

CLINICAL STUDY

Merits and pitfalls of mifepristone in Cushing's syndrome

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Abstract

Objective: Mifepristone is the only available glucocorticoid receptor antagonist. Only few adult patients with hypercortisolism were treated to date by this drug. Our objective was to determine effectiveness and tolerability of mifepristone in Cushing's syndrome (CS).

Design: Retrospective study of patients treated in seven European centers.

Methods: Twenty patients with malignant ($n=15$, 12 with adrenocortical carcinoma, three with ectopic ACTH secretion) or benign ($n=5$, four with Cushing's disease, one with bilateral adrenal hyperplasia) CS were treated with mifepristone. Mifepristone was initiated with a median starting dose of 400 mg/day (200–1000). Median treatment duration was 2 months (0.25–21) for malignant CS, and 6 months (0.5–24) for benign CS. Clinical (signs of hypercortisolism, blood pressure, signs of adrenal insufficiency), and biochemical parameters (serum potassium and glucose) were evaluated.

Results: Treatment was stopped in one patient after 1 week due to severe uncontrolled hypokalemia. Improvement of clinical signs was observed in 11/15 patients with malignant CS (73%), and 4/5 patients with benign CS (80%). Psychiatric symptoms improved in 4/5 patients within the first week. Blood glucose levels improved in 4/7 patients. Signs of adrenal insufficiency were observed in 3/20 patients. Moderate to severe hypokalemia was observed in 11/20 patients and increased blood pressure levels in 3/20 patients.

Conclusion: Mifepristone is a rapidly effective treatment of hypercortisolism, but requires close monitoring of potentially severe hypokalemia, hypertension, and clinical signs of adrenal insufficiency. Mifepristone provides a valuable treatment option in patients with severe CS when surgery is unsuccessful or impossible.

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Introduction

Cushing's syndrome (CS) is a rare but serious disease with significant morbidity and mortality due to cardiovascular, metabolic, and infectious complications (1, 2). Transsphenoidal surgery is the treatment of choice for Cushing's disease (CD) and is usually followed by pituitary irradiation or by bilateral adrenalectomy if surgery has failed (3). In malignant CS, surgery remains the first-line treatment in adrenocortical carcinoma (ACC) and ectopic ACTH secretion (EAS) while chemotherapy and/or radiotherapy are reserved for advanced disease (4, 5). Medical management of hypercortisolism can thus be used in four circumstances: during the period required for localization of the ACTH source, in preparation for surgery, following

radiation therapy to bridge its delayed efficacy or in metastatic disease as part of a multimodal approach. Several drugs have been advocated, each having advantages and drawbacks. For example, o,p'-dichlorodiphenildichloroethane is effective in controlling cortisol excess in about 50–80% of cases, and also has antitumoral effects due to its adrenolytic activity (6). However, maximum efficacy is delayed and the drug is frequently poorly tolerated due to a narrow therapeutic window (7, 8). Other drugs like ketoconazole or metyrapone may act more rapidly but are often only partially effective and associated with significant adverse events (e.g., serious hepatotoxicity, hypertension or hypokalemia) (9, 10). In cases of drug intolerance or unresponsiveness, an alternative medical treatment should be useful.

Mifepristone is the first and only available glucocorticoid receptor antagonist (11, 12). It was discovered in the early 1980's (13), but due to its strong antiprogesterin activity it has mainly been used as a contraceptive pill. Owing to the controversy related to this use of mifepristone, there is presently limited experience concerning the use of mifepristone in hypercortisolism. To date only 21 patients (including two children) were reported to have been treated with mifepristone, mostly for short periods (14–19). Most of these cases were published as case reports, except for one study including 10 patients (20). However, four of these patients were treated for <10 days due to adverse effects, although these adverse events may have been unrelated to mifepristone therapy. Moreover, only 12 patients were treated with mifepristone for CS for more than 2 weeks. All of these patients showed rapid regression of clinical signs of cortisol excess suggesting that mifepristone could become a valuable treatment option in poorly controlled hypercortisolism. Adverse events included nausea and fatigue, which could be attributed to adrenal insufficiency in three cases. These scarce data also drew attention to the limitations of biochemical parameters for follow-up as the blockade of glucocorticoid receptors by mifepristone may lead to variable increase in plasma ACTH and consequently cortisol concentrations (12, 16). Thus, the diagnosis of both persistent hypercortisolism and adrenal insufficiency is difficult and largely based on clinical assessment and close follow-up.

Owing to the lack of sufficient clinical data on mifepristone in cases of glucocorticoid excess, we decided to evaluate retrospectively the use of mifepristone as a treatment of CS in seven European centers. We report here the results of mifepristone therapy in 20 patients. Owing to the various etiologies of CS, we divided this group into malignant and benign CS. We tried to define the efficacy and adverse events of mifepristone to better define the potential role of this drug in endogenous glucocorticoid excess.

Patients and methods

We retrospectively evaluated the effectiveness and tolerability of mifepristone. We included in our study 20 patients with CS who had been treated with mifepristone (Mifegyne, Exelgyn Laboratories, Paris, France; Mifepristone, HRA Pharma, Paris, France). These patients were followed in seven European centers: France (Marseille $n=4$, Paris $n=1$, Le Kremlin-Bicetre $n=2$, Lille $n=1$), Germany (Würzburg, $n=9$), Italy (Orbassano $n=2$), and Spain (Alicante, $n=1$). Mifepristone was used on a compassionate basis after all patients had given their written informed consent; they had previously received detailed information on the potential side effects and benefits of mifepristone. Patient charts were retrospectively

analyzed in detail for changes in clinical status, adverse events, and changes in standard biochemical and hormonal parameters.

The diagnosis of CS was based on the combination of clinical features of hypercortisolism and biochemical assessment according to recommended guidelines (21). The study population comprised 13 females (including five post-menopausal women) and seven males, with a mean age of 48.5 years (range 20–63) at the time of diagnosis of CS (Table 1). None of them presented cyclic CS. Mifepristone was initiated due to the lack of efficacy ($n=6$) or limited tolerance (e.g. hepatotoxicity) ($n=7$) of previous medical treatments, increase in liver enzymes due to metastatic disease leading to contra-indication for adrenostatic drugs ($n=3$) or as additional symptomatic therapy in combination with metyrapone or etomidate ($n=2$). In these two patients, metyrapone and etomidate were considered as only partially effective, and the dose was not modified during mifepristone treatment. In addition, mifepristone was given to two patients with CD as first adjunctive treatment after unsuccessful transsphenoidal surgery ($n=2$). All patients had undergone complete clinical and hormonal evaluation prior to mifepristone treatment. In all centers, efficacy and adverse events of mifepristone were assessed every 15–30 days by careful clinical evaluation (clinical signs of hypercortisolism, psychiatric symptoms, clinical signs, and symptoms suggestive of adrenal insufficiency, blood pressure) or earlier if justified by the patient's condition. Every 15–30 days biochemical follow-up included control of serum electrolytes, liver enzymes, and kidney function. In diabetic patients, frequent glycemic controls were performed with modification of diabetes treatment, if necessary. TSH levels were measured after 3–6 months of treatment or in case of clinical evidence of hypothyroidism, as one case of Hashimoto thyroiditis has been described previously during mifepristone therapy (20). Random samples of ACTH and serum cortisol concentrations were taken in monthly intervals (during outpatient visits). Owing to its antiprogesterin effects, mifepristone has been reported to induce endometrial hyperplasia (22). Accordingly, transvaginal ultrasound examination was performed in a patient of our series treated for 18 months, as previously recommended. All adverse events occurring during treatment were recorded with special attention to the problems of adrenal insufficiency and hypokalemia.

Results

Individual data of the 20 patients treated with mifepristone for CS are given in Table 1. Mifepristone was initiated at a median dose of 400 mg/day (range 200–1000). The initial dose was decided by each investigator and varied with the severity of clinical signs of hypercortisolism. The median maximal dose

Table 1 Individual data of the 20 patients treated by mifepristone.

	Etiology	Sex/age	Previous treatments		Pre-mifepristone				
			Surgery	Anticortisolic drugs	Clin. signs	Psy. signs	Hypertension	HypoK	Diab.
1	ACC	M/63	Y	Mitotane	+	+	+	+	+
2		F/39	Y	Mitotane	+	-	+	+	-
3		F/52	Y	Mitotane	+	-	+	-	-
4		F/52	Y	Mitotane	+	-	+	-	+
5		F/45	Y	Mitotane, ketoconazole	+	-	-	-	-
6		F/63	N	Mitotane, ketoconazole	+	-	+	-	-
7		M/20	Y	Mitotane, ketoconazole	+	-	+	+	+
8		F/47	Y	Mitotane, ketoconazole	+	-	+	-	-
9		F/38	N	Mitotane, metyrapone	+	-	-	-	-
10		F/44	Y	Mitotane, metyrapone	+	-	-	-	-
11		M/64	Y	Mitotane, metyrapone	+	-	-	-	-
12		M/52	N	Mitotane, etomidate	+	+	-	+	+
13	EAS	M/55	N	Etomidate, metyrapone	+	-	-	+	+
14		F/43	N	Ketoconazole	+	+	+	+	+
15		F/38	Y	Ketoconazole	+	-	+	+	-
16	CD	M/45	Y	Ketoconazole	+	-	-	-	-
17		M/56	Y	Ketoconazole	+	-	-	-	-
18		F/50	N	None	+	+	-	+	-
19		F/45	N	None	+	-	-	-	-
20	BAH	F/52	N	Ketoconazole	+	-	+	+	+

Etiology: ACC, adrenocortical carcinoma; CD, Cushing's disease; BAH, bilateral adrenal hyperplasia; EAS, ectopic ACTH secretion. Sex/age: F, female; M, male; age in years. Previous treatment: surgery, Y when surgery was performed before mifepristone, N when no surgery was performed. Pre-mifepristone, clinical or biochemical signs before mifepristone treatment; clin. signs, clinical signs of hypercortisolism (hirsutism, bruising, facial fullness, edema, truncal obesity); psy. signs, psychiatric signs or cognitive deficit; hypertension, high blood pressure level (>140/90 mmHg); hypoK, low serum potassium level (<3.5 mmol/l); diab., diabetes; for each criterion, + is marked when the criterion was reported, - when the criterion was absent.

during the treatment was 600 mg/day (400–2000). The maximal dose was decided by each investigator according to clinical efficacy and tolerance (mainly blood potassium level, signs of adrenal insufficiency). The median duration of treatment was 2.5 months (5 days to 24 months). Efficacy and adverse events of the treatment are reported in Table 2.

Mifepristone in malignant CS

Effectiveness and adverse events in patients with ACC Twelve patients received mifepristone for advanced ACC. Nine of them were treated unsuccessfully by surgery, cytotoxic chemotherapy, and/or mitotane, two were treated by chemotherapy and mitotane only, and one received only mitotane for a few days, which was then stopped due to a sharp increase in liver enzymes (patient no. 12, Table 1). Anticortisolic drugs including ketoconazole ($n=4$), metyrapone ($n=3$) or etomidate (case no. 12), had been used without sufficient response or were stopped due to poor tolerance. The median starting dose of mifepristone was 400 mg/day (200–1000 mg) with a median maximal dose of 600 mg/day (400–2000) and a median duration of treatment of 2 months (5 days to 6 months).

In eight patients (66%), the clinical signs of hypercortisolism improved rapidly within the first month. In these cases, both patient and attending physician judged the treatment as success. However, in most cases symptoms did not disappear completely.

Psychiatric symptoms improved within the first week in one of two affected patients and blood pressure decreased in four of seven patients with hypertension (57%). Cessation of insulin treatment and switch to oral drugs was possible in one out of four patients with diabetes mellitus. In three out of four patients with low serum potassium prior to mifepristone, hypokalemia worsened during mifepristone treatment requiring high doses of supplemental potassium (up to 16 g/day), spironolactone (up to 100 mg/day), and, in case no. 12, cessation of mifepristone within 1 week of treatment. In patient no. 1, low serum potassium concentrations remained unchanged during mifepristone. Three other patients presenting initially with normal serum potassium concentrations developed moderate to severe hypokalemia during treatment with mifepristone. Thus, 7 out of 12 patients (58.3%) experienced significant problems with serum potassium during mifepristone treatment.

Mifepristone treatment was stopped due to death or tumor progression ($n=8$), lack of significant benefit ($n=2$), and uncontrolled severe hypokalemia ($n=1$). None of the patients died because of adverse effects of mifepristone. Patient no. 9 is still on treatment after 3 months with clinical signs of hypercortisolism improved despite tumor progression.

Effectiveness and adverse events in patients with EAS A total of three patients were treated with mifepristone for metastatic EAS (thymic carcinoma $n=1$, small cell lung cancer $n=2$). All had been

Table 2 Efficacy and adverse events of mifepristone in the 20 patients of the series.

	Etiology	Dose initial/final	Duration (months)	During mifepristone treatment					Reason for cessation of mifepristone treatment
				Clin. signs	Psy. signs	Hypertension	HypoK	Diab.	
1	ACC	1000/1000	6	↓	↓	↓	↔	↓	Death (tumor progression)
2		400/400	2.5	↓	—	↔	↑	—	Death (tumor progression)
3		400/600	3	↓	—	↓	↑	—	Death (tumor progression)
4		400/600	3	↓	—	↓	↑	↔	Death (tumor progression)
5		400/2000	1	↔	—	—	↑	—	No significant benefit
6		600/600	2	↔	—	↔	—	—	No significant benefit
7		600/1200	1	↓	—	↓	↑	↔	Death (tumor progression)
8		400/1200	2	↔	—	↔	↑	—	Death (tumor progression)
9		400/600	3	↓	—	—	—	—	Ongoing treatment
10		200/600	2	↓	—	—	—	—	Tumor progression
11		200/400	1.5	↓	—	—	—	—	Death (tumor progression)
12		600/600	0.25	↔	↔	—	↑	↔	Uncontrolled hypokalemia, cessation after 1 week of treatment
13	EAS	400/600	1	↓	—	↓	↑	↓	Tumor progression, hypokalemia
14		600/600	2	↓	↓	↑	↑	↓	Bilateral adrenalectomy
15		400/800	18	↓	—	↑	↑	—	Ongoing treatment
16	CD	400/800	12	↓	—	—	—	—	Bilateral adrenalectomy
17		600/1200	24	↓	—	—	—	—	↑ Radiosurgical treatment efficacy
18		600/600	0.5	↔	↓	—	↔	—	Neurosurgical treatment made possible due to psychosis improvement
19		600/600	3	↓	—	↑	↑	—	Ongoing treatment
20	BAH	600/600	6	↓	—	—	↔	↓	Bilateral adrenalectomy

Etiology: ACC, adrenocortical carcinoma; CD, Cushing's disease; BAH, bilateral adrenal hyperplasia; EAS, ectopic ACTH secretion. Dose: mg/day. In the column « during mifepristone treatment, ↔ when the criterion was unchanged, ↑ if the criterion appeared or was worsened during the treatment, — if the criterion was still absent, ↓ if the criterion decreased or disappeared with the treatment; Adr. Ins., clinical signs during the treatment were evocative of adrenal insufficiency (+), or no sign of adrenal insufficiency was present (—); note that patients 2, and 14 presented severe fatigue during the treatment.

unsuccessfully treated by surgery. The median starting dose was 400 mg/day (400–600 mg) with a median maximal dose of 600 mg/day (600–800 mg), and a median duration of treatment of two months (1–21 months). Patient no. 13 was treated concomitantly with metyrapone, making it difficult to correctly interpret the results. Clinical signs of hypercortisolism improved in all patients. One patient with severe psychosis showed rapid improvement during the first week after initiation of mifepristone. Two patients who presented with high blood pressure and low serum potassium experienced worsening of hypokalemia and hypertension during mifepristone treatment and required high doses of spironolactone (up to 400 mg/day) and potassium supplementation (up to 20 g/day). Severe hypokalemia was also observed in the remaining patient who had moderately lowered serum potassium prior to therapy. In two patients with diabetes mellitus at diagnosis, insulin doses could be rapidly decreased allowing good glycemic control with reduced insulin doses or a switch to oral antidiabetic drugs. Mifepristone was eventually stopped due to tumor progression and/or profound hypokalemia ($n=2$). The third patient (patient no. 15) with metastatic thymic carcinoma is still on treatment. In this patient, withdrawal of mifepristone after cytotoxic chemotherapy worsened clinical signs and symptoms of hypercortisolism and, therefore, treatment with mifepristone was reinitiated. Presently, she has no clinical signs of hypercortisolism. Moderate hypokalemia

and elevated blood pressure levels are well controlled by spironolactone and potassium administration after 21 months of treatment.

Mifepristone in benign CS

Effectiveness and adverse events in patients with CD

Four patients with CD were treated with mifepristone in our centers. Two of them underwent unsuccessful transsphenoidal surgery, in one followed by gamma-knife radio surgery. The third patient (no. 18) presented with severe psychosis making surgery impossible. The fourth patient (no. 19) had no pituitary adenoma image on magnetic resonance imaging and ketoconazole was poorly tolerated. The median starting dose of mifepristone was 600 mg/day (300–600 mg), median maximal dose 700 mg/day (600–1200), and median duration of treatment was 9 months (0.5–24 months).

Clinical signs of hypercortisolism improved rapidly in three out of four patients (75%). The patient with psychosis showed rapid improvement of psychiatric symptoms within the first week of treatment. None of the patients had hypertension. However, patient no. 19 developed high blood pressure and severe hypokalemia during mifepristone. In one patient (no. 18), low serum potassium remained unaffected by the treatment with mifepristone. In all patients, ACTH and cortisol levels

increased during mifepristone (up to three times of pretreatment levels).

Mifepristone was eventually stopped in three patients because of bilateral adrenalectomy ($n=1$), eventual efficacy of gamma-knife radio surgery ($n=1$), and neurosurgical treatment after regression of psychosis ($n=1$). Patient no. 19 is still on treatment six months after initiation of mifepristone therapy.

Effectiveness and adverse events in a patient with bilateral adrenal hyperplasia This patient was treated with mifepristone (600 mg/day) because of severe clinical signs of hypercortisolism, intolerance to ketoconazole, and refusal of bilateral adrenalectomy. Signs of hypercortisolism and hypertension improved progressively during the first three months of treatment. Hypokalemia was present before initiation of mifepristone and remained unchanged during treatment. Metformin treatment could be stopped after one month of treatment, and HbA1c decreased from 7.1 to 6.4% after six months of mifepristone. Eventually, the patient underwent bilateral adrenalectomy after six months of treatment with mifepristone.

Adrenal insufficiency during mifepristone treatment

Three of our 20 patients presented clinical signs suggestive of adrenal insufficiency (fatigue, nausea, and vomiting). All were treated by dexamethasone followed by a reduction of mifepristone dose to 50% of the last dosage prior to adrenal insufficiency. Patients received 1 mg dexamethasone/400 mg mifepristone as recommended previously (23). Two patients reported extreme fatigue, but no other clinical signs of adrenal deficiency (patients nos 3 and 14). Their treatment was not modified.

Other potential adverse effects of mifepristone

One non-diabetic patient had a transient episode of hypoglycemia. No increase in liver enzymes or alterations in thyroid function or kidney function was observed in relation to mifepristone treatment. In the female patient (patient no. 15) who received mifepristone for 18 months, no endometrial hyperplasia was observed.

Discussion

The antiglucocorticoid activity of mifepristone is well established *in vitro* (14). However, in long-term studies mifepristone has been mainly used as an anti-progestin in meningioma, myoma or other progesterone-dependent diseases (24, 25). It is used as an antiglucocorticoid in patients with hypercortisolism

and was hampered by the controversy related to its use for inducing abortion leading to legal restrictions in several countries. Accordingly, as shown in Table 3, only 21 patients (including two children) have been treated by mifepristone for CS (14, 15, 17, 20, 22, 26–29). Thus, our study of 20 patients doubles the database of mifepristone treatment for CS and, therefore, allows a better appreciation of its effectiveness and adverse effects.

Our study clearly indicates that mifepristone has significant potential to improve clinical signs and symptoms related to CS. Of note, all four patients not benefitting from mifepristone suffered from very advanced ACC (the fifth patient, who presented rapid regression of psychosis signs, was only treated for 15 days). In general, most of our patients were heavily pretreated and, in most cases, anticortisol drugs had failed to control CS or were not tolerated. An important advantage of mifepristone is the rapid onset of its action making it especially helpful for patients presenting with psychosis. In three out of four patients, psychosis signs indeed disappeared within one week of therapy.

Our study highlights two main challenges in the treatment of patients with CS with mifepristone: hypokalemia and adrenal insufficiency. In our study, 55% patients presented relevant hypokalemia. The percentage of hypokalemia in our study is higher than the 20% previously reported (16). In CS, hypokalemia is directly related to glucocorticoid excess as massive hypercortisolemia leads to incomplete renal inactivation of cortisol by 11- β -dehydrogenase, and hence mineralocorticoid excess (30). 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 CS, particularly with CD due to alterations in negative feedback. Other mechanisms that probably contributed to the higher incidence of hypokalemia in our study may be related to the fact that in many patients adrenostatic therapy was stopped prior to mifepristone treatment because of drug intolerance. Thus, in these patients, increase in cortisol concentrations could be related to cessation of adrenostatic therapy or tumor progression, leading to hypercortisolism and severe hypokalemia. Furthermore, even if this mechanism seems less likely, it has been shown that progesterone acts as an anti-mineralocorticoid and the antiprogesterin activity of mifepristone may have reduced this anti-mineralocorticoid action of endogenous progesterone further enhancing mineralocorticoid excess (31). In many of our cases, profound hypokalemia was thus probably multifactorial. However, the fact that severe hypokalemia was observed even with the use of spironolactone and potassium supplementation draws attention on the fact that hypokalemia may become a treatment limiting side-effect of mifepristone, mainly

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