

# Medical Treatment of Cushing's Syndrome: Glucocorticoid Receptor Antagonists and Mifepristone

Frederic Castinetti · Bernard Conte-Devolx · Thierry Brue

Service d'endocrinologie, diabète et maladies métaboliques, et Centre de référence des maladies rares d'origine hypophysaire DEFHY, Hôpital de la Timone, Marseille, France

## Key Words

Cushing's disease · Anticortisolic drug · Ectopic ACTH secretion · Adrenal carcinoma · Bilateral adrenal hyperplasia · Glucocorticoid receptor antagonist

## Abstract

Mifepristone is the first and only available glucocorticoid receptor antagonist. It was initially mainly considered as a so-called 'contragestive' pill due to its antiprogestin activity. In this review, we summarize the results of mifepristone reported in the literature as a treatment of Cushing's syndrome. Most of the patients were treated due to unsuccessful surgery and/or partially effective anticortisolic drugs. The majority of them presented a rapid decrease of clinical signs of hypercortisolism during the first month of treatment; about half experienced a reduction in their elevated blood pressure, and half of the diabetic patients presented improved blood glucose levels. Mifepristone treatment has 2 main drawbacks: (1) the blockade of glucocorticoid receptors leads to increased ACTH and cortisol levels, making it difficult to adapt the treatment and diagnose adrenal deficiency, and (2) increased cortisol levels can also lead to severe hypokalemia. Follow-up of efficacy should only be clinical (weight, blood pressure, skin lesions) and biological (regular blood potassium sampling). Dose adjustment will be performed based on these parameters. The lack of a large avail-

able prospective cohort of patients on mifepristone, and the scarcity of data on its long-term effects, does not allow recommending it as a first-line drug in the treatment of hypercortisolism. However, as mifepristone is a rapidly effective drug, it can play a role in the management of hypercortisolism. The main indication is the partial efficacy or bad tolerance of other well-known anticortisolic drugs, either by replacement (bad tolerance, lack of effectiveness) or addition (multimodal approach) of mifepristone.

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## Introduction

Cushing's syndrome can be caused by adrenal, pituitary or ectopic tumors. Surgery remains the first-line treatment, and can be followed by pituitary irradiation or bilateral adrenalectomy if necessary. Medical management remains, however, of major interest when surgery is impossible, in preparation for surgery, or when surgery is partially effective. The efficacy of usual anticortisolic drugs (ketoconazole, metyrapone, mitotane, etc.) is not constant and may be limited by their poor tolerance [1, 2]. Mifepristone, a glucocorticoid receptor antagonist initially considered as a so-called 'contragestive' pill, may represent an alternative [3]. Our recent European collaborative retrospective study [3] allowed to discuss the po-

**Fig. 1.** Clinical picture of a patient before (left) and 6 months after (right) treatment with mifepristone for an ectopic ACTH syndrome. Note the decrease in upper body obesity and facial erythrosis after treatment.



tential future role of this drug in the management of Cushing's syndrome. In the present review, we will mainly talk about mifepristone, as data about other potential glucocorticoid receptor antagonists are only experimental.

### Pharmaceutical Properties

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11 $\beta$ -[*p*-(dimethylamino)phenyl]-17 $\beta$ -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. It is the first and currently only available glucocorticoid receptor antagonist treatment [4]. Other glucocorticoid receptors are currently evaluated, but no clinical trial has been published to date [5]. Mifepristone has also a strong anti-progestin activity, and a weak anti-androgen activity: its relative binding affinity at the glucocorticoid receptor is more than three times that of dexamethasone and more than ten times that of cortisol; affinity at the progesterone receptor is more than twice that of progesterone, and affinity at the androgen receptor is less than one third that of testosterone. It does not bind to the estrogen receptor or the mineralocorticoid receptor. Following oral administration of a single dose of 400–600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration occurring approximately 90 min after ingestion. Of note, in the absence of progesterone or cortisol, mifepristone can also act as a weak agonist [5, 6].

### Efficacy

Mifepristone appears as a rapidly effective drug in controlling signs of hypercortisolism. To date, 37 patients, mainly adults, have been reported in the literature

as having received mifepristone for various etiologies of Cushing's syndrome (table 1) [7–16]. Most of them were treated due to unsuccessful surgery and partially effective or badly tolerated medical treatment. Up to 85% presented a decrease of their clinical signs of hypercortisolism (weight loss, improvement of skin signs) during the first month of mifepristone (fig. 1). About half experienced a reduction in their elevated blood pressure and half of the diabetic patients also presented improved blood glucose levels, sometimes leading to withdrawal of antidiabetic drugs. The majority of the patients have been treated for an advanced adrenal carcinoma, ectopic ACTH secretion or Cushing's disease.

#### *Adrenal Carcinoma*

Seventeen patients have been reported to date. In the majority of cases, mifepristone was given in advanced adrenal carcinomas after failed surgery, and lack of efficacy of classical anticortisol drugs (including mitotane). Median duration of treatment was 3 months (range 0.25–9). Clinical signs of hypercortisolism improved in 76% of the cases during the first month of treatment. In our series, 60% of the patients presented improved blood pressure levels. Interestingly, one patient with severe psychosis had a drastic improvement of psychiatric signs in the first few days of mifepristone treatment.

#### *Ectopic ACTH Secretion*

Twelve patients have been treated with mifepristone after unsuccessful surgery or lack of identified tumor. Median duration of treatment was 5.5 months (range 0.3–18). All patients presented an improvement of their clinical signs. About half of them experienced decreased blood pressure levels. Severe psychosis signs improved in the first few days of mifepristone treatment in 1 patient.

**Table 1.** Individual data of patients treated with mifepristone for adrenal carcinoma (patients 1–17), ectopic ACTH secretion (18–29), Cushing’s disease (30–34) or other causes (35–37)

Patient No.	Sex/age	Dose mg/day	Previous treatments	Duration months	High BP	Hypokalemia	Adrenal insufficiency	Diabetes
1	F/45	5–22 mg/kg		2				
2	F/32	400		2				
3	F/NA	20–30 mg/kg		4				
4	M/62	400		9			↑	
5	M/43	400–800 mg		0.5				
6	M/63	1,000	M	6	↓	↔		↓
7	F/39	400	M	2.5	↔	↑		–
8	F/52	400–600	M	3	↓	↑		–
9	F/52	400–600	M	3	↓	↑		↔
10	F/45	400–2,000	M+K	1	–	↑		–
11	F/63	600	M+K	2	↔	–	↑	–
12	M/20	600–1,200	M+K	1	↓	↑	↑	↔
13	F/47	400–1,200	M+K	2	↔	↑		–
14	F/38	400–600	M+m	3	–	–		–
15	F/44	200–600	M+m	2	–	–		–
16	M/64	200–400	M+m	1.5	–	–		–
17	M/52	600	M+E	0.25	–	↑		↔
18	M/36	5–22 mg/kg		10			↑	
19	M/42	5–22 mg/kg		12				
20	F/63	5–22 mg/kg		4			↑	
21	F/55	5–22 mg/kg		2.5				
22	F/46	800–1,600		0.3				
23	M/25	5–20 mg/kg	m+chemotherapy	2.5	↓	↓		↓
24	F/2	75–300	none	2	↓	–		↓
25	F/46	600	chemotherapy	2	↑	↑		↓
26	F/37	800	chemotherapy	10	↑	↑		–
27	M/55	400–600	E+m	1	↓	↑		↓
28	F/43	600	K	2	↑	↑		↓
29	F/38	400–800	K	18	↑	↑		–
30	M/45	400–800	K	12	–	–		–
31	M/56	600–1,200	K	24	–	–	↑	–
32	F/50	600	–	0.5	–	↔		–
33	F/45	600	–	3	↑	↑		–
34	M/51	400–2,000	K	18	↔	↑	↑	–
35	F/38	5–22 mg/kg	–	1.5				
36	F/52	600	K	6	–	↔		↓
37	F/14	400	–	8	–	–		–

Previous treatments are treatments administered before the start of mifepristone therapy: M = mitotane; K = ketoconazole; m = metyrapone; E = etomidate. High blood pressure (BP), hypokalemia, adrenal insufficiency and diabetes: ↓ = alleviation or improvement on mifepristone; ↑ = worsening or onset on mifepristone; ↔ = unchanged on mifepristone; – = absent before treatment, unchanged on mifepristone; blank space for patients 1–5 = not available.

### Cushing’s Disease

Five patients have been treated to date because of the lack of pituitary adenoma visualized on MRI, failed surgery, bad tolerance to other anticortisolic drugs or partial efficacy of a radiosurgical procedure. Mean duration of

treatment was 11 months (range 0.5–24). All but one patient presented improved clinical signs. Again, 1 patient with severe psychosis had a drastic improvement of psychiatric signs in the first few days of mifepristone treatment.

Of note, 1 patient has been treated for bilateral adrenal hyperplasia, and 2 for a likely benign adrenal adenoma (but the precise etiology is unclear). All of them experienced a rapid improvement of clinical signs of hypercortisolism during the first month of mifepristone treatment [10].

### Tolerance

In Cushing's syndrome, hypokalemia is directly related to glucocorticoid excess as massive hypercortisolemia leads to incomplete renal inactivation of cortisol by  $11\beta$ -dehydrogenase, and hence mineralocorticoid excess. Mifepristone requires careful medical attention and a close follow-up of this specific point. As mifepristone blocks only glucocorticoid action, the mineralocorticoid activity of cortisol excess is not affected by mifepristone treatment, thus leading to hypokalemia. On the contrary, mifepristone may lead to an increase of plasma ACTH and consecutively of cortisol levels in some patients with Cushing's syndrome, particularly with Cushing's disease due to alterations in negative feedback (a mechanism of hypokalemia similar to the one observed in Cushing's syndrome without treatment) [5]. Mifepristone-induced hypokalemia was observed in one third of the 37 Cushing's patients reported to date. In a few cases, hypokalemia was very severe, requiring high doses of oral and intravenous potassium, and intensive anti-aldosterone treatment. Severe hypokalemia should thus represent a contraindication for this treatment and potassium levels need to be carefully monitored. The same mechanism can induce increased blood pressure levels, which was observed in 5 patients, despite an improvement of clinical signs of hypercortisolism. The ideal treatment remains high dose anti-aldosterone treatment: there is no need for a systematic prescription at the onset of mifepristone, except in case of low-normal hypokalemia.

Moreover, the lack of available biological parameters of follow-up on treatment obviously represents a limitation for the use of mifepristone. Signs suggestive of adrenal insufficiency have been reported in 16% of the 37 patients reported to date. The blockade of glucocorticoid receptors does not allow determining the efficacy of the drug by measuring ACTH and cortisol levels that are increased by mifepristone treatment. However, this low rate of adrenal deficiency is puzzling taking into account the mechanism of action of mifepristone: it is probably due to a partial blockade of glucocorticoid receptor antagonists, or a weak agonist effect of the drug [5]. Manage-

ment of adrenal deficiency is also difficult: hydrocortisone is not effective; dexamethasone (1 mg for 400 mg of mifepristone) should be given during 48 h in parallel with mifepristone withdrawal. Mifepristone can be re-initiated at a lower dose after the treatment of adrenal deficiency [17].

Antiprogesterin effects are also important to notice as they can induce an endometrial hyperplasia (relative hyperestrogenia). Three patients have been reported in the literature with this adverse effect [14]. Pelvic ultrasonography should be performed yearly in every woman before menopause.

### Dose and Follow-Up

Mifepristone should be initiated at a low dose (200–400 mg/day), and increased every 2–4 weeks based on clinical efficacy and tolerance. The maximal dose given should be around 400–800 mg/day. Increasing the dose up to 1,000 mg/day is usually not necessary, and increases the risk of adverse effects. However, increase in the dose of mifepristone could be performed more rapidly in case of severe signs of psychosis [10].

Follow-up of efficacy, and dose adjustments should mainly rely on clinical and necessarily imperfect parameters like weight, blood pressure or skin lesions. ACTH and cortisol levels will be increased, and do not represent a good marker of the efficacy of the drug. Adrenal deficiency should be suspected in case of weakness, fatigue, nausea, vomiting, and hypoglycemic episodes [10].

As mentioned previously, only a limited number of patients have been treated long-term with mifepristone, probably because more than a third of patients reported to date presented an advanced adrenal carcinoma. If long-term treatment is considered, pelvic ultrasonography should be performed at least yearly in nonmenopausal women. No specific adverse effects other than the ones seen at short-term have been reported.

### Pros and Cons in Comparison with Other Anticortisolic Drugs

The potential risks and benefits of mifepristone have to be weighed against alternative treatment options. The majority of other anticortisolic drugs have the major advantage to induce decreased cortisol levels: they are thus easier to follow (regular measures of plasma cortisol levels), whereas during mifepristone, cortisol concentration

provides no guidance for treatment. However, the other anticortisolic drugs classically expose patients to frequent and/or severe side effects without superior efficacy. Ketoconazole has been reported to induce serious and life-threatening hepatotoxicity, although this side effect is rare (1/15,000 cases). Moreover, ketoconazole is no longer available in some European countries (e.g. Germany) [2]. Metyrapone, an inhibitor of 11 $\beta$ -hydroxylase, is not easily available in several European countries and may also be associated with significant side effects [18]. Etomidate can only be used intravenously and, therefore, should be reserved for severe cases [19]. The use of mitotane can be difficult due to a narrow therapeutic window, and overall bad tolerance (gastrointestinal and neurotoxic effects). Moreover, most of these treatments are not as rapidly effective as mifepristone. This is particularly true for mitotane, which requires several weeks before being fully effective [20, 21].

Thus, treatment with mifepristone may be of significant value in the medical treatment of Cushing's syndrome in a high percentage of cases. Its place must be defined in regards of the severity of the disease. Due to the low number of patients reported, mifepristone cannot be recommended as a first-line treatment, even in comparison with more classical anticortisolic drugs. Mifepristone should be reserved to patients with lack of/partial efficacy and/or bad tolerance of well-known therapeutic procedures, i.e. surgery, radiotherapy and other anticortisolic drugs. Of note, mifepristone can be added to other anticortisolic drugs, as they have different mech-

anisms of actions. In this case, follow-up (mainly in terms of signs of adrenal deficiency and potassium levels) should be very strict.

## Conclusion

Mifepristone represents a rapidly effective treatment to control signs of hypercortisolism with the main drawback of the impossibility to follow blood cortisol levels. The risk of severe hypokalemia needs to be closely monitored and further limits its widespread use. Despite these promising results, the lack of a large available prospective cohort of patients on mifepristone, and the scarcity of data on its long-term effects, does not allow recommending it as a first-line drug in the treatment of hypercortisolism. However, as mifepristone is a rapidly effective drug, its main indication is the partial efficacy or bad tolerance of other well-known anticortisolic drugs especially in patients with psychiatric signs of hypercortisolism. Only a limited number of patients have been treated long-term with mifepristone and if long-term treatment is considered, one should keep in mind the anti-progestin activity of mifepristone, as this can lead to endometrial hyperplasia.

## Disclosure Statement

The authors have nothing to disclose.

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