the aberrant receptor can be effective (1). However, in many patients with Cushing's syndrome there is a role for medical therapy in certain specific circumstances. It is common practice to prepare patients for surgery by lowering circulating cortisol levels to reverse the metabolic consequence of cortisol excess and by implication reduce the complications of surgery. This clearly depends on the interval to surgery and disease severity. As any clinician dealing with Cushing's syndrome is aware establishing the precise aetiology is a challenge and it is not always possible to make a definitive diagnosis at first investigation, and in such cases medical therapy can be used as a stop gap to control signs and symptoms and thereby allow time for re-investigation. In patients not cured by surgery or in patients with metastatic disease medical therapy can be used to control manifestations of the disease. Pituitary radiotherapy is extremely effective at controlling hypercortisolaemia but can take several years to have its full effect and medical therapy is often required in the interim (see figure 1).

Medical therapy can be separated into agents that inhibit adrenal steroidgenesis and those that modulate pituitary ACTH release. Currently in clinical practice, the most effective, reliable and widely use agents are those that inhibit steroidgenesis.

A major challenge of medical therapy is the monitoring of its effectiveness. Urinary free cortisol (UFC) measurement is widely used but has several major limitations and is intrinsically a poor solution to the problem of disease monitoring. Only a small proportion of cortisol is excreted unaltered in urine and UFC immunoassays to varying extent detect biologically inactive cortisol metabolites, which may be raised in patients treated with agents such as metyrapone. UFC has the additional disadvantages of relying on complete collection and of being unable to detect over-treatment induced hypoadrenalism.

Although more labour intensive, measurement of serum cortisol is a more appropriate means of assessing disease activity. The best validated technique is calculation of a mean serum cortisol from multiple measurements taken during a single day. Studies comparing isotopically calculated cortisol production rates

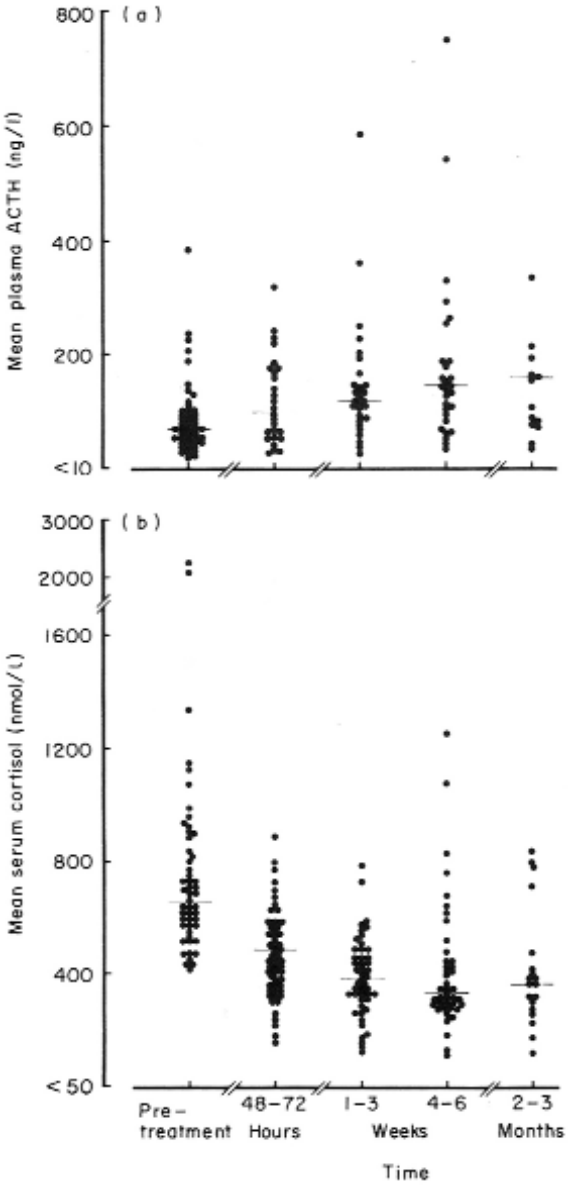

Figura 1. Mean plasma ACTH levels **(a)** and serum cortisol levels **(b)** during short-term metyrapone therapy in 53 patients with Cushing's syndrome. The bars represent the median values. ACTH ng/L x 0.225 = pmol/l. [Courtesy of Verhelst JA, Trainer PJ, Howlett TA, et al. Short- and long-term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. Clin Endocrinology (Oxf) 1991;35:169-78]

to serum levels indicate that a mean serum cortisol in the range 150–300 nmol/l equates to a normal cortisol production rate, and this should be the target of medical therapy (2).

The cyclical nature of Cushing's syndrome in some patients means that even after disease control has been achieved regular treatment monitoring is required.

STEROIDOGENESIS INHIBITION

These agents are the most consistently effective means of controlling cortisol secretion.

Metyrapone

In the era before it was possible to measure plasma ACTH, the metyrapone test was used to investigate suspected Cushing's syndrome and hypoadrenalism but its use now is exclusively therapeutic (3,4). It acts primarily on the final step in cortisol synthesis namely the conversion of 11-deoxycortisol to cortisol and therefore results in a dramatic increase in circulating 11-deoxycortisol levels, which can cross-react in serum and urine cortisol immunoassays. This cross-reactivity may result in spuriously elevated cortisol levels and a failure to appreciate that a patient is over-treated and hypoadrenal.

Metyrapone is the most potent, short-acting inhibitor of cortisol synthesis with a rapid onset of action. Serum cortisol levels fall within four hours of an initial dose and care is required to avoid over-treatment. The routine starting dose is 250 mg three times per day with reassessment of cortisol levels 72 hours later and dose titration as appropriate until a mean cortisol level of between 150 and 300 nmol/l is achieved. In patients with severe hypercortisolaemia up to 8 gm per day in 3–4 divided doses may be necessary. Most patients tolerate the drug without difficulty as long as hypoadrenalism is avoided. Nausea, anorexia and abdominal pain can occur but usually this is a sign of over-treatment. The major limitation of metyrapone is in women as the accumulation of cortisol precursors results in elevated androgens, which frequently is manifest as hirsutism and acne. Although mineralocorticoid precursors levels are elevated, hypokalaemia, hypertension and oedema are not problems, presumably because of the benefits of lower circulating cortisol levels (5,6). In patients with pituitary-dependent Cushing's disease, ACTH levels rise but there is no evidence that this results in tachyphylaxis (5,7).

Ketoconazole

Ketoconazole is an imidazole derivative developed as an oral antifungal agent that inhibits cholesterol, sex steroid and cortisol synthesis by acting on the 11β-hydroxylase and C17-20 lyase enzymes (8-11). It is the most frequently used agent in the treatment of Cushing's syndrome with the starting dose being 200 mg twice daily increasing as necessary to 1200 mg/day in four divided doses (12,13). In contrast to metyrapone it can take several weeks to see the full benefit of a dose adjustment and there is less risk of over-treatment and hypoadrenalism. With time it is effective at controlling the symptoms of Cushing's syndrome and in women its antiandrogenic properties are a virtue but in men, gynaecomastia and reduced libido have been reported. The most common side effects are gastrointestinal upset and skin rashes but liver enzyme dysfunction can occur in up to 10% of cases, which rarely has proceeded to acute liver failure and fatality (14-17). Ketoconazole has the added benefit of reducing the total cholesterol and LDL cholesterol (18).

Metyrapone and ketoconazole can be very successfully co-administered as the former controls cortisol secretion while waiting for the slower onset of action of the latter agent, which in turn lowers androgens and thus negates one of the major limitations of the former.

Mitotane

Mitotane reduces cortisol production by blocking cholesterol side-chain cleavage and 11β-hydroxylase (19-21). It was introduced in 1960 for the treatment of adrenal carcinoma and subsequently used for the treatment of benign causes of Cushing's syndrome. The onset of mitotane action is slow with sustained action maintained after discontinuation in up to a third of patients (22). When used to control serum cortisol levels in benign disease, mitotane is initiated at a dose of 0.5–1 gm per day which is increased gradually by 0.5–1 gm every few weeks to minimise side effects. Adverse effects such as nausea, anorexia and diarrhoea are common with doses of 2 gm per day and almost universal at doses greater than 4 gm per day (23). Adrenal insufficiency and neurological side effects including abnormal gait, dizziness, vertigo, confusion and problem of language expression are often seen at higher dose (22). Abnormal liver enzymes, hypercholesterolaemia, skin rash, hyperuricaemia, gynaecomastia in male and prolonged bleeding time are also well recognized (24,25). Changes in hormone binding globulins may result in total hor-

mone measurement being unreliable during treatment and thus caution is required when interpreting serum cortisol levels (26,27). Mitotane increases the metabolic clearance of exogenously administered steroid and the replacement dose of steroid is increased by about a third (28). In order to minimise side effects mitotane dose should be gradually titrated up, taken with meals or at bedtime with food. Changing the schedule to once daily or alternate day may help with gastrointestinal problems. If side effects are severe mitotane can be stopped for a week and restarted at a lower dose. Mitotane may induce spontaneous abortion and is a teratogen. Its effect may persist for a number of months after discontinuation and so a female patient should avoid pregnancy for up to five years after stopping the drug (29).

Aminoglutethimide

Aminoglutethimide, which was introduced in 1959 as an anticonvulsant, has also been used in the treatment of breast cancer and was noticed to induce adrenal insufficiency. It inhibits the side-chain cleavage of cholesterol to pregnenolone and therefore inhibits cortisol, oestrogen and aldosterone production and additionally inhibits 11β-hydroxylase, 18-hydroxylase and aromatase activity (30,31). Initially aminoglutethimide decreases cortisol production in Cushing's syndrome but appears to be less effective in treating Cushing's disease (32). The suggested mechanism may be an increase in ACTH overcoming the enzymatic blockade or it may be induction of hepatic enzyme accelerating aminoglutethimide metabolism (33,34). Adverse effects such as lethargy, dizziness, ataxia and rashes are common on initiation and limit its use although they do resolve with time (32,35). There are better agents for controlling hypercortisolaemia and aminoglutethimide does not have a place in the modern treatment of Cushing's syndrome (36).

Trilostane

Trilostane is a competitive inhibitor of 3β-hydroxysteroid dehydrogenase, which is an essential enzyme in the synthesis of cortisol, aldosterone and androstenedione. It is an effective inhibitor of steroid synthesis in vitro but in man the results have been disappointing (37). However, it is used in veterinary practice as it is very effective in controlling pituitary-dependent Cushing's in dogs (38). The maximum daily dose is 1,440 mg and patients may experience side effects such as abdominal discomfort, diarrhoea and paraesthesia. Trilostane has largely fallen out of clinical use but the very fact that it is so effective in dogs may mean it justifies reconsideration in man.

Etomidate

Etomidate is a parenteral anaesthetic agent which when first introduced was associated with excessive mortality in patients in intensive care which was ultimately explained by the recognition it lowered circulating cortisol levels by inhibiting 11β-hydroxylase, 17-hydroxylase, c17-20 lyase as well as cholesterol side chain at cleavage (39-41). A number of case reports have shown etomidate at 2.5 mg/hour to be effective at correcting hypercortisolaemia in seriously ill patients with ectopic ACTH production (42-44). Etomidate's use is limited by the need to be given intravenously but it has a place in acutely sick patients unable to be treated orally where rapid correction of hypercortisolaemia may be life saving.

HYPOTHALAMIC-PITUITARY NEUROMODULATORY AGENTS

Pituitary ACTH secretion is regulated by a number of neurotransmitters including catecholamines, serotonin, acetylcholine, GABA and peptides. In Cush-

Table 1. Agents inhibiting steroidogenesis in clinical use.

Agent	Dose	Properties
Metyrapone	750–8000 mg daily	Hypoadrenalism Side effects: nausea, abdominal pain, hirsutism, acne
Ketoconazole	400–1200 mg daily	Slow onset of action Side effects: gastro-intestinal upset, rashes, abnormal LFT, gynaecomastia & reduced libido in men
Mitotane	500–8000 mg daily	Gradual dose titration, taken with meal Side effects: gastro-intestinal upset, neurological disturbances, abnormal LFT, hypercholesterolaemia Avoid pregnancy up to five years after stopping the drug

ing's disease the pituitary tumour still remains partially responsive to hypothalamic stimuli, illustrated by responsiveness to exogenous CRH and dexamethasone. Reports exist advocating the virtues of various agents but, to-date, none have gained widespread acceptance. However recent data have renewed interest in the possibility of treating Cushing's disease with centrally acting drugs that modulate through dopamine, somatostatin and PPAR receptors function.

Dopamine agonists

Bromocriptine is a dopamine agonist which has been widely used in the treatment of hyperprolactinaemia and acromegaly. It is unclear if the action in lowering ACTH secretion by bromocriptine is via CRH or directly on the pituitary (45-47). A single dose of bromocriptine will cause a fall in ACTH in half of the patients with Cushing's disease but unfortunately this effect is not maintained in the long term (47,48). There are reports that suggest with high dose bromocriptine (40 mg/day) there may be clinical improvement in up to 50% of patients but others have found response rate of only 1–2% in the long term (49,50). Potential side effects of bromocriptine include nasal congestion, nausea, postural hypotension, headaches and hallucination.

The use of cabergoline in the management of Cushing's disease remains anecdotal. In mixed pituitary tumour secreting prolactin and ACTH with florid clinical signs of Cushing's disease treatment with cabergoline resulted not only in the normalisation of prolactin but also clinical and biochemical resolution of the features of Cushing's (51). It has also been use to control Cushing's disease in failed pituitary surgery (52,53). Recently there has been renewed interest in cabergoline with the publication by Pivonello et al. of a case of lung carcinoid with Cushing's syndrome treated with a combination of lanreotide and cabergoline successfully normalising plasma ACTH and UFC levels (54). In a study of six patients with ACTH-secreting neuroendocrine tumours, dopamine D2 receptors were expressed in five patients on immunohistochemistry and treatment with cabergoline 3.5 mg/week for six months normalised UFC in two patients although one patient later did have treatment escape (55). Case reports of cabergoline use in Nelson's syndrome have been more encouraging. Casulari et al. reported a case of Nelson's syndrome with failed treatment on cyproheptadine (12 mg/day) and bromocriptine (7.5 mg/day) but cabergoline (0.5 mg twice weekly) normalised the ACTH plasma levels and induced complete resolution of the pituitary adenoma on MRI (56). There has also been a case report of cabergoline (1.5 mg/week) treatment of Nelson's syndrome for six years with normalisation of ACTH levels and stable residual pituitary tumour (57).

The role of dopamine agonists in the management of Cushing's disease remains limited to the occasional patient and long-term evidence of efficacy is very poor but interest in their use remains unabated. The available data are case based anecdote, there is a need for a controlled study before treatment can be recommended.

PPAR-γ receptor agonists

In 2002, the nuclear hormone receptor, peroxisome proliferator-activated receptor-γ (PPAR-γ) was identified in ACTH-secreting pituitary tumour (58). In an in vivo experiment, innoculating mice with corticotroph AtT20 tumour cells, treating with extremely high dose of rosiglitazone (150 mg/kg/day) prevented the development of tumours. In mice with already established corticotroph tumours, rosiglitazone treatment decreased tumour volume in 75% of cases and prevented signs of hypercortisolaemia in all cases, with 75% reduction in ACTH level and 96% reduction in cortisol levels (58). These observations caused great interest but are yet to impact on clinical practice.

In a study of two patients with pituitary-dependent Cushing's syndrome treated with rosiglitazone 8 mg daily for 33 and 20 days (the second patient was also taking metyrapone 1 gm/day), 24 hours UFC fell in both patients although only in the patient co-treated with metyrapone did it reach statistical significance (59). In a second study of ten patients, four prior to surgery, four following relapse after surgery and two immediately after failed surgery treated with 4–16 mg of rosiglitazone for 1–8 months (median 3 months), there was no consistent reduction in urinary free cortisol, plasma ACTH or serum cortisol levels (60). Side effects reported included oedema, weight increase, somnolence and increased hirsutism. In one of the larger studies, fourteen patients with active Cushing's disease (seven untreated and seven post unsuccessful transsphenoidal pituitary surgery) were treated with 8–16 mg of rosiglitazone for 1–7 months (61). In six patients, plasma ACTH, serum cortisol and 24 hours UFC were lowered but only UFC reached significance. Two of the six patients also noted clinical improvement on follow up at seven months. No clinical side effects were noted but one patient developed hypercholesterolaemia. In a study of seven patients with Nelson's syndrome who took 8 mg of rosiglitazone for 12 weeks, no significant fall in ACTH was seen (62). Sim-

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