PAPERS AND ORIGINALS

Metyrapone in long-term management of Cushing's disease

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Summary

Metyrapone was used in the long-term management of 13 patients with pituitary-dependent bilateral adrenal hyperplasia (Cushing's disease). The total length of treatment ranged from two to 66 months, with a mean of 21 months. The clinical features of the disease rapidly improved on metyrapone and this improvement was maintained. Although plasma ACTH concentrations rose in all patients, the increase was insufficient to overcome the adrenal blockade induced by the drug. Eight of the 13 patients had additional external pituitary irradiation as definitive treatment of their disease and one underwent a transfrontal hypophysectomy. Radiotherapy cured one patient, and after three years metyrapone was withdrawn. Slight hirsuties was noted in four of the seven women who received the drug for six months or more. A fifth woman had more severe hirsuties and this led to bilateral adrenalectomy. Other than hirsuties, side effects were few and the routine use of metyrapone is recommended as an adjunct to more definitive treatment in all patients who present with Cushing's syndrome, irrespective of aetiology.

Introduction

After its introduction in 1958 metyrapone (2-methyl-1,2, -bis-(3-pyridyl)-1-propanone) was studied intensively and was shown

to lower production of cortisol and other 11 β -hydroxylated corticosteroids by a relatively selective inhibition of 11 β -hydroxylase.^{1 2} This ability to lower the level of circulating corticosteroids led to its being adopted in two main diagnostic clinical roles: as a test of ACTH reserve^{1 3-7} and in the differential diagnosis of Cushing's syndrome.^{3 4 7} Reports of its use in treatment have been few and virtually confined to the treatment of adrenal tumours^{3 8} and the ectopic ACTH syndrome.^{9 10} It has been claimed that the compensatory rise in plasma ACTH that occurs with the use of adrenocortical enzyme blocking agents in patients with pituitary-dependent Cushing's disease would effectively overcome the blockade.^{11 12}

Our object was to show that long-term control of patients with pituitary-dependent disease is possible. We elected to treat all patients with oral metyrapone and to give them also a course of external pituitary irradiation (unless contraindicated).

Patients and methods

Thirteen patients with Cushing's disease (pituitary-dependent bilateral adrenal hyperplasia) were treated (see table). Treatment lasted for two to 66 months (mean of 22). The diagnosis of Cushing's disease was made on standard criteria¹³: clinical features, raised urinary excretion of 11-hydroxycorticosteroids; loss of circadian rhythm of plasma ACTH and cortisol; failure of plasma ACTH and cortisol to suppress fully with dexamethasone (0.5 mg six hourly for 48 hours); lack of response of plasma cortisol to insulin-induced hypoglycaemia; exaggerated 17-hydroxycorticosteroid response to metyrapone (750 mg four hourly for 24 hours); and the appearance of the pituitary fossa on skull radiographs (abnormal in five). Seven patients underwent air encephalography: one (case 1) had a partially infarcted tumour, and another (case 13) had a suprasellar extension with upper bitemporal visual field defects.

One patient (case 11) had inappropriately low and often undetectable plasma ACTH concentrations (<10-32 ng/l), although by all other criteria she had pituitary-dependent disease. Retrograde adrenal venograms showed nodular enlargement of each gland, and semi-autonomous bilateral nodular adrenal hyperplasia in pre-existing Cushing's disease was diagnosed. The patient was treated with metyrapone for two months before undergoing elective bilateral adrenalectomy. She was not given pituitary irradiation. Three other

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Details of patients studied

Case No	Sex	Age at presentation	Pituitary irradiation given	Total duration of treatment (months)	Note
1	F	60	—	66	Partially infarcted pituitary tumour
2	F	52	+	33	
3	F	44	+	30	
4	M	27	+	27	Cured
5	M	37	+	25	
6	F	56	+	22	
7	F	16	+	11	Bilateral adrenalectomy performed after 11 months Later stabilised on bromocriptine
8	F	24	+	7	
9	F	21	+	7	
10	F	44	+	3	Semi-autonomous nodular adrenal hyperplasia, adrenalectomy Died of coronary thrombosis Transfrontal hypophysectomy
11	F	48	—	2	
12	F	60	—	2	
13	F	44	—	2	

patients were not irradiated: one (case 1) had an infarcted pituitary tumour; one (case 12) had very mild longstanding disease and died of a myocardial infarction soon after treatment with metyrapone was started; and the third (case 13) had an elective transfrontal hypophysectomy after two months' preoperative preparation with metyrapone.

After diagnosis, treatment with oral metyrapone was started. An impression of each patient's sensitivity to the drug was gained by following the plasma fluorogenic corticosteroid concentrations every hour for four hours and then at 24 hours during a diagnostic metyrapone test, and the starting dose was selected accordingly. The dose used varied from 0.25 g twice daily to 1.0 g four times daily. The aim was to reduce the mean plasma fluorogenic corticosteroid concentration to 300–400 nmol/l (11 to 14.5 µg/100 ml). The mean was derived from four to seven separate samples taken over 24 hours. Covering corticosteroid treatment was not given.

During the study patients were readmitted to hospital every three to six months for reassessment of their pituitary and adrenal function. At each admission the "day curve" of plasma cortisol and ACTH (as outlined above) was measured. Whenever possible a 50-g oral glucose tolerance test; a 200 µg intravenous thyrotrophin-releasing hormone (TRH) test for thyrotrophin; a 100-µg intravenous gonadotrophin-releasing hormone (GRH) test for luteinising hormone and follicle-stimulating hormone; an insulin tolerance test (unless contraindicated by the presence of ischaemic heart disease); and basal estimations of serum prolactin and testosterone concentrations were also performed. For the insulin-tolerance test soluble insulin 0.15 to 0.3 U/kg body weight was given intravenously, and blood sugar, cortisol, growth hormone (GH), and ACTH were measured. Some of the patients were started on treatment before the prolactin assay was available.

Plasma fluorogenic corticosteroid concentrations were measured by Mattingly's method.¹⁴ All other hormones were measured by radioimmunoassay. External pituitary irradiation was given by 4-MeV and 15-MeV linear accelerators; a total lesion dose of 4500 rads was given in 25 fractions over 35 days (administered by a three-field technique).

Results

During the first three months of treatment we had to check the response to metyrapone about every four to six weeks because sensitivity to the drug showed some initial variation. Thereafter the plasma corticosteroid concentrations needed checking only every three to six months.

After starting treatment with metyrapone the clinical features of the disease rapidly improved. Facial plethora was noticeably diminished within days and the skin started to flake and itch, as after bilateral adrenalectomy. Muscle weakness also improved rapidly. Patients with pronounced psychiatric stigmata—for example, frank psychosis or mania—had a similar rapid improvement, which accompanied the fall in plasma cortisol. Patients with only minor psychiatric symptoms—non-specific malaise and depression—had no immediate changes. Seven of the 13 patients had an abnormality of glucose tolerance at presentation. After three months' treatment this was corrected in all but two (one of the seven (case 11) died before restudy). Of the 12 who had hypertension (diastolic blood pressure >90 mm Hg supine, after resting), only five remained hypertensive on metyrapone. This improvement was steadily maintained for as long as treatment continued.

The thyrotrophin response to intravenous TRH was suppressed in three patients before treatment (cases 1 and 4 were not studied). In all three the response returned within 18 months. The gonadotrophin

responses to GRH showed no consistent changes. The GH response to hypoglycaemia was impaired (peak <20 mU/l) in all the nine patients who were tested before treatment. After treatment the GH response improved in four of the six who were retested. Basal serum prolactin concentrations rose with time (irrespective of radiotherapy) in all but one of the nine patients in whom more than one value was obtained (fig 1).

The plasma ACTH concentration rose after the start of treatment from a mean value of 106 ng/l (range 61–233 ng/l) to 227 ng/l (range 140–480 ng/l); the highest mean daily value in any patient in the first

FIG 1—Change in serum prolactin concentrations after treatment with metyrapone started. O = Before radiotherapy. ● = After radiotherapy. Horizontal dotted line represents upper limit of normal (<360 mU/l).

FIG 2—Effect of radiotherapy on plasma ACTH. Mean of four to seven values taken over single 24-hour period in 11 patients before treatment and in five patients who received pituitary irradiation and in whom metyrapone had been temporarily withdrawn. Normal range at 0900 <10–80 ng/l.

12 months of treatment was 571 ng/l. In none was this rise sufficient to cause a breakthrough in control. Metyrapone was withdrawn from five patients at some stage in their treatment, and their ACTH levels while they were off treatment for at least 28 days are shown in fig 2. The fall from the mean pretreatment ACTH concentration of 127 ng/l to 52 ng/l in these five was the effect, presumably, of pituitary irradiation. The mean interval from the time of radiotherapy to the time of withdrawal was 20 months (range 13 to 30 months).

Side effects—The expected side effects of long-term metyrapone treatment are sodium and water retention and virilisation. No patient showed evidence of worsening sodium and water retention; hypertension did not deteriorate in any patient and ankle swelling tended to improve rather than worsen. But of the seven women who received metyrapone for six months or more five noticed either some deterioration in hirsuties or persistence of acne. In most cases this was only mild, but in one (case 7) it was severe enough to lead to discontinuation of metyrapone; she underwent bilateral adrenalectomy. Her plasma testosterone concentration was very high at 55.5 nmol/l (16.0 ng/ml) (normal female range 0.7–2.7 nmol/l (0.2–0.78 ng/ml)). In one patient (case 11) facial hirsuties improved.

Discussion

It has been claimed that adrenal blocking drugs would be ineffective in cases of pituitary-dependent Cushing's disease because the rise in plasma ACTH which accompanies their use would break through the blockade. We have shown, however, that breakthrough does not occur and that long-term clinical control is possible. Indeed, we have only ever seen breakthrough twice, and in each case the patient had the ectopic ACTH syndrome. By controlling the clinical manifestations of disease in our patients metyrapone allowed time for the pituitary irradiation to become fully effective.

Serious side effects were few. No patient had clinical evidence of sodium and water retention. None had the gastrointestinal symptoms that are well recognised in patients undergoing the metyrapone test used for assessing pituitary ACTH reserve. We therefore conclude that gastrointestinal side effects are encountered only when plasma cortisol falls to subnormal concentrations and not when it is carefully controlled. Four patients felt curiously lightheaded for several minutes about 20 minutes after ingesting each dose, but the most troublesome side effect was hirsuties, although in only one patient (case 7) was this serious enough to lead to her treatment being discontinued. In all others who complained the hirsuties took the form of slight coarsening of pre-existing facial hair. Enlargement of the clitoris which was present at diagnosis did not regress or worsen except in one patient (case 7). Some virilisation is to be expected from long-term use of an 11 β -hydroxylase inhibitor—the result of accumulating 11-deoxycorticosteroids with androgenic properties. There was a correlation between the severity of clinical hirsuties and the height of plasma testosterone values on treatment. The patient with severe virilisation had exception-

ally high testosterone concentrations, and the other two patients with concentrations greater than 3.5 nmol/l (1.0 ng/ml) were among those who complained of persistent hirsuties. The testosterone antiserum used in our assay had full cross-reaction with dihydrotestosterone and only partial cross-reaction (0.2–11%) with androsterone, epitestosterone, androstenediol, DHEA sulphate, and DHEA (unpublished data).

For pituitary-dependent disease we recommend the use of metyrapone to control the clinical manifestations of the disease as an adjunct to definitive treatment with pituitary irradiation by linear accelerator. It would, however, also be suitable as an adjunct to pituitary microdissection, cryosurgery, or implantation and bilateral adrenalectomy. Indeed, we now treat with metyrapone all patients who present with Cushing's syndrome, irrespective of aetiology. Apart from the 13 patients described here we have recently successfully managed four patients with the ectopic ACTH syndrome and three patients with adrenal tumour. By controlling the plasma cortisol concentration with metyrapone the clinical features of the disease rapidly regress. Subsequent surgery, if indicated, is greatly simplified and is less hazardous for the patient. Similarly, if it is difficult to make a final differential diagnosis between the causes of Cushing's syndrome, treatment with metyrapone allows time for investigations to be completed in a patient who may otherwise be critically ill.

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