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**Medical management of Cushing's disease: when and how?**

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## **ABSTRACT**

Transsphenoidal surgery is the first line treatment of Cushing's disease. However, medical treatment can be given in a high proportion of patients with this rare condition. This is especially the case in severe hypercortisolism for which medical treatment will be given for a short period of time to prepare the patient for surgery, or on a long-term basis after failed transsphenoidal surgery, or while waiting for the maximal beneficial effect of radiation techniques. These different situations all however require that hypercortisolism be perfectly controlled. Severe hypercortisolism is frequently treated by a block and replace approach during which a substitutive treatment is given after the induction of adrenal insufficiency. Mild hypercortisolism, the most frequent situation, is usually treated with a titration approach with a progressive dose increase. This approach requires certainty of eucortisolism, as patients may be treated for a prolonged period. This review will detail the main situations during which medical treatment should be considered, and the way in which to monitor them to avoid the long-term consequences of mild hypo- or hypercortisolism.

## Introduction

The aim of this short review is to define the roles of medical treatment in the management of Cushing's disease (CD), and to define how eucortisolism can be achieved with such drugs. This review should be considered as a global overview of the medical management of CD, rather than a precise description of the efficacy and side effects of each drug, as this has already been published in several detailed manuscripts and reviews over the last 10 years (1, 2). Though the management of CD is based on transsphenoidal surgery as a first line treatment, there are several situations in which medical treatment should be considered. In the first part of this manuscript, we will detail these situations. In the second part, we will focus on the different biochemical approaches that should be of interest for monitoring the medical treatment. This article forms part of a special issue: "Cushing's syndrome update: 100 years after Minnie G".

### 1. When should we consider medical management of CD?

Transsphenoidal surgery is the first line treatment for CD (3, 4)(+Ref Special issue "Surgery and perioperative management of patients with Cushing's disease" - Juergen Honegger), but mid to long-term efficacy is usually 50-70%, thus requiring additional treatments. The roles of medical treatment can be basically divided into 3 main indications: as pre-surgical medical treatment, especially in the case of severe hypercortisolism (short term expectations to consider), after failed transsphenoidal surgery, or as a first-line treatment in patients with contra-indications or refusal of surgery (long-term expectations), while waiting for the maximal efficacy of radiation techniques usually administered after failed transsphenoidal surgery (mid-term expectations).

#### A. As a presurgical medical treatment

In this setting, the aim is to try to obtain a biochemical control of hypercortisolism to improve comorbidities before surgery. This means short-term follow-up, and presumes rapid efficacy of the drug, with a good immediate tolerance profile.

This is a hotly debated topic especially in "classical" *i.e.*, non-severe hypercortisolism, as there is no clear evidence in the literature that a short-term control of hypercortisolism is sufficient to have a true impact on peri- and post-operative comorbidities of hypercortisolism. One study, from the ERCUSYN registry, analysed the perioperative mortality of patients managed with medical pre-surgical treatment of Cushing's syndrome (CS). The main limitation with this study was that it also included patients with severe hypercortisolism, a rare situation that should probably be considered separately as detailed in the following paragraph. A total of 242 patients were reported, the majority being treated with a single treatment (197 patients, with ketoconazole or metyrapone or cabergoline or mifepristone) for a mean duration of 3-6 months. Dose titration was not optimal, with a mean dose of only 600 mg of ketoconazole or 1250 mg of metyrapone, for example. The results of this retrospective study did not show any significant difference in perioperative mortality (during the month following surgery) between patients who were pretreated or not. However, this criterion was probably difficult to evaluate given the low number of events (7 deaths in the whole population) (5). In a systematic review of the literature, Ritzel et al. likewise did not identify any increased risk of mortality or morbidity in patients treated by bilateral adrenalectomy, whether they had received a prior medical treatment or not (Mortality 1 vs. 2%, morbidity 19% vs. 21%, respectively) (6). In 2014, we have reported pre-operative outcomes for 40 patients who had been treated with ketoconazole as a presurgical treatment for a mean duration of 3.9 months: most of these patients had non-severe hypercortisolism. Before surgery, hypertension improved in 50% of cases (n=26 with hypertension at diagnosis), diabetes in 50% (n=16 with diabetes at diagnosis), and hypokalaemia in 38% of cases (n=13 with hypokalaemia at diagnosis) (7). It is likely that the delay to diagnosis, or the period of exposure to hypercortisolism, may modify the time necessary to normalise comorbidities, *i.e.*, a longer period of pretreatment might have been necessary to improve these rates in some of these patients. Finally, data are lacking on the per-operative outcomes (length of hospital stay, side-effects of surgery, bleeding during the intervention etc.) in pretreated patients. In the absence of a long-term prospective randomised study, management consisting of giving systematic medical treatment for several months, with uncertainty of achieving true eucortisolism (as detailed in the second part of this manuscript), rather than

immediately performing potentially curative surgery in patients with mild comorbidities, cannot be recommended. Indeed, this was stated in the recent Pituitary Society guidelines on the management of CD (4). Moreover, while the immediate post-operative cortisol level is currently considered the gold standard to predict the risk of long-term recurrence, medical presurgical treatment could also bias this result by suppressing the negative feedback loop on normal corticotroph cells, making such a prediction impossible.

The discussion is different in patients presenting with severe hypercortisolism. In such cases, comorbidities such as hypokalaemia, hypertension, diabetes with ketoacidosis, pulmonary embolism, opportunistic infections, and acute psychosis, can be life-threatening. From a theoretical viewpoint, it thus makes more sense to try to improve the general condition of the patient before sending them to surgery. While bilateral adrenalectomy has long been considered the gold standard in this situation, fast-acting medical treatments have shown their efficacy in a few studies based on a relatively low number of patients. The association of ketoconazole and metyrapone, sometimes with mitotane (when a long-term treatment is discussed), and the use of mifepristone or etomidate, have all shown a very rapid improvement of the patient's condition in parallel with their biochemical results. As an example, the association of ketoconazole and metyrapone given at high doses led to a normal urinary free cortisol (UFC) in 15-30 days in 63-73% cases (with 14-36% of patients presenting with adrenal insufficiency thereafter), associated with a major decrease in cortisol levels beginning on day 3 of medical treatment (8, 9). Etomidate, a drug used for induction of anaesthesia, also induced a rapid powerful blockade of steroidogenesis, as shown by 83% normal UFC in 12 cases recently reported (10). Finally, Haissaguerre *et al.* reported a normal UFC level in 3 patients presenting with adrenal carcinoma and severe hypercortisolism, while on osilodrostat (3-44 mg/day) (11). The fact that most of the patients reported in these series were not presenting with CD, emphasises the rarity of severe hypercortisolism in these patients. However, the good results reported in the literature suggest that, in addition to symptomatic measures which should be provided (insulin, potassium, mineralocorticoid receptor antagonist, antibiotic prophylaxis, proton pump inhibitors...), medical treatment using high dose steroidogenesis inhibitors should now be considered the first-line treatment of patients with life-threatening hypercortisolism, while surgery may then be considered after improvement of the general condition of the patient.

#### **B. While waiting for the efficacy of radiation techniques after unsuccessful surgery**

In CD, radiation techniques are used in patients with biochemical hypercortisolism and a visible remnant on the pituitary MRI, usually after failed transsphenoidal surgery. The aim of this review is not to detail the different types of radiation techniques (Ref special issue "Role of radiosurgery in treatment of Cushing's disease – Marco Losa") nor the case of aggressive corticotroph tumors (Ref special issue "Aggressive corticotroph tumors" - Gerald Raverot). All radiation techniques have a major drawback, which is the time required to reach normal cortisol levels. While antitumour efficacy is usually observed during the first year, hormonal control can take several years, depending on the initial hormone levels and the type of radiation technique used. Proper control of hypercortisolism is thus necessary during this period. It is usually recommended to be certain of the anti-secretory efficacy of drugs before performing radiation techniques. In this setting, all appropriate drugs can be used, and these should be withdrawn at regular intervals (for instance, every year or when signs of hypocortisolism appear) to check the efficacy of the radiation technique. In contrast, drugs with a pituitary target should be withdrawn before using radiation techniques (and reinitiated a few weeks after the end of the procedure), as they may possibly decrease the efficacy of radiation by decreasing the proliferation rate of the tumor. This has been suggested in the cases of acromegaly and prolactinomas treated using Gamma Knife (12). We have also previously reported a potential radioprotective effect of ketoconazole when delivered at the time of radiosurgery (13). While these data remain controversial, we consider that a 1–3-month withdrawal (depending on the drug) should be performed before the use of radiation techniques.

#### **C. After failed transsphenoidal surgery or when transsphenoidal surgery is not performed as a first-line treatment**

This is the main indication of medical treatment in CD. While one situation is generally accepted by everyone, the second is a matter of debate. Long-term recurrence after transsphenoidal surgery has been reported in up to 30% of cases, frequently with no visible remnant on pituitary MRI. In this situation, radiation techniques are not usually performed. Medical treatment can thus be given for a long period of time (this specific point is covered in another review in this special issue "Bilateral adrenalectomy versus medical therapy for treatment of Cushing's disease after unsuccessful pituitary surgery(ies) - Ashley Grossman & Mark Gurnell).

Another situation is where there is an obvious diagnosis of CD and a negative pituitary MRI (for further explanation, please refer to "Special issue Challenges in neuroimaging of Cushing's disease - short expert view (Jean Francois Bonneville): this situation remains controversial as some neurosurgeons prefer not to operate and recommend medical treatment as a first line treatment. The literature provides conflicting results when comparing the efficacy of surgery in patients with and without a positive image on pituitary MRI. The most recent paper was by a French group in which the results of a monocentric approach with systematic surgery in 195 patients with a diagnosis of CD was evaluated. The authors reported that remission rates were not statistically different in these two situations. However, even though the difference was not significant, remission was obtained in 85%-94% cases for patients with a positive MRI, and 73%-75% in patients who had an inconclusive or negative MRI. When considering these results, the historical nature of the study should be kept in mind, and the fact that patients with a more recent diagnosis had benefited from improved MRI techniques. These results must be compared with the antisecretory efficacy observed with medical treatment (with a control usually observed in between 50%-80% cases depending on the drug, but no definitive cure). On the other hand, giving a medical treatment at an optimal dose to reach eucortisolism might aid in being able to wait for pituitary MRI to be more conclusive (as we have reported in our French retrospective study on ketoconazole (7)). This would, however, require a prolonged period of time (3-5 years), and result in additional expense compared to transsphenoidal surgery.

## **2. How should we monitor the medical management of CD?**

Looking at the physiology of cortisol secretion emphasises three main characteristics: a cortisol peak in early morning, a progressive decrease in cortisol levels during the day, and a cortisol nadir at night. This pattern should be what we achieve with drugs aimed at obtaining "eucortisolism". Attempting to obtain all these characteristics has proven challenging, and therefore most studies define eucortisolism using an area under the curve of urinary free cortisol obtained over 24 hours (14). The aim of this part of this review is to give insights into the best biochemical markers of eucortisolism, given the fact that mild hypo- or hypercortisolism, especially in the frequent situations reported in paragraph 1B, could lead to comorbidities over a long-term. Obviously, clinical signs of hyper- or hypocortisolism must also be looked for during follow-up, even though prolonged exposure to hypercortisolism might lead to sequelae, with a risk of confusion between comorbidities suggesting persistent hypercortisolism and metabolic sequelae (as shown for persistent comorbidities after bilateral adrenalectomy (15). A proposed programme of monitoring of these patients is shown in Figure 1. These suggestions can only be applied in the classical "titration" approach, in which the dose of cortisol lowering drug is progressively increased until eucortisolism is reached. The "block-and-replace approach" is detailed in the final paragraph of this section of the manuscript. We will not outline the side effects of each drug in this section of the paper.

### **A. 24h-urinary free cortisol**

24h-urinary free cortisol provides an imperfect image of cortisol secretion but controlling it should be considered the first step to reach when targeting eucortisolism. The most recent phase 3 studies on cortisol-lowering drugs have used this parameter as a surrogate to define the antisecretory efficacy of a given drug (7, 16, 17). While UFC does not take into account the nycthemeral rhythm of cortisol, a pattern that is abolished in patients with CD, it also has several limitations, especially due to daily fluctuations (18). Variability between two samples suggested that a decrease of 24h-UFC inferior to 50% could be due to variations in the marker rather than to efficacy of the drug. Adding two additional

24h samples increased the accuracy of the marker when evaluated as a mean, but also increased intra-patient variability. This was particularly important in patients with high UFC at the time of commencing cortisol-lowering drugs.

#### **B. Bedtime cortisol**

Bedtime cortisol could ideally be evaluated in the serum, but this would require frequent hospital stays, a procedure that would be both costly and difficult to envisage on a long-term basis. This would only be possible in patients with severe hypercortisolism, for whom a hospital stay is mandatory to check for improvement of comorbidities. Bedtime salivary cortisol is an easier way to determine the cortisol nadir, even though this marker also has issues with variability. Indeed, Danet-Lamassou *et al.* reported that repeating the measurement of late-night salivary cortisol 3-4 times on successive days would be required to get a real image of cortisol nadir (19). In this study, bedtime salivary cortisol was used as a diagnostic procedure, but the same variability would probably be observed when used as a tool for therapeutic monitoring. The variability of both UFC and late-night salivary cortisol likely explains why there was only a mild correlation between both markers in a study depicting the efficacy of pasireotide in CD (20).

#### **C. Early morning serum cortisol**

Morning serum cortisol measurement is mandatory to rule out overdosing leading to mild or patent adrenal insufficiency. The thresholds used in the case of cortisol lowering drugs are the same as those used to diagnose adrenal insufficiency (21). Of note, some teams perform repeated measurements of serum cortisol during the day ("day-curves") to define eucortisolism, as stated in the *Endocrine Society* guidelines (3). Though this approach can give a global overview of daytime cortisol secretion, and is easy to perform in routine, it should not, in our opinion be the only method used to measure long term efficacy of cortisol lowering drugs as it does not give detailed information on night-time secretion, a parameter that may be involved in metabolic comorbidities of CD. This was suggested by the approach of De Bono *et al.*, who gave different doses of metyrapone at 3 different times of the day (lowest dose in the morning, highest dose in the evening) with the aim of obtaining a lowest cortisol level at night (22). This approach can only be proposed when using drugs with a short half-life, such as metyrapone. Of note, serum cortisol can be of limited use in night-shift workers or in patients treated with 11-beta hydroxylase inhibitors (such as metyrapone or osilodrostat), depending on the immunoassay used. Indeed, these drugs increase the levels of 11-deoxycortisol, which can cross-react with cortisol measurements in some immunoassays (23, 24). Although the mechanism is different, the use of estrogens, by increasing the cortisol binding globulin, can also lead to falsely increased levels of serum cortisol (25).

#### **D. Combined parameters**

The best approach is probably to combine several markers, since they can all provide different elements of information: 24h-UFC as an imprecise image of overall secretion, bedtime salivary cortisol to obtain insights into cortisol nadir (both parameters being used to avoid underdosing), and early morning serum cortisol to rule out overdosing (25). This would be an optimal immediate approach, even though each of these parameters can vary from day to day, and this would ideally require 48h-measurements. Recently, Newell-Price *et al.* compiled the data of a phase 3 study on long-acting pasireotide. As the primary marker of efficacy was 24h-UFC, they also looked for additional information on a combined approach with bedtime salivary cortisol, considering that in such a protocol, early morning serum cortisol was also regularly monitored. Mean late-night salivary cortisol was evaluated in 137 patients based on two samples, measured the same day as the first two of three 24h-UFC measurements. At months 7 and 12, less than half of the patients who were considered controlled based on UFC also showed normal bedtime salivary cortisol. This subgroup of patients did however present the best metabolic profiles, in terms of improvement compared to baseline, suggesting that a combined score should be used to define eucortisolism for patients on medical treatments (26). Of note, reaching normal bedtime salivary cortisol with prolonged half-life drugs implies that the early morning cortisol level might be lower than expected, especially on a long-term basis: this approach would thus require regular monitoring and fine dose titration. This also means that education on signs



of adrenal insufficiency should be provided to all patients on cortisol-lowering drugs, and an emergency kit including hydrocortisone provided.

#### **E. Block-and-replace strategy**

One of the difficulties in managing patients on medical treatment is being certain of the lack of mild hypo- or hypercortisolism, which necessitates regular monitoring. Some authors have therefore suggested that a “block-and-replace” approach might be more efficient and safer than the classical “titration” approach (25). In a block-and-replace approach, steroidogenesis inhibitors are given at high doses to induce adrenal insufficiency, which is then replaced by a substitutive hormonotherapy as is done for adrenal insufficiency. The first steps are challenging, as substitutive therapy should not be given unless hypocortisolism is certain. Therefore, some teams have suggested that dexamethasone be used instead of hydrocortisone, to be able to trust measured serum cortisol levels on drug treatment, and to replace using hydrocortisone when adrenal insufficiency is obtained. At that time, proper education of the patient on the signs of adrenal insufficiency is performed. The block-and-replace approach has not been evaluated in the literature other than with mitotane treatment. However, it seems the most appropriate approach for patients for whom very rapid control of hypercortisolism is necessary. Patients with severe hypercortisolism usually require high doses of cortisol lowering drugs, and the dose increase can be very rapid, increasing the risk of sudden adrenal crisis. Another rare situation is that of patients with cyclic hypercortisolism, in whom a properly titrated drug dose could lead to adrenal crisis during the poorly secreting phase of their disease. Drawbacks of this approach are the cost (with an increased global drug dosage), and long-term compliance (with an increased number of tablets).

#### **Conclusions**

Though transsphenoidal surgery is the first line treatment of CD, medical treatment remains the cornerstone of management of patients with CD, either before surgery (especially in severe hypercortisolism), after failed surgery or while waiting for efficacy of radiation techniques to be established. The manner in which to use and monitor medical treatment depends on the situation: while severe hypercortisolism requires a fast-acting therapeutic scheme and should probably be treated with a block-and-replace approach, most other patients should probably be treated using a classical titration approach. This is however a little trickier since achieving eucortisolism with certainty can prove challenging. In this context, and while waiting for other markers of cortisol exposure such as hair cortisol, combined biochemical parameters should be used, to be able to check for global secretion, as well as checking for the peak (to avoid overdosing) and the nadir (to avoid underdosing). As these biochemical parameters show a high day-to-day variability, repeated measurement should be the rule, keeping in mind that even a perfectly controlled patient can escape or present with adrenal crisis. Therefore, educating and involving the patient in his/her treatment is also an obligatory step, especially when long-term monitoring is anticipated.

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#### **Figure Legend**

Figure 1: Proposed algorithm of titration for medical treatment of Cushing’s disease.



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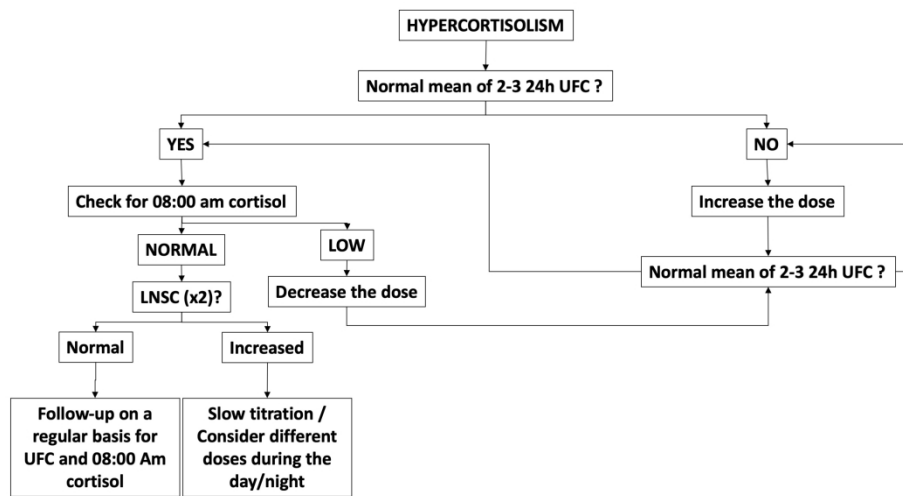


Figure 1: Proposed algorithm of titration for medical treatment of Cushing's disease.

Proposed algorithm of titration for medical treatment of Cushing's disease.

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