Mitotane, Metyrapone, and Ketoconazole Combination Therapy as an Alternative to Rescue Adrenalectomy for Severe ACTH-Dependent Cushing's Syndrome

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Context: Mitotane is highly effective in the long-term management of Cushing's syndrome but has a slow onset of action. Mitotane combined with fast-acting steroidogenesis inhibitors might avoid the need for emergency bilateral adrenalectomy in patients with severe hypercortisolism.

Objective: Our objective was to assess the efficacy and safety of combination therapy with mitotane, metyrapone, and ketoconazole in severe ACTH-dependent Cushing's syndrome.

Patients, Design, and Setting: Eleven patients with severe Cushing's syndrome participated in this follow-up study in a tertiary referral hospital.

Interventions: High-dose therapy combining mitotane (3.0–5.0 g/24 h), metyrapone (3.0–4.5 g/24 h), and ketoconazole (400–1200 mg/24 h) was initiated concomitantly. Twenty-four-hour urinary free cortisol (UFC) excretion (normal values 10–65 μg/24 h) was monitored.

Results: Data are reported as medians (range). All 11 patients experienced a marked clinical improvement. UFC excretion fell rapidly from 2737 μg/24 h (range 853–22,605) at baseline to 50 μg/24 h (range 18–298) ($P = 0.001$) within 24–48 h of treatment initiation and remained low to normal on the combination therapy. In seven patients, metyrapone and ketoconazole were discontinued after 3.5 months (range 3.0–6.0) of combination therapy, and UFC excretion remained controlled by mitotane monotherapy (UFC 17 μg/24 h, range 5–85; $P = 0.016$). Five patients became able to undergo etiological surgery and are presently in remission. Four of them recovered normal adrenal function after mitotane discontinuation. Adverse effects were tolerable, consisting mainly of gastrointestinal discomfort and a significant rise in total cholesterol and γ-glutamyl transferase levels ($P = 0.012$ and $P = 0.002$, respectively).

Conclusions: When surgical treatment for severe ACTH-dependent Cushing's syndrome is not feasible, combination therapy with mitotane, metyrapone, and ketoconazole is an effective alternative to bilateral adrenalectomy, a procedure associated with significant morbidity and permanent hypoadrenalism. **(*J Clin Endocrinol Metab* 96: 2796–2804, 2011)**

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Abbreviations: γ-GT, γ-Glutamyl transferase; ICU, intensive care unit; UFC, 24-h urinary free cortisol.

Untreated ACTH-dependent Cushing's syndrome is associated with a risk of life-threatening cardiovascular, infectious, and metabolic complications (1–3). The risk of death increases with the rate of cortisol secretion. Successful surgery of ACTH-secreting tumors can normalize cortisol secretion and lower the mortality rates of such patients to that of the general population (1, 3).

However, when curative surgery is not feasible in urgent, high-risk situations and/or when severe hypercortisolism remains difficult to manage, bilateral adrenalectomy provides immediate control of hypercortisolism (4). Unfortunately, both open and laparoscopic adrenalectomy in critically ill Cushing's syndrome patients are associated with increased risk of morbidity and mortality (5–8). It also results in permanent hypoadrenalism, requiring lifelong glucocorticoid and mineralocorticoid replacement therapy (9–11), as well as regular pituitary magnetic resonance imaging and plasma ACTH monitoring to rule out possible Nelson's syndrome (12, 13).

Because of its adrenolytic action, mitotane is highly effective in the long-term management of ACTH-dependent Cushing's syndrome, even after treatment withdrawal, because the drug is stored in adipose tissue and has a long half-life (14, 15). Contrary to other steroidogenesis inhibitors, its mechanism of action prevents the escape phenomenon (14, 16). However, the prolonged onset of its anticortisol activity renders mitotane as unsuitable for use in patients with severe hypercortisolism and life-threatening complications. Metyrapone and ketoconazole, used alone or in combination, are effective in blocking hypercortisolism (17, 18) but frequently fail to control Cushing's syndrome, either because ACTH overrides their cortisol-blocking actions (16) or because of intolerable side effects.

In this report, we assessed the efficacy and safety of combination therapy, using mitotane, metyrapone, and ketoconazole in patients with severe ACTH-dependent Cushing's syndrome. We postulate that the two fast-acting steroidogenesis inhibitors provide rapid clinical and biological control of severe hypercortisolism, thus covering the lag period before mitotane starts to act. This combination provides an alternative to emergency high-risk bilateral adrenalectomy.

Patients and Methods

Patients

From a cohort of 64 consecutive patients with ACTH-dependent Cushing's syndrome recruited between October 2006 and September 2010 at the Endocrinology Department of Bicêtre University Hospital, we selected 11 patients with severe hypercortisolism for enrollment in this study. Eligibility for the study was based on clinical severity exclusively. All 11 patients had ACTH-dependent Cushing's syndrome associated with clinical disorders such as severe cardiovascular, respiratory, or infectious complications precluding surgical removal of the source of excessive ACTH as well as bilateral surgical adrenalectomy. The diagnosis of Cushing's syndrome was based on clinical phenotype, associated with elevated urinary free cortisol (UFC) excretion (Table 1), a loss of the circadian plasma cortisol pattern, and a lack of cortisol suppression in the overnight 1-mg dexamethasone suppression test (1, 16, 19)

Baseline characteristics

The patients' baseline clinical and hormonal characteristics are summarized in Table 1. Hypercortisolism was associated with severe complications in all the patients. Several patients were critically ill and required at least one stay in the intensive care unit (ICU). Briefly, patient 1 was a 17-yr-old male with Cushing's disease complicated by acute pulmonary embolism that occurred during a transatlantic flight from the West Indies to France for pituitary surgery. He then developed acute heart failure with global alteration of ventricular function (left ventricular ejection fraction $< 20\%$) and recurrent pulmonary edema (Fig. 1A) necessitating several ICU stays. Patient 2 was a

TABLE 1. Baseline clinical and hormonal parameters

Patient	Age/sex	UFC (μg/24 h)	ACTH (pg/ml)	K (mmol/liter)	Complications
1	17/M	2737	206	2.9	Pulmonary embolism, heart failure
2	46/M	853	102	3.5	Heart failure
3	38/F	3764	250	3.3	Femoral osteonecrosis
4	23/F	1227	59	3.4	Preterm induction of delivery
5	65/F	3190	154	2.8	Pelvic abscesses
6	75/F	1190	140	3.3	Acute respiratory distress
7	29/F	1457	76	3.0	Pulmonary embolism
8	66/F	1150	156	2.8	Pulmonary embolism
9	73/M	5687	1023	3.4	Pulmonary embolism, sepsis
10	46/M	4391	24	2.7	Pneumocystosis, sepsis
11	39/F	22605	653	2.4	Ketoacidosis, pneumonia, herpes zoster

The normal range of UFC excretion values in 120 normal individuals was 10–65 μg/24 h; the normal range of plasma ACTH values was 10–50 pg/ml; the normal range of plasma potassium values was 4.0–4.7 mmol/liter. Patient 10 had excessively elevated lipotropin concentrations (2522 pg/ml, normal value = 87 $\pm$ 38 pg/ml). F, Female; M, male.

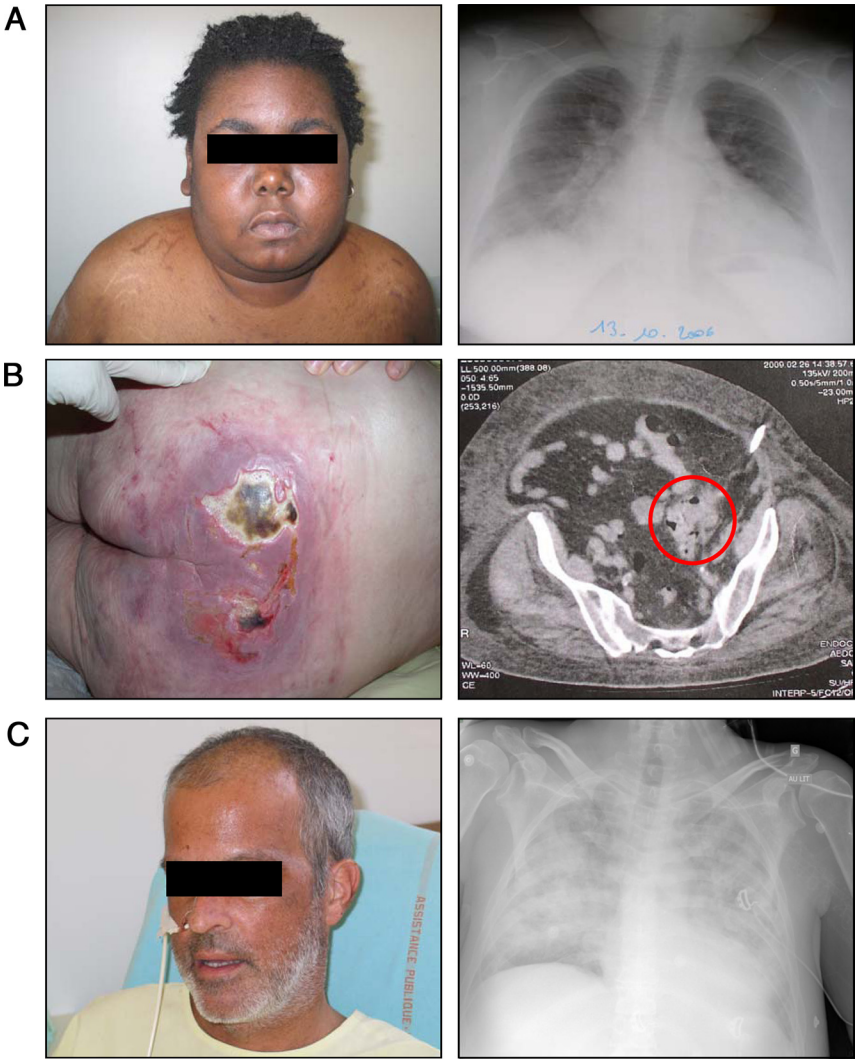

FIG. 1. Clinical features of several representative patients (see text for details). A, Patient 1, acute heart failure; B, patient 5, sacral bedsore and pelvic abscesses (*red circle*); C, patient 10. *Pneumocystis jirovecii* pneumonia.

46-yr-old man with Cushing's disease and specific dilated cardiomyopathy with severe left ventricular dysfunction (left ventricular ejection fraction 30%, negative coronary angiography) and multiple vertebral fractures that reduced his respiratory capacity and caused a height loss of 14 cm. Patient 3 was a 38-yr-old woman with Cushing's disease, poor tissue status, femoral head osteonecrosis, severe refractory arterial hypertension, and hypokalemia. Patient 4 was a 23-yr-old woman with Cushing's disease who had a recurrence of hypercortisolism during pregnancy as well as severe hypertension and diabetes, requiring induction of labor at 32 wk of amenorrhea. Medical treatment was chosen because of her worsening clinical status and because two previous pituitary surgeries had failed to remove a corticotrope microadenoma. Patient 5 was a 65-yr-old woman with rapidly progressive hypercortisolism probably due to ectopic ACTH secretion. She was admitted with sepsis due to pelvic abscesses, a sacral bedsore measuring 10 × 7 cm (Fig. 1B), heart failure, and profound hypokalemia. The pelvic infection prevented petrosal sinus sampling and etiological therapy. Patient 6 was a 75-yr-old woman with severe hypercortisolism probably due to ectopic ACTH secretion. She had an acute respiratory distress syndrome of mixed etiology (bilateral pneumonia, heart failure, and acute polyradiculoneuropathy) that required a 5-month ICU stay because of her dependency on mechanical ventilation. Patient 7 was a 29-yr-old woman with ectopic ACTH secretion. Medical therapy was chosen in this case because she required anticoagulation for acute pulmonary embolism and because the source of ACTH secretion was initially difficult to locate (finally identified as a mediastinal carcinoid tumor) (Table 2). Patient 8 was a 66-yr-old woman with metastatic thymic neuroendocrine carcinoma associated with histologically proven ectopic ACTH secretion. When transferred to our department, she had jugular vein thrombosis complicated by acute pulmonary embolism and then developed a superior vena cava syndrome. Patient 9 was a 73-yr-old man with metastatic undifferentiated neuroendocrine lung cancer secreting ACTH. He was admitted with pulmonary embolism and

TABLE 2. Etiology of hypercortisolism, duration of treatment, and treatment outcomes

Patient	Etiology	Tumor	Duration of combination therapy (months)	Duration of mitotane monotherapy (months)	Follow-up (months)	Outcome
1	CD	Micro	3.5	27	42	Surgery, remission
2	CD	Micro	3.5	3	14	Surgery, mitotane
3	CD	Micro	3	3	14	Surgery, remission
4	CD	Micro	3	3	25	Surgery, remission
5	EAS?	Occult	6	13	19	Mitotane
6	EAS?	Occult	9		9	Death (respiratory distress)
7	EAS	Occult	4	2	35	Surgery, remission
8	EAS	Metastatic	4	10	14	Death (tumor progression)
9	EAS	Metastatic	1		1	Death (myocardial infarction)
10	EAS	Metastatic	4		4	Death (tumor progression)
11	EAS	Metastatic	1		6	Surgery, remission

CD, Cushing's disease; EAS, ectopic ACTH secretion; Micro, microadenoma. For details, see text.

Escherichia coli pyelonephritis complicated by sepsis. Patient 10 was a 46-yr-old man with undifferentiated metastatic neuroendocrine carcinoma of the pancreas expressing ACTH at immunochemistry, associated with ectopic ACTH and lipotropin secretion (lipotropin level = 2522 pg/ml; normal value = 87 ± 38 pg/ml) (20), causing fulminant Cushing's syndrome. When transferred to our department, he had severe cachexia, sepsis due to a *Pseudomonas aeruginosa*-infected catheter, and *Pneumocystis jirovecii* pneumonia (Fig. 1C) requiring intubation and mechanical ventilation during a 2-wk ICU stay. Patient 11 was a 39-yr-old woman with a neuroendocrine tumor of the small intestine associated with histologically proven ectopic ACTH secretion causing major hypercortisolism complicated by diabetic ketoacidosis, profound hypokalemia, atypical bilateral pneumonia, and thoracic herpes zoster.

In all 11 patients, curative surgery of the source of ACTH and bilateral adrenalectomy were ruled out by severe complications of hypercortisolism and very poor clinical status, and patients 1, 7, 8, and 9 were also receiving anticoagulation.

Interventions

The study conformed to the Helsinki Declaration on Human Experimentation and was approved by the local ethics committee. The patients or family members gave their written informed consent before the combination therapy was initiated.

All the patients received orally combination therapy with metyrapone (Metopirone 250 mg; Novartis Pharma, Rueil-Malmaison, France), ketoconazole (Nizoral 200 mg; Janssen-Cilag, Berchem, Belgium), and mitotane (Lysodren 500 mg; HRA Pharma, Paris, France), the three drugs being introduced concomitantly. The starting doses were as follows: metyrapone 2.25 g/24 h (nine capsules), ketoconazole 800 mg/24 h (four tablets), and mitotane 3.0 g/24 h (six tablets). These dosages were then adjusted to clinical severity, UFC excretion, and tolerance. The median doses were as follows: metyrapone 3.0 g/24 h (range 3.0–4.5), ketoconazole 800 mg/24 h (range 400-1200), and mitotane 3.0 g/24 h (range 3.0–5.0). Oral hydrocortisone replacement therapy was also given to prevent iatrogenic adrenal insufficiency at a median dose of 32.5 mg/d (range 15–60).

Follow-up included regular assessment of clinical status and UFC excretion, morning serum total cortisol assay, and routine biochemical parameters including blood cell counts, blood glucose, Na and K levels, the lipid profile, and liver enzyme activities. If possible, UFC excretion was determined after hydrocortisone withdrawal. Salivary cortisol was not assayed in all the patients and is therefore not reported. Biochemical and hormonal parameters were determined daily during the first week, once a week during the first month, and once a month thereafter. Serum mitotane concentrations were monitored monthly.

Assays

Baseline UFC excretion is reported as the average of individual determinations in three consecutive daily urine samples. The normal range of UFC excretion (10–65 μg/dl) was determined in 24-h urine specimens from 120 healthy volunteers recruited by the Clinical Investigations Center at Georges Pompidou European Hospital, Paris, France. The accuracy of urine specimens was verified by measuring 24-h urinary creatinine excretion (normal values for women are 0.12–0.20 mmol/kg·d, and for men, 0.18–0.23 mmol/kg·d). Urinary cortisol was measured with a specific RIA using polyclonal antibodies (Orion Diagnostica, Spectria, Espoo, Finland) after dichloromethane extraction and celite separation of cortisol from deoxycortisol (compound S). The intra- and interassay coefficients of variation were, respectively, 4.5 and 5.5% at 22 μg/liter and 4.2 and 4.3% at 269 μg/liter, and the detection limit was 5 μg/liter. Morning (0800–0900 h) serum cortisol concentrations were measured directly with a chemiluminescent competitive immunoassay using a polyclonal antibody (Immulite; Siemens, Deerfield, MI) highly specific for cortisol and displaying no significant cross-reactivity with other steroids or precursors, except for prednisone. The intra- and interassay coefficients of variation were, respectively, 6.9 and 9% at 24 μg/dl, and the detection limit was 0.2 μg/dl. ACTH concentrations were determined with a solid-phase, two-site sequential chemiluminescent immunometric assay (Siemens Healthcare Diagnostics Products, Llanberis, UK). The intra- and interassay coefficients of variation were, respectively, 4.6 and 5% at 20 pg/ml (4.4 pmol/liter) and 3.4 and 4.8% at 64 pg/ml (14.2 pmol/liter). The detection limit was 5 pg/ml (1.1 pmol/liter). Normal serum ACTH values in the morning (0800–0900 h) were between 10 and 50 pg/ml. Fasting morning plasma mitotane concentrations were measured by HPLC as previously described (21).

Statistical analyses

UFC excretion values were used to evaluate the response to treatment. Data are expressed as medians (range). The effects of treatment were assessed with Wilcoxon's nonparametric two-tailed paired test. GraphPad Prism biostatistics software version 4 was used for all analyses. Significance was assumed at $P < 0.05$.

Results

Response to treatment

On the three-drug combination, all 11 patients experienced a rapid and substantial improvement in the clinical features of Cushing's syndrome. Left ventricular function improved or normalized in the three patients with congestive heart failure at baseline. Infectious complications were controlled by systemic antiinfective therapy and, in one case, by drainage. Soft-tissue status also improved markedly. Body weight fell significantly, from 66 kg (range 56–130) to 63 kg (range 48–128), and body mass index fell from 24.3 kg/m^2 (range 21.3–43.9) to 23.1 kg/m^2 (range 18.3–43.3) ($P = 0.012$ for both). Antihypertensive therapy could be discontinued in two of the nine patients concerned and could be reduced in another three cases. Systolic blood pressure fell from 170 mm Hg (range 130–183) to 120 mm Hg (range 105–160) ($P = 0.008$). Diastolic blood pressure fell from 100 mm Hg (range 60–113) to 70 mm Hg (range 60–89) ($P = 0.055$). Eight patients were diabetic at baseline, seven requiring insulin and one an oral antidiabetic drug. During combination therapy, four patients were able to stop using insulin, and oral antidiabetic therapy could be discontinued in the patient concerned. The plasma fasting glucose level fell from 9.2 mmol/liter (range 5.8–22.7) to 4.7 mmol/liter

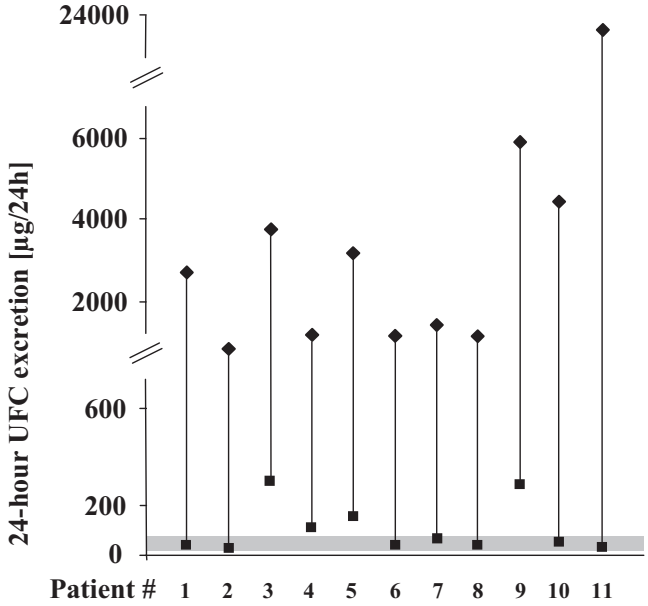

FIG. 2. UFC levels in each of our 11 patients before and 1–3 d after the initiation of triple therapy (see text for details). The *gray area* indicates the normal range of UFC excretion (10–65 µg/24 h) determined in 24-h urine specimens from 120 healthy volunteers. ♦, Baseline UFC excretion (each value is the average of individual determinations in three consecutive daily urine samples); ■, UFC excretion on triple therapy.

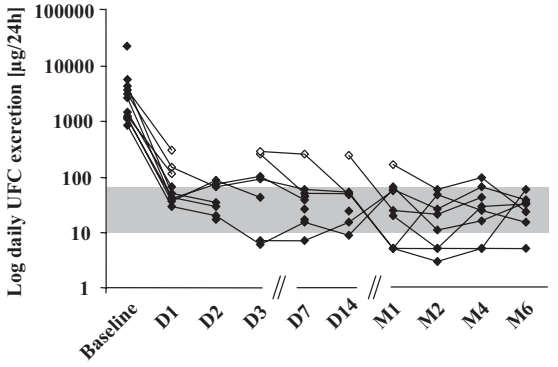

FIG. 3. Serial UFC levels in our patients before and during therapy (see also Table 2). The *gray area* indicates the normal range of UFC excretion (10–65 µg/24 h). Note the log scale of the y-axis. D, Day after start of therapy; M, months; ◇, UFC excretion determined without hydrocortisone withdrawal; ♦, UFC excretion determined during hydrocortisone withdrawal.

(range 4.0–8.7) ($P = 0.008$). Glycated hemoglobin values showed a trend to decrease (6.9%, range 4.8–10.7, *vs.* 5.8%, range 5.3–9.2; $P = 0.31$). Finally, all 11 patients had hypokalemia at baseline (Table 1) (22), requiring potassium supplementation in eight cases and spironolactone in five cases. After initial transient hypokalemia (see below), the plasma median potassium increased from 3.0 mmol/liter (range 2.4–3.5) to 3.9 mmol/liter (range 3.5–4.9) ($P = 0.004$). Potassium supplementation and spironolactone could both be discontinued in five patients.

Individual durations of three-drug combination therapy and after mitotane monotherapy are detailed in Table 2.

Median UFC excretion dropped sharply, from 2737 µg/24 h (range 853–22605) at baseline to 50 µg/24 h (range 18–298) ($P = 0.001$) after 24–48 h of combination treatment (Fig. 2). Median morning serum cortisol concentrations also fell after 24–48 h of treatment, from 54 µg/dl (range 30–176) to 7 µg/dl (range 2–22) ($P = 0.002$). During the first 2 months of combination therapy, mitotane levels were 2.9 mg/liter (range 1.9–6.0).

UFC excretion remained low to normal throughout the period of combination therapy and then under mitotane monotherapy (Fig. 3). Indeed, metyrapone and ketoconazole were discontinued in seven patients, after an average of 3.5 months (range 3.0–6.0), mitotane being continued in monotherapy in these patients during a median period of 3.0 months (range 2.0–27.0) (Table 2). UFC excretion and morning plasma cortisol concentrations remained controlled during mitotane monotherapy (measured 1 month after metyrapone and ketoconazole discontinuation): UFC 17 µg/24 h (range 5–85), $P = 0.016$; morning plasma cortisol 7 µg/24 h (range 3–24), $P = 0.031$. The median plasma mitotane concentration during mitotane monotherapy was 10.1 mg/liter (range 4.3–13.9).

Outcome

Median follow-up after the initiation of anticortisolic combination therapy was 14 months (range 1–42). All patients with Cushing's disease were able to undergo pituitary surgery, 5–22 months after the initiation of combination therapy, after an improvement in their clinical status. Patients 1, 3, and 4 are currently in remission from hypercortisolism, whereas mitotane was reintroduced in patient 2 because hypercortisolism recurred after pituitary surgery. Three patients (nos. 5–7) had occult ectopic ACTH secretion at baseline. Repeated imaging during mitotane therapy identified the source of ACTH secretion in one of these patients (no. 7), who is currently in remission from hypercortisolism after curative surgery of her ACTH-secreting bronchial carcinoid, performed 6 months after the initiation of combination therapy. Patient 5 still has an occult tumor and is currently receiving mitotane monotherapy (2 g/d). Finally, one patient with occult ectopic ACTH secretion (no. 6) and three patients (nos. 8–10) with metastatic disease died, after 10, 14, 1, and 4 months of combination therapy, from an acute cardiovascular event or cancer progression. Patient 11 was kept on combination therapy for 1 month before exploratory surgery, which led to remission from hypercortisolism (currently lasting 5 months) (Table 2).

Among the five patients in remission, four (nos. 3, 4, 7, and 11) who had received mitotane for a short period (Table 2) recovered normal adrenal function. Patient 1,

who received mitotane for longer time period (30.5 months, Table 2), still presents adrenal insufficiency.

Tolerability and toxicity

The most frequent adverse events attributed to the combination therapy were nausea and vomiting (seven of 11 patients, 63%). However, these gastrointestinal disorders were transient and, given the context, did not require treatment discontinuation. Gastrointestinal tolerance was improved by giving the medication in divided doses and by using antiemetic drugs. The only significant neurological adverse effects were dizziness and confusion in patient 8 (the concomitant plasma mitotane concentration was 15.3 mg/liter). These neurological disorders regressed completely when the mitotane dose was reduced from 2.5 to 2.0 g/24 h. Acute adrenal insufficiency occurred in four patients (36%) and was due either to intentional discontinuation (one patient) or to inappropriate continuation (three patients) of oral glucocorticoid replacement therapy during episodes of vomiting.

As expected, significant liver function test abnormalities (at least three times upper limit of normal) were observed during combination therapy (4, 23). However, before treatment, the aspartate aminotransferase was elevated in one patient, the alanine aminotransferase was elevated in two patients, and the γ-glutamyl transferase (γ-GT) was elevated in two patients. No symptomatic worsening of liver function was observed during combination therapy. Increases in aspartate aminotransferase, alanine aminotransferase, and γ-GT levels were observed during combination therapy in two, three, and nine patients, respectively ($P = 0.13$, 0.59, and 0.002, respectively). Liver toxicity led us to reduce the ketoconazole dosage in two patients (nos. 8 and 9) and to withdraw this drug in one patient (no. 1). The doses were maintained in the other patients. Figure 4 compares liver function test results before and during treatment.

All the patients initially experienced episodes of hypokalemia during treatment, probably owing to a transient increase in deoxycorticosterone concentrations induced by metyrapone (24). The lowest potassium concentration during treatment was 2.9 mmol/liter (range 2.6–3.5). Nine patients required oral potassium supplementation, and eight patients also received the antimineralocorticoid spironolactone. Nevertheless, a long-term improvement in plasma potassium concentrations occurred during treatment (see above).

Moderate hypercholesterolemia was present in two patients before treatment and in all but one of the patients during treatment. Cholesterol levels before and under combination therapy were, respectively, 5.21 mmol/liter (range 2.75–7.60) and 7.36 mmol/liter (range 2.15–8.99)

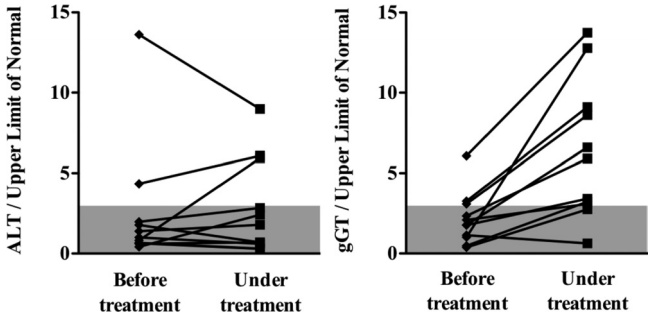

FIG. 4. Parameters of hepatic function in our patients before and after triple therapy (see text for details). ALT, Alanine aminotransferase; gGT, γ-GT. Data are expressed as a ratio of the upper limit of the normal range. Note that patient 1 presented marked elevation of ALT (~14 times above the upper limit of normal) already at baseline, before any treatment, probably as a consequence of congestive heart failure responsible for cardiac liver. Despite this enzyme's elevation, the patient received the triple therapy, maximal ALT values being approximately nine times above the upper limit of normal during the therapy. Ketoconazole was stopped approximately 2 months after initiation, as soon as clinical improvement was achieved, in respect of this hepatotoxicity.

($P = 0.012$). Low-density lipoprotein cholesterol values were elevated at baseline in one patient and during treatment in five patients [baseline, 2.82 mmol/liter (range 1.22–5.40); during treatment, 4.55 mmol/liter (range 0.95–5.67); $P = 0.19$]. Plasma triglyceride concentrations were elevated in three patients before treatment and in five patients during treatment [baseline, 1.47 mmol/liter (range 1.01–3.00); during treatment, 1.98 mmol/liter (range 1.08–3.75); $P = 0.65$].

Discussion

In ideal conditions, treatment of ACTH-dependent Cushing's syndrome is based on excision of the ACTH-secreting corticotrope adenoma or extrapituitary neuroendocrine tumor (4, 16, 19, 25). However, the tumor must be both visible and removable, and the patient's general condition must be compatible with general anesthesia and an often lengthy surgical procedure. Severe Cushing's syndrome can be accompanied by acute cardiovascular, infectious, and metabolic complications (1–3, 16, 26) that may hamper etiological investigations (tumor location) and particularly curative surgery (27). Bilateral adrenalectomy, although dangerous in this context, is frequently proposed as an alternative for these severely ill patients (4, 16, 25, 28). Even though endoscopic techniques have reduced surgical morbidity and mortality, this operation remains dangerous in critically ill patients (5–8). Moreover, bilateral adrenalectomy causes permanent adrenal insufficiency, the long-term consequences of which (mortality, episodes of acute adrenal insufficiency) are increasingly highlighted (9–11). An alternative to surgery is the use of

drugs to inhibit cortisol production by the adrenal glands. Three oral drugs of this type are currently available in France for both hospital and ambulatory use, namely mitotane, metyrapone, and ketoconazole. The efficacy of metyrapone and ketoconazole as anticortisol agents is well documented (17, 18, 29–33), whether used alone or in combination (34). However, cases of therapeutic escape have been attributed to these drugs' rapidly reversible effect and to the need for several daily intakes, which raises problems of compliance and digestive tolerability (4, 16, 29).

Mitotane is an approved treatment for adrenocortical carcinoma (35, 36). A few reports (14, 15, 28, 37) suggest that it has satisfactory efficacy and safety when used as an anticortisol agent in ACTH-dependent Cushing's syndrome. However, the delayed onset of mitotane action is a major drawback in severe Cushing's syndrome (15) (Salenave, S., C. Droumaguet, R. Chadarevian, C. Jublanc, P. Kamenicky, L. Cazabat, S. Trabado, S. Brailly, P. Chanson, and J. Young, manuscript in preparation). We therefore examined the feasibility of concomitant treatment with these three anticortisol agents in Cushing's syndrome patients with severe acute complications. The aim was to achieve rapid control of hypercortisolism and its life-threatening complications, then to discontinue ketoconazole and metyrapone while maintaining mitotane therapy. We found that this approach was possible with relatively low doses of mitotane, thus limiting the risk of overdose and major adverse effects. Importantly, mitotane was effective on hypercortisolism at plasma concentrations that were often lower than the therapeutic thresholds proposed in adrenocortical carcinoma (35, 36), in line with recently published findings and our own experience (15) (Salenave, S., C. Droumaguet, R. Chadarevian, C. Jublanc, P. Kamenicky, L. Cazabat, S. Trabado, S. Brailly, P. Chanson, and J. Young, manuscript in preparation). Some of our patients were able to receive treatment for ACTH-dependent Cushing's syndrome a few months after their hypercortisolism had been brought under control by the combination therapy and thereafter by mitotane monotherapy; general anesthesia and surgery became possible because the patients' general status had improved and they were not longer on anticoagulants. Importantly, four patients in remission recovered normal adrenal function after mitotane discontinuation, indicating that the adrenolytic effect of mitotane does not induce irreversible chemical adrenalectomy. This is an additional advantage of this therapeutic approach compared with surgical adrenalectomy.

The triple therapy led to a striking decrease of UFC excretion on the first to second day. Whether two fast-acting drugs are necessary for these early effects or one of them might have been sufficient to obtain the fast control of hypercortisolism remains to be investigated. We have used the triple-therapy approach basically for two reasons. First, facing desperately ill patients, we wanted to guarantee an efficient and rapid inhibition of cortisol production because (some) patients could easily die from the life-threatening complications of hypercortisolism. In addition, by adding ketoconazole, we wanted to prevent metyrapone-induced excessive deoxycorticosterone production frequently responsible of worsening in hypokalemia and hypertension (4).

Oral hydrocortisone was used to prevent iatrogenic adrenal insufficiency. Alternatively, small doses of dexamethasone could be more appropriate for adrenal substitution in this context because this drug binds less to the elevated cortisol binding globulin induced by mitotane and would not interfere with urinary and serum cortisol estimations.

Mifepristone can also be used in severe Cushing's syndrome but is difficult to monitor because of the persistence of elevated UFC values during treatment (38). Here, we monitored hormonal status by simply measuring serum and urinary cortisol levels. The specific immunoassay we used for serum cortisol does not recognize cortisol precursors, levels of which may be elevated at the outset of treatment (34), before the cytolytic effects of mitotane occur.

Etomidate has also been proposed as a fast-acting anticortisol agent (39), but this hypnotic drug has only been assessed in a small number of patients and requires parenteral administration.

In conclusion, when immediate etiological treatment of severe ACTH-dependent Cushing's syndrome is not feasible, combination therapy with mitotane, metyrapone, and ketoconazole is an effective alternative to emergency bilateral adrenalectomy, a procedure associated with significant morbidity and permanent hypoadrenalism. This therapeutic approach may also be useful during palliative care of patients with diffuse disease. Close patient monitoring in a specialized endocrine unit is essential, notably to correct the initial transient hypokalemia and to limit the adverse effects of mitotane-induced adrenal insufficiency.

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