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Effectiveness of metyrapone in treating Cushing's Syndrome: a retrospective multicenter study in 195 patients

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Abstract

Background: Cushing's syndrome is a severe condition with excess mortality and significant morbidity necessitating control of hypercortisolemia. There are few data documenting use of the steroidogenesis inhibitor metyrapone for this purpose.

Objective: To assess the effectiveness of metyrapone in a contemporary series of patients with Cushing's syndrome.

Design: Retrospective, multicenter.

Setting: Thirteen university hospitals.

Patients: 195 patients with proven Cushing's syndrome: 115 Cushing's disease (CD), 37 ectopic ACTH (EAS); 43 ACTH-independent disease (Adrenocortical Cancer [ACC] 10; adrenal adenoma [AA] 30; ACTH-independent adrenal hyperplasia (3)

Measurements: Biochemical parameters of activity of Cushing's syndrome: mean serum cortisol day curve (CDC) (target 150-300nmol/L); 09.00h serum cortisol; 24h-UFC.

Results: 164/195 received metyrapone monotherapy. Mean age was 49.6 +/- 15.7 years; mean duration of therapy 8 months (median 3 months, range 3 days to 11.6 years). There were significant improvements on metyrapone - first evaluation to last review: CDC [91 patients, 722.9nmol/L (26.2µg/dl) vs. 348.6nmol/L (12.6µg/dl), p<0001]; 09.00h cortisol [123 patients, 882.9nmol/L (32.0µg/dl) vs. 491.1nmol/L (17.8µg/dl), p<0.0001]; UFC [37 patients, 1483nmol/24h (537µg/24h) vs. 452.6nmol/24h (164µg/24h), p=0.003]. Overall control at last review: 55%, 43%, 46% and 76% of patients who had CDCs, UFCs, 09.00h cortisol <331nmol/L (12.0µg/dl) and 09.00h cortisol

<ULN/600nmol/L (21.7µg/dl). Median final dose: CD 1375mg; EAS 1500mg; benign adrenal disease 750mg; ACC 1250mg. Adverse events occurred in 25% of patients, mostly mild GI upset and dizziness, usually within 2 weeks of initiation or dose increase, all reversible.

Conclusions: Metyrapone is effective therapy for short- and long-term control of hypercortisolemia in Cushing's syndrome.

Introduction

Cushing's syndrome (CS) is a severe condition with excess mortality and significant morbidity necessitating effective biochemical control (1). Where a cause amenable to surgical intervention is identified, surgery at a center with appropriate expertise is the optimum management. Nevertheless, many patients need urgent control of severe or persisting hypercortisolemia. Options for medical treatment include steroidogenesis enzyme inhibitors suitable for all causes of CS (ketoconazole, metyrapone, mitotane), agents to suppress ACTH in Cushing's disease (CD), such as dopamine agonists and pasireotide, and the glucocorticoid receptor antagonist, mifepristone (2,3). The modern use of ketoconazole has recently been reported in a multicenter French Study (4), although its availability in the United States has been restricted following an FDA safety warning for hepatotoxicity in 2013 (5,6), but it is widely available in Europe in 2015 (7).

The cortisol-lowering effect of metyrapone was described as early as 1958 by Liddle and co-workers, with later reports confirming metyrapone as a potent inhibitor of the steroidogenesis enzyme 11β-hydroxylase (8,9). Since then, it has been used as a diagnostic test of adrenal reserve and to treat the hypercortisolism of CS. Despite its widespread use, data on metyrapone are scarce, with the largest study to date (including 91 patients) being published over 25 years ago (10). Here, we have assessed the effectiveness of metyrapone therapy in a contemporary series of patients with CS, by performing a retrospective study of patients treated in the UK.

Methods

A multicenter, retrospective study was performed across thirteen University Hospital centers in England and Wales, members of the UK Endocrine Neoplasia Collaboration. Patients treated with metyrapone were identified through pharmacy records and electronic databases. Patients with a diagnosis of CS and treated with metyrapone between 1997 and 2013 were included.

The same proforma was used in all centers to record anonymized data. Data were gathered from case records and electronic record systems. Baseline, demographic and safety data, the indication for treatment and dose of metyrapone therapy, any therapeutic intervention and any recorded adverse events were documented. Monitoring tests included early morning (09.00h) serum cortisol, 24-hour urinary free cortisol (UFC), serum potassium, plasma ACTH and serum cortisol 'day-curves' (CDC). In CDCs multiple samples for serum cortisol are collected across the day with the mean calculated (11). All tests performed during the monitoring period were collected and analyzed. All centers used immunoassay-based cortisol assays.

Patients were treated either with a dose titration regimen i.e. metyrapone dose was up-titrated according to response to achieve a biochemical target for cortisol, or a block-and-replace regimen where the dose of metyrapone was quickly up-titrated to achieve blockade of cortisol synthesis and a replacement dose of glucocorticoid was added to provide background physiological levels.

Biochemical targets for treatment (eucortisolemia) were defined as a mean CDC value of 150-300nmol/l (10.9µg/dl), which has been shown to equate to a normal cortisol production rate as assessed by stable isotopic methodology (11), a UFC level below the upper limit of normal (ULN) for the assay used or a 09.00h serum cortisol within target. Although 09.00h serum cortisol is occasionally being used as a sole test for evaluating patients' response to treatment there is currently no standardized agreement for what values of this test represent appropriate control. Two different levels of target 09.00h cortisol were therefore assessed; (i) below the upper limit of normal for the assay used, or less than 600nmol/l (21.7µg/dl) if the ULN was higher than this value, and (ii), a recommended value of 331nmol (12.0µg/dl) (12). Cortisol levels were reported in nmol/L and divided by 27.59 to calculate the equivalent value in µg/dl. There was a wide range of UFC assays used with variable reference range of normal values; therefore UFC values were converted to multiples of the upper limit of normal (ULN) for the assay and this value was used for statistical comparisons. Patients with sufficient monitoring data (i.e. at least one test as described above repeated at least twice during the study period) were included in the efficacy analysis. For the efficacy analyses we compared the mean values at each monitoring test (CDC, 09.00h serum cortisol, UFC) before treatment to (i) the mean values on the last review on treatment (diagnosis vs. last review), and (ii) the mean of all tests performed in all patients during treatment (diagnosis vs. treatment), unless otherwise stated. The change of the biochemical markers between (i) baseline (at diagnosis/ pre-treatment) and the last review on treatment for 09.00h cortisol, and (ii) the first and the last biochemical review for CDCs

(CDCs were not routinely performed prior to initiation of treatment) on treatment was also analyzed.

Statistical analysis was performed using the two-tailed Student's t test (GraphPad prism 6.0, GraphPad Software Inc., La Jolla, USA). Except where stated, values given are means +/- standard deviations. A p-value of less than 0.05 was considered significant. The study was approved as an institutional case notes review at each participating center.

Results

<u>Baseline characteristics</u>

One hundred and ninety-five patients were treated with metyrapone across the 13 centers. The majority of patients had CD (115 patients, 37 macroadenoma) with the remainder having ectopic ACTH syndrome (EAS, 37), adrenocortical carcinoma (ACC, 10), and benign adrenal disease [30 adrenal adenoma (AA), ACTH-independent macronodular adrenal hyperplasia (2) and primary pigmented nodular adrenal hyperplasia (1)] (Table 1). There was a female predominance in all causes of CS except EAS (female patients: 74% CD, 49% EAS, 86% AA, 80% ACC). Patients were treated with metyrapone between 1997 and 2013 (83% between 2007-2013). The average duration of treatment was eight months (median 3 months, range 3 days to 11.6 years). At initiation of treatment there was a wide age distribution, with 76% of patients aged 30-69 years (age range 1-81, median age 48, average age 49.6 +/- 15.7 years), and 32% of patients (n=63) were women in the reproductive ages 18 to 45 (Figure 1). Co-morbidities at presentation included hypertension (64.6%) and diabetes mellitus (35.3%). For patients with CD, baseline contrast-enhanced pituitary MRI was positive in all patients with a macroadenoma and in 53 out of 72 (73%) patients with a microadenoma.

The main indication for metyrapone therapy was the control of severe symptoms of CS (CD 58%, EAS 77%, benign adrenal disease 44% and ACC 80%). Medical therapy was initiated as part of routine local practice in 8 out of 13 centers for the management of patients after diagnosis and prior to definitive therapy (e.g. surgery) regardless of the level of hypercortisolemia in a smaller number of patients (CD 25%, EAS 11%, benign adrenal disease 37%, ACC 0%). Delay in definitive treatment for CS (either due to medical reasons or requested by the patient) was a reason for starting medical therapy in 19% of patients. 25/195 patients (12.8%) received only cortisol-lowering treatment for their CS because of either inconclusive surgical target, palliation of aggressive malignancy (ACC or lung carcinoma), patients' own preference, or high surgical risk.

Biochemical changes during metyrapone treatment

Monitoring data during metyrapone therapy were available for 193 patients. The frequency of the monitoring visits was variable with some centers opting for inpatient tests at the introduction of treatment and other centers using outpatient monitoring every few weeks. 81% of patients were treated with dose titration and 19% with 'block-and-replace'.

Metyrapone monotherapy

One hundred and sixty four patients received metyrapone monotherapy and all monitoring tests showed significant improvement during treatment; CDC [91 patients, mean at diagnosis 722.9nmol/L (26.2µg/dl) vs. during treatment 396.4nmol/L (14.4µg/dl), p<0.0001, last review 348.6nmol/L (12.6µg/dl), p<0001], 09.00h cortisol [123 patients, mean at diagnosis 882.9nmol/L (32.0µg/dl) vs. treatment 527.8nmol/L (19.1µg/dl), p<0.0001, last review 491.1nmol/L (17.8µg/dl), p<0.0001], UFC [37 patients, mean at diagnosis 1483nmol/24h (537µg/24h) vs. treatment 1070nmol/24h (388µg/24h), p=0.588, last review 452.6nmol/24h (164µg/24h), p=0.003], UFC:ULN [mean at diagnosis 7.2 vs. treatment 5.4, p=0.556, last review 2.5 p=0.020]. At the last review, 55%, 43%, 46% and 76% of patients who had CDCs, UFCs, 09.00h cortisol <331nmol/L (12.0µg/dl) and 09.00h cortisol< ULN/600nmol/L (21.7µg/dl) were controlled.

Ninety-one patients were monitored with cortisol 'day-curves' during treatment; 47/91 (52%) patients achieved a mean CDC < 300nmol/L (10.9µg/dl) during treatment (i.e. normalized cortisol target) and 81% of those who did not normalize had an improvement between the first and the last assessment on treatment (Figure 2a). A total of 123 patients had 09.00h serum cortisol levels monitored; during treatment 83% (102/ 123) had a 09.00h serum cortisol bellow 600nmol/L (21.7µg/dl) or the ULN for the assay used and 56% (69/ 123) had a 09.00h level bellow 331nmol/L (12.0µg/dl) with 86% of patients showing an improvement in cortisol levels (mean improvement 566nmol/L, median 467nmol/L) even if these biochemical targets were not achieved (Figure 2b).

Effectiveness of metyrapone monotherapy before surgery

The majority (124/164) of patients treated with metyrapone monotherapy received treatment before any surgical intervention (CD 81, EAS 11, benign adrenal disease 25, ACC 7) for an average of 4.0 months. Monitoring data on CDCs were available in 70 patients, 09.00h serum cortisol in 82 and UFC in 25 patients. There was a significant improvement in the biochemical targets during metyrapone therapy: 09.00h serum cortisol [mean at diagnosis 779.7nmol/L (28.3µg/dl) vs. treatment 508.0nmol/L (18.4µg/dl) ($p<0.0001$), last review 495.6nmol/L (18.0µg/dl) ($p<0.0001$)]; mean CDC [diagnosis 691.5 nmol/L (25.1µg/dl) vs. treatment 407.7nmol/L (14.8µg/dl) ($p<0.0001$), last review 351.5nmol/L (12.7µg/dl) ($p<0.0001$)]; UFC [mean UFC to ULN ratio at diagnosis 6.4 vs. treatment 5.5 ($p=0.553$), last review 2.9, ($p=0.014$)]. At the last review, 50%, 35%, 40% or 72% of patients who had CDCs, UFCs, 09.00h cortisol <331nmol/L (12µg/dl) or 09.00h cortisol< ULN/600nmol/L (21.7µg/dl) were controlled (for dose see Table 2).

At the time of the first normalization, 91% were treated with dose titration and 9% with block-and-replace. In ACTH-dependent disease plasma ACTH levels were measured too sporadically to allow meaningful analysis. 10/18 (56%) patients who did not achieve a biochemical target also had a reduction of cortisol levels.

Metyrapone monotherapy as secondary treatment

Thirty-one patients (29 CD, 1 EAS, 1 benign adrenal disease) received metyrapone as secondary treatment following either surgery (21) or pituitary radiotherapy (17): 21/31 as monotherapy; 10/31 as combination therapy. Of the patients who received metyrapone following primary surgery, 19 had pituitary surgery for CD (9 had a macroadenoma); one had a pancreatectomy for a neuroendocrine tumor; and one a repeat adrenalectomy for an incomplete excision of an adrenal adenoma. Of the patients with CD 7/19 also received pituitary radiotherapy. For the patients on monotherapy (n=21), the mean starting dose of metyrapone was 1300mg (Table 2). Patients were treated for an average of 17.1 months. At the last review, 76%, 78% or 94% of patients who had CDCs, 09.00h cortisol <331nmol/L (12μg/dl) or 09.00h cortisol <ULN/600nmol/L (21.7μg/dl) were controlled. At normalization 35% (6/17) of patients were treated with block-and-replace, and 65% (11/17) with dose titration. All biochemical tests improved during treatment; mean CDC [mean at diagnosis 478.5nmol/L (17.3μg/dl) vs. treatment 311.0nmol/L (11.3μg/dl), p=0.001, last review 248.9nmol/L (9.0μg/dl), p=0.001], 09.00h cortisol [mean at diagnosis 659.6nmol/L (23.9μg/dl) vs. treatment 361.3nmol/L (13.1μg/dl), p=0.0001, last review 281.3nmol/L (10.2μg/dl), p=0.002]. Only four patients had UFCs during treatment, therefore the change in UFC for this group of patients was not analyzed.

Long-term treatment with metyrapone monotherapy

Monitoring data were available on 38 patients who received metyrapone monotherapy for longer than 6 months. The average duration of treatment was 18.6 months and 6 patients had block-and-replace at some point during their treatment. Biochemical tests improved during treatment; mean CDC [at diagnosis 451.4nmol/L (16.4μg/dl) vs. treatment 339.5nmol/L(12.3μg/dl) p=0.07, last review 366.2nmol/L (13.3μg/dl), p=0.35], 09.00h cortisol [diagnosis 734.2nmol/L (26.6μg/dl) vs. treatment 428.2nmol/L (15.5μg/dl), p<0.0001, last review 384.5nmol/L (13.9μg/dl), p<0.0001]. Overall, eucortisolemia was achieved in 72% (18/25) of patients who had CDCs, 77% (24/31) and 94% (29/31) of patients who had 09.00h cortisols (based on <331nmol/L or <ULN/600nmol/L cut-offs) or 64% (9/14) of patients who had UFCs.

Starting and final dose (Table 2)

Mean, median and range of doses on metyrapone monotherapy at the initiation of treatment and at final review are shown in Table 2. On 'block-and-replace' the starting dose of metyrapone was higher (mean dose 1432mg vs. 939.2mg, p<0.0001). There were, however, no significant differences in the mean 09.00h serum cortisol levels during treatment or at the last review in the two groups [block-and-replace group during treatment 461.2nmol/L (16.7μg/dl) vs. dose titration group 507.8nmol/L (18.4μg/dl), p=0.50, last review 510.8nmol/L (18.5μg/dl) vs. 376.3nmol/L (13.6μg/dl), p=0.26].

Combination treatment

Twenty-nine patients were treated with a combination of metyrapone and other cortisol-lowering medication (mainly ketoconazole or mitotane, 7 patients had combination treatment from the start of therapy, whilst in 22 combination therapy was instigated after initial treatment with metyrapone). The CDC or 09.00h serum cortisol levels at diagnosis were not significantly different in the patients treated with combination compared with the patients treated with metyrapone monotherapy [CDC combination 830.8nmol/L (30.1µg/dl) vs. monotherapy 722.9nmol/L (26.2µg/dl), p=0.558, 09.00h cortisol, combination 1149nmol/L (41.6µg/dl), vs. monotherapy 882.9nmol/L (32.0µg/dl) p=0.077]. There was a significant improvement in monitoring tests during treatment [CDC diagnosis 830.8nmol/L (30.1µg/dl) vs. treatment 314.2nmol/L (11.4µg/dl), p<0.0001, last review 278.7nmol/L (10.1µg/dl), p<0.0001. 09.00h cortisol diagnosis 1149nmol/L (41.6µg/dl) vs. treatment 522.9nmol/L (19.0µg/dl), p<0.0001, last review 471.9nmol/L (17.1µg/dl), p=0.003]. Only three patients on combination therapy had UFC monitoring, precluding analysis. At the last review, 47%, 52% or 75% of patients who had CDCs, 09.00h cortisol <331nmol/L (12µg/dl) or 09.00h cortisol <ULN/600nmol/L (21.7µg/dl) were controlled. Patients who at the last review were controlled on a dose titration regimen based on CDCs and UFCs received 1850mg mean total daily dose (median 1500mg, range 750-6000mg). No subgroup analysis for efficacy was performed for this group due to small numbers.

Safety considerations

Side effects were noted in 48/195 patients (25%): 88% were managed as outpatients, whereas 12% (7/57 events) required either admission for evaluation or prolongation of a current admission. The rate of adverse events in patients on therapy for >6months was 11% (4/38 patients). There were no pregnant women, and no deaths recorded due to an adverse event. The average dose of metyrapone at the time of an adverse event was 1600mg. Gastrointestinal upset (23%) and hypoadrenalism (7% - symptoms of dizziness, hypotension, with biochemical confirmation) were the most common side effects. Most adverse events (39/56) occurred within 15 days of initiation of metyrapone or after a dose increase. Gastrointestinal upset and dizziness were the main reasons for discontinuing treatment. Patients with confirmed hypoadrenalism were managed either by addition of glucocorticoid (regimen change to a block-and-replace) or temporary cover with glucocorticoid and simultaneous reduction of metyrapone dose. In 15% of cases the metyrapone dose was reduced. In 12 cases (23%) metyrapone was withdrawn temporarily or permanently, with 11/12 showing full resolution, and in one symptoms continued but became less severe - muscle aches at presentation worsened during metyrapone therapy but returned to pre-treatment levels after drug withdrawal. Symptoms of hyperandrogenism were not frequent; hirsutism was not reported and there was only one case of worsening acne during treatment. Similarly edema was only reported in one case but the causative drug was thought to be a calcium channel blocker. Hypoglycemia was reported in three patients on diabetic medications and was associated with improvement of hypercortisolism.

Potassium levels were monitored and actively treated at presentation and during therapy. In 138 patients on metyrapone monotherapy, with no other treatment interventions for their CS, mean potassium levels increased from 3.68nmol/L to 3.90nmol/L ($p=0.003$) during treatment (Figure 3).

Discussion

We report the effectiveness of metyrapone in clinical practice for the treatment of CS. To our knowledge this is the largest study of metyrapone use as either monotherapy or metyrapone in combination with other cortisol-lowering medications. Overall more than 80% of patients showed an improvement in levels of circulating cortisol with over 50% achieving biochemical eucortisolemia when on monotherapy when assessed by the stringent criterion of control on a CDC. It is likely that additional therapies were added because of the severity of disease and clinician preference, but the retrospective and multicenter nature of our study precludes a formal assessment of this. Furthermore, our data support that metyrapone monotherapy is an effective treatment for hypercortisolemia either before or after surgical intervention to the primary cause of CS.

Metyrapone is widely used in CS in the UK and other countries but less so in the USA. To date, the efficacy of metyrapone in reducing cortisol levels in CS has been described in case reports and small case series (13-16), with the largest series reported 25 years ago by Verhelst et al (10). In this single center experience, metyrapone was effective in reducing cortisol levels in 75% of 91 patients with CD, EAS and ACC based on a mean CDC level <400nmol/L that is higher than the more stringent <300nmol/L level that we used in this study. Most patients in the Verhelst study received a short course of metyrapone except for 24 patients who had metyrapone for a median of 27 months following radiotherapy to the pituitary gland. Smaller studies have reported the efficacy of metyrapone in patients with CD undergoing radiotherapy (13-15) and EAS (17). Overall, in 200 cases of metyrapone monotherapy published in the English literature, biochemical control was achieved in 75% (18). We report similar efficacy. It is of note, however, that the majority of patients with CD in our study here were not treated in conjunction with pituitary radiotherapy, and there did not appear to be evidence of an escape of control phenomenon, although we cannot comment on plasma ACTH levels during monitoring.

Ketoconazole, an antifungal agent and inhibitor of adrenal steroidogenesis, has also been widely used as a cortisol-lowering agent in CS. In the largest report to date, Castinetti et al reported biochemical control in 50% of patients with CS treated with ketoconazole monotherapy with biochemical improvement in 75% and evidence of regression of clinical features in up to 60% (4). Overall, in 456 published cases treated with ketoconazole monotherapy, 60% achieved control (18). Combination treatment with metyrapone and ketoconazole is commonly used (19), especially for the rapid control of hypercortisolism prior to definite treatment. In 22 patients with severe hypercortisolism due to EAS (n=14) and ACC (n=8), combination treatment of metyrapone and ketoconazole dramatically improved UFC levels within a month of treatment, while half of the patients also started mitotane during this time (20). Kamenicky et al used a triple-medication protocol with simultaneous administration of ketoconazole, metyrapone and mitotane in 11 patients with hypercortisolism and life-threatening complications as an alternative to bilateral adrenalectomy; all patients showed rapid clinical and biochemical improvement (21). In both studies, the initial biochemical control is mainly due to the combination of ketoconazole and metyrapone as the onset of action of mitotane is usually delayed by several weeks due to accumulation in adipose tissue (22). In one of the few prospective studies of medical treatment of CD, Feelders et al used a stepwise approach to treat 17 patients with CD with a combination of pituitary and adrenal-acting agents. Patients were initially treated with the somatostatin analog pasireotide, followed by cabergoline, and ketoconazole was later introduced if biochemical control was suboptimal. Nine out of 17 patients normalized with pasireotide/ cabergoline and ketoconazole induced biochemical control in 6/8 remaining patients (75%) within 20 days of treatment (23).

Metyrapone increases cortisol metabolites in the serum and urine due to the predominant inhibition of 11β-hydroxylase, and to a lesser extent the other steroidogenesis enzymes (10,24). In particular, 11-deoxycortisol levels may become profoundly elevated in patients on metyrapone therapy, especially in patients with CD (25,26). 11-deoxycortisol is structurally very similar to cortisol and may cross-react with cortisol immunoassays resulting in an overestimation of serum cortisol values in patients on metyrapone (26,27). The importance of this is underscored by the fact that symptoms of adrenal insufficiency may overlap those of side effects of metyrapone. Thus, cortisol estimation by more accurate methods such as mass spectrometry is preferable and should be used where available (28). Moreover, it is likely that our data may underestimate the efficacy of metyrapone therapy when assessing serum measurements of cortisol as the cross-reactivity in immunoassays results in approximate 20% elevated bias (25).

Hypokalemia has been described as a potential serious complication of metyrapone therapy (24,29) due to the increase in steroid precursors with mineralocorticoid activity (11-deoxycorticosterone). Our data suggest clinicians using metyrapone are well aware of the importance of monitoring and managing serum potassium levels since we found that these increase significantly with supportive measures during treatment. It is important to stress, however, that such active monitoring is required, as hypokalemia is also a potentially harmful feature of CS. The most common adverse effects observed were mild gastrointestinal symptoms and hypoadrenalism, the latter a positive response to treatment provided that it is recognized and managed early. Patients on long-term treatment are more likely those who tolerate metyrapone well, therefore the rate of adverse events was favorable in this subgroup. Interestingly, hirsutism was not reported.

This study carries the limitations imposed by its retrospective design. Furthermore, there is currently no standardized monitoring and dosing regimen for patients on metyrapone therapy. The monitoring of hypercortisolemia in patients with CS on medical treatment is important to ensure that patients are treated with the correct dose and that hypoadrenalism, if present, is recognized early; measurement of serum cortisol allows this. Even though the study was conducted in University centers with significant expertise in the management of CS, the choice of biochemical monitoring test and frequency of monitoring varied. This has affected the uniformity of the data presented. During the period of the study the common clinical practice was to aim for a 09.00h cortisol bellow the upper limit of normal for the assay used or less than 600nmol/L. Any results above these levels would prompt up-titration of the dose or addition of a second agent. Therefore we have reported these cut-offs as the criteria for normalization of hypercortisolemia. More stringent 09.00h serum cortisol levels to define control have been proposed recently (12), with suggested values below 331 nmol/L (12μg/dL). It is not possible to know whether clinicians would have up-titrated the dose of metyrapone had this criterion been used, and therefore we can only speculate that the overall control when using this criterion might have been better if applied in practice.

In conclusion, our data show that metyrapone is effective and safe in treating hypercortisolemia in patients with Cushing's syndrome.

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Conflict of interest

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Figure legends

Figure 1
Age of patients at initiation of metyrapone therapy and diagnosis of Cushing's syndrome

Figure 2
Mean serum cortisol day curve (CDC) and 09.00h serum cortisol levels during treatment with metyrapone monotherapy*.*

a), Change in mean CDC in 91 patients treated with metyrapone monotherapy between the 1st review *following* initiation of metyrapone and the last review on treatment: 52% (47/91) patients achieved biochemical normalization, 89% showed an improvement).
b), Change in the pre-treatment 09.00h cortisol level in 123 patients treated with metyrapone monotherapy and the last review on treatment: 86% showed an improvement; 102 (83%) patients had a 09.00h serum cortisol value below the ULN for the assay used or 600nmol/L (whichever was lowest) and 69 (56%) had a 09.00h level<331nmol/L.

Figure 3
Potassium levels before and during metyrapone monotherapy in 138 patients.

Table 1 Baseline patient characteristics

Etiology	No of patients	Female/ Male	Average age at diagnosis (years)	Average age at metyrapone onset (years)
Cushing's disease	115	85/30	45.9	47.4
Macroadenoma	37			
Microadenoma	77			
Ectopic ACTH syndrome	37	18/19	52.6	52.9
Benign Adrenal Disease	33	27/5	50.3	51.2
Adrenal adenoma	30			
AIMH	2	26/4		
PPNAD	1	1/1		
Adrenocortical Carcinoma	10	8/2	56.0	56.4

Table 2 *Total daily dosage of metyrapone for patients treated with a dose titration regimen*

	*Starting dose (mg)	*Final dose (mg)
Metyrapone monotherapy (n=164)	1040, 750, 250-3750	1425/ 1500/ 500-4000
CD (n=96)	1020, 750, 250-3000	1380/ 1375/ 500-3500
EAS (n=27)	1260, 1000, 500-3750	1990/ 1500/ 500-3750
Benign adrenal disease (n=31)	820, 1000, 250-2250	1210/ 750/ 500-4000
ACC (n=10)	1230, 1500, 750-2000	1190/ 1250/ 750-1500
Pre-surgery (n=124)	1000, 750, 500-2250	1440, 1500, 500-4000
CD (n=81)	980, 750, 500-2250	1400, 1500, 500-3500
EAS (n=11)	1200, 1500, 500-2000	2120, 2250, 500-3750
Benign adrenal disease (n=25)	880, 750, 500-2250	1230, 1000, 500-4000
ACC (n=7)	1250, 1500, 750-2000	1080, 1000, 750-1500
Secondary treatment (n=25)	1300, 1125, 500-3000	1400, 1500, 500-2250
Long-term treatment (>6months) (n=38)	940, 750, 500-3000	1560, 1500, 500-4000

**given in 2-4 divided doses; mean/ median/ range*

Figure 1

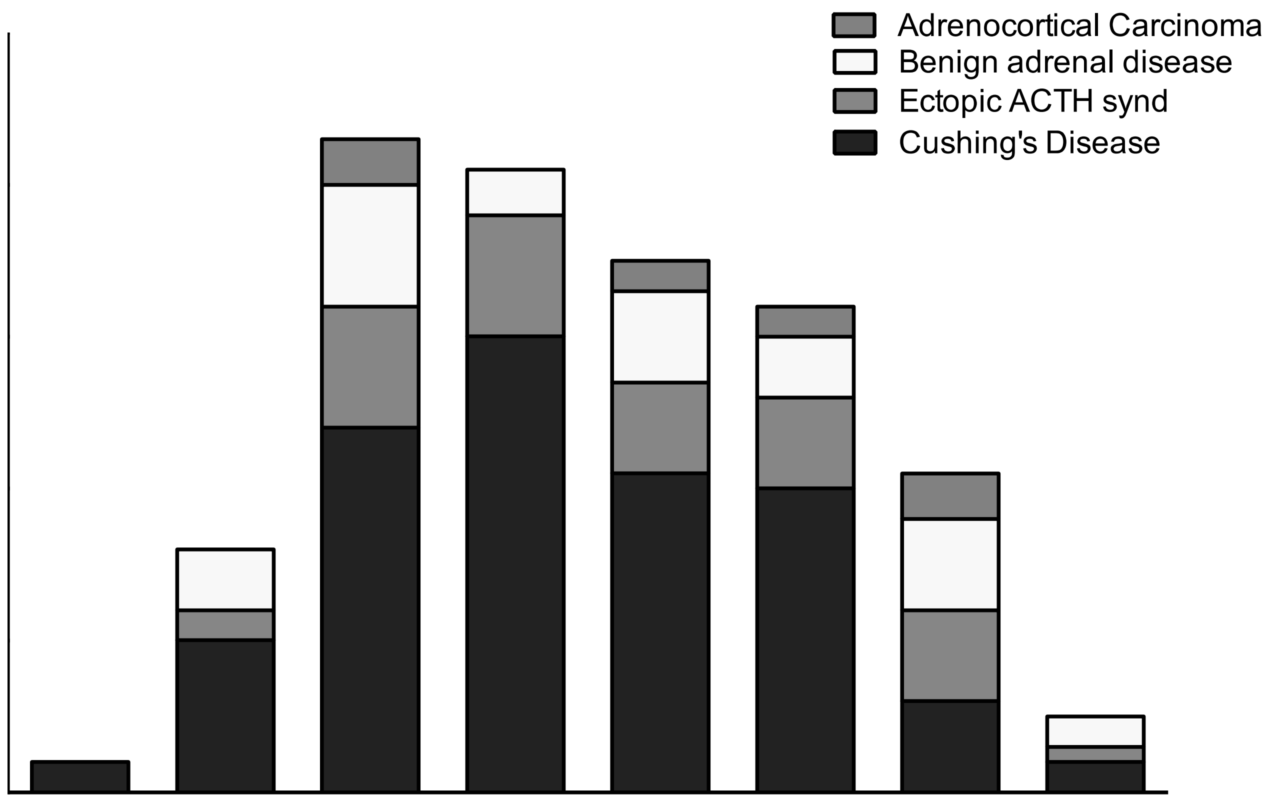
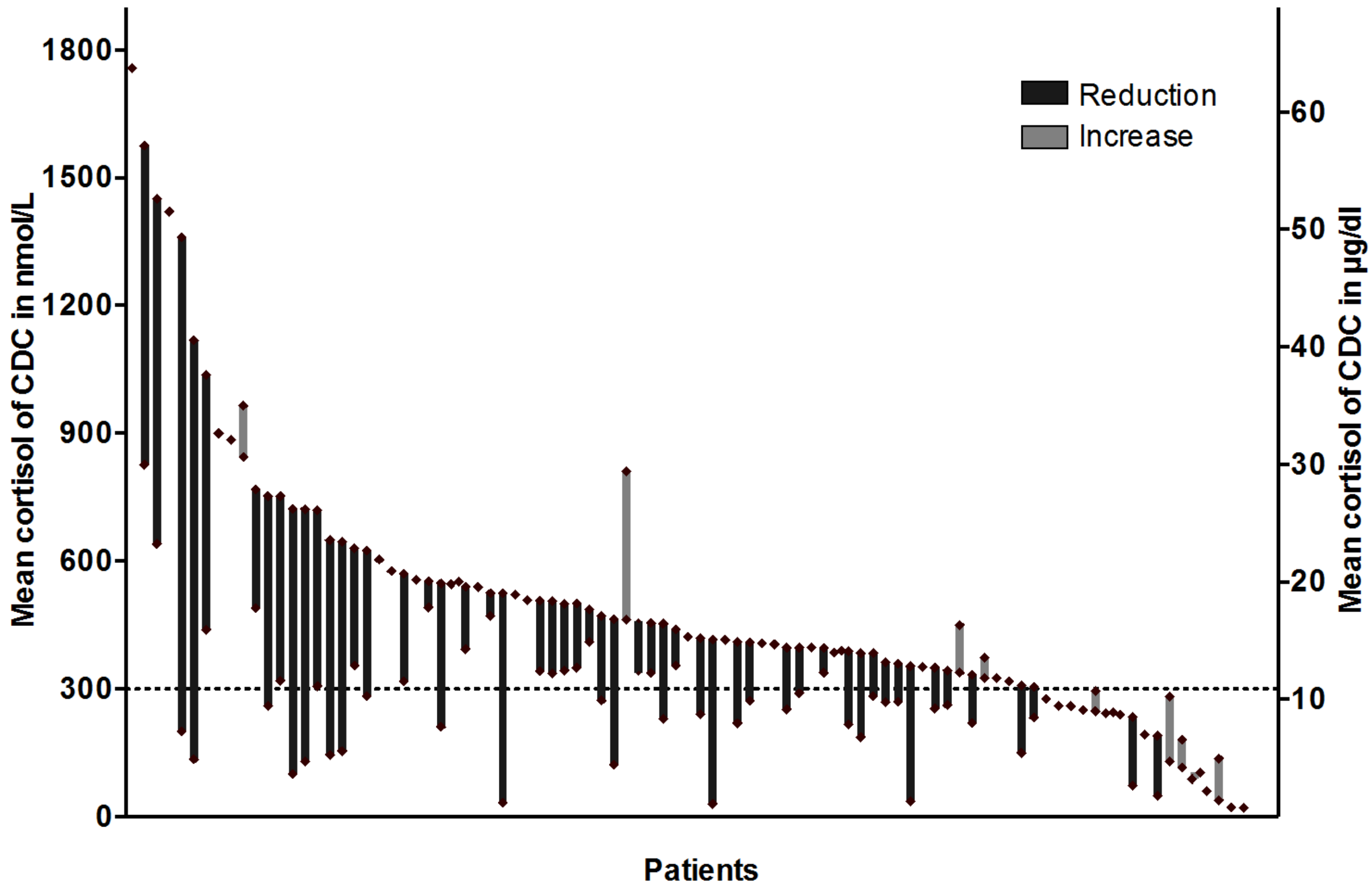

Adrenocortical Carcinoma
Benign adrenal disease
Ectopic ACTH synd
Cushing's Disease

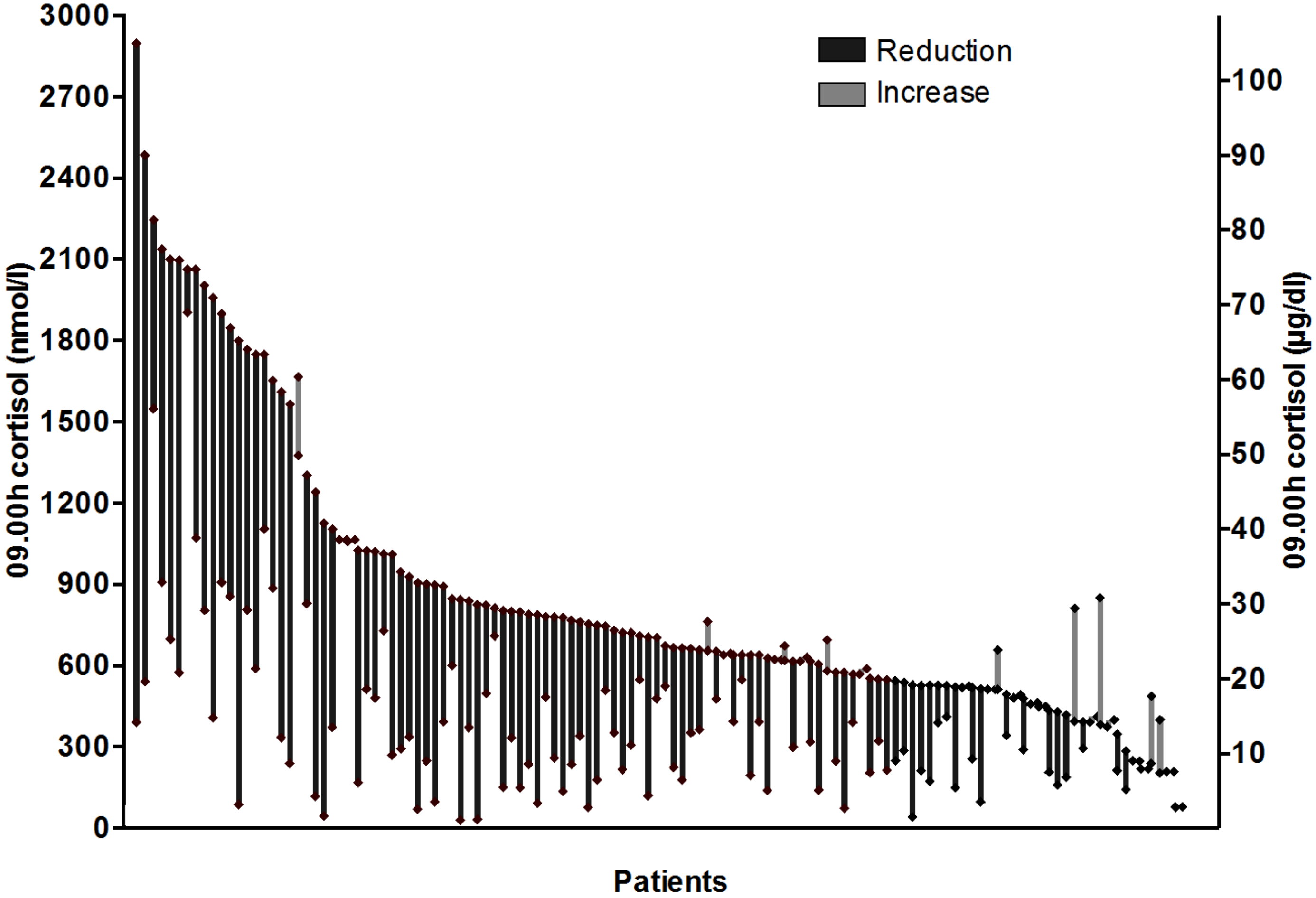
Figure 2

(a)



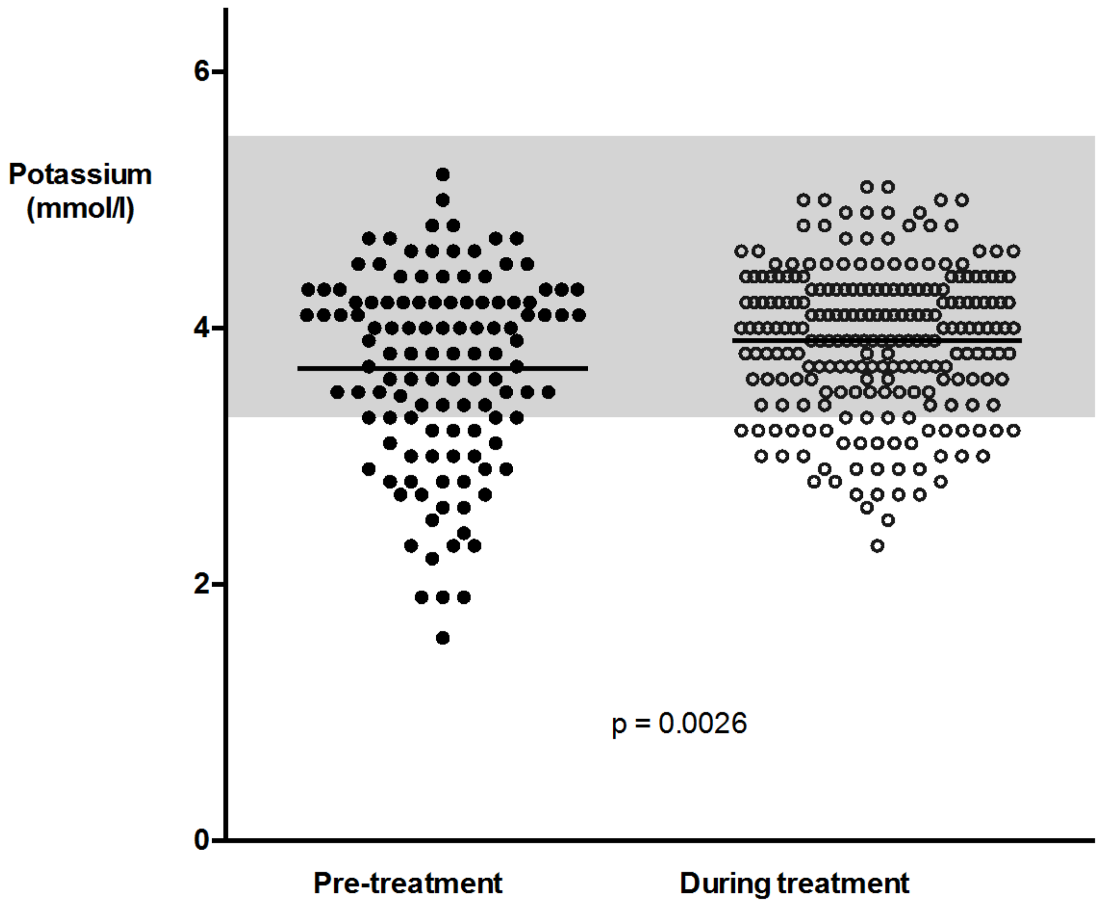
1800
1500
1200
900
600
300
0
Mean cortisol of CDC in nmol/L
Reduction
Increase
60
50
40
30
20
10
Mean cortisol of CDC in µg/dl
Patients

(b)



Reduction
Increase
3000
2700
2400
2100
1800
1500
1200
900
600
300
0
09.00h cortisol (nmol/l)
100
90
80
70
60
50
40
30
20
10
09.00h cortisol (µg/dl)
Patients

Figure 3



Potassium
(mmol/l)
6
4
2
0
p = 0.0026
Pre-treatment
During treatment