MEDICAL TREATMENT OF CUSHING'S SYNDROME WITH AMINOGLUTETHIMIDE AND KETOCONAZOLE

H L Kong, K O Lee, J S Cheah

ABSTRACT

We report a 54-year-old Chinese man with Cushing's syndrome from bilateral adrenal adenomata in whom surgery was contraindicated because of his intercurrent medical conditions. Instead, he was successfully treated with aminoglutethimide 0.75 gm/day (which reduced his 24-hour urinary free cortisol from 628 nmol/day to 177nmol/day in 4 weeks), followed by ketoconazole 0.6gm/day which continued to suppress the urinary free cortisol level. We conclude that aminoglutethimide or ketoconazole offers a viable non-surgical alternative to the treatment of Cushing's syndrome.

Keywords: Cushing's Syndrome, non-surgical treatment, Aminoglutethimide, Ketoconazole

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INTRODUCTION

Cushing's syndrome is a group of disorders with signs and symptoms resulting from excess cortisol. Other than iatrogenic causes, about 80% of the remaining patient with Cushing's syndrome have pituitary overproduction of adrenocorticotropic hormone (ACTH) (or Cushing's disease, first described by Harvey Cushing in 1932). Another 5 to 10% are attributable to primary adrenal adenomata[1].

Without treatment, Cushing's syndrome has significant morbidity and mortality. The standard management of Cushing's syndrome is geared towards the identification of the primary source of ACTH or cortisol overproduction, followed by its surgical removal if that is feasible. To date, surgical ablation of the pituitary or adrenal tumours remains the only treatment modality which may offer a permanent cure of the disease. In certain situations, however, surgical approach may not be feasible or is refused by the patients; medical therapy then becomes the only option available. Experience with medical treatment is extremely limited, and is often a fine balance between restoring eucortisolism and producing an addisonian crisis. Furthermore, sensitivity of the local Chinese population to medical treatment of Cushing's syndrome has not been previously studied. We describe a Chinese patient with Cushing's syndrome from bilateral adrenal adenomata who was successfully treated with aminoglutethimide and ketoconazole.

CASE REPORT

TKG is a 54-year-old Chinese gentleman who was first diagnosed to have hypertension in 1986. He also suffers from ischaemic dilated cardiomyopathy since 1987; coronary angiography showed triple-vessel disease.

In September 1990, he was noted to have a plethoric and dusky complexion. Further physical examination revealed truncal obesity, conjunctival suffusion, cutaneous telangiectasia over upper chest and the neck, mild bilateral pedal oedema, borderline hypertension 150/90 mmHg (on treatment), cardiomegaly and mild proximal myopathy.

Preliminary investigations confirmed polycythaemia with a haemoglobin of 16.5 g/dL. He was also found to have diabetes mellitus, with a random blood sugar level of 15.4 mmol/L and a total glycosylated haemoglobin level of 7.3% (ie excellent diabetic control). Serum sodium level was 133 mmol/L, serum potassium 4.2 mmol/L, and serum bicarbonate 17 mmol/L.

The 24-hour urinary free cortisol level was 501 nmol/L (27-221); 12 midnight serum cortisol was 561 nmol/L (55-345); and 8 AM serum cortisol was 606 nmol/L (180-690). The serum ACTH levels were below detection limits on three separate occasions.

Low-dose dexamethasone suppression test showed non-suppressibility: pre-dexamethasone serum cortisol and 24-hour urinary free cortisol levels were 556 nmol/L and 682.5 nmol/day respectively; the corresponding post-dexamethasone levels were 608 nmol/L and 491 nmol/day respectively. Likewise, high-dose dexamethasone suppression test failed to show suppressibility: pre-dexamethasone serum cortisol and 24-hour urinary free cortisol levels were 600 nmol/L and 546 nmol/day respectively; the corresponding post dexamethasone levels were 983.4 nmol/L and 545 nmol/day respectively.

Computerised tomography of the adrenals revealed bilateral adrenal masses — the right one measuring 1.5 cm in diameter, and the left 3.5 cm in diameter. Adrenal venogram confirmed the presence of two tumours.

Computerised tomography of the pituitary fossa suggested the presence of a pituitary microadenoma. Serum prolactin level, thyroid function test and luteinising hormone-releasing hormone (LHRH) stimulation test were found to be normal. Thyroid-stimulating hormone (TSH) stimulation test yielded a flat response[2]; serum growth hormone and gastrin levels were normal.

The diagnosis was therefore that of Cushing's syndrome from bilateral adrenal adenomata and an incidental non-functioning pituitary tumour.

Two expert cardiologists advised against surgery for the removal of his adrenal adenomata in view of the ischaemic dilated cardiomyopathy. He was then started on 4 weeks of oral aminoglutethimide 250 mg thrice daily, followed by oral ketoconazole 300 mg twice daily. The patient reported definite improvement in his general well-being after he was started on the medical therapy; blood pressure was reduced from 150/90 mmHg to 120/80 mmHg over a 6-week treatment period. The biochemical response to the medical therapy is shown in Fig 1.

With aminoglutethimide, the 12 MN serum cortisol decreased from a pre-treatment level of 622 nmol/L to 294 nmol/L; the 8 AM serum cortisol decreased from 625 nmol/L to 341 nmol/L with treatment. The 24-hour urinary free cortisol level decreased from 628 nmol/day to 177 nmol/day. With ketoconazole at 200 mg twice daily, the suppression of plasma cortisol and 24-hour urinary free cortisol was less marked. This is probably related to the low dose used. The patient did not suffer from any signifi-

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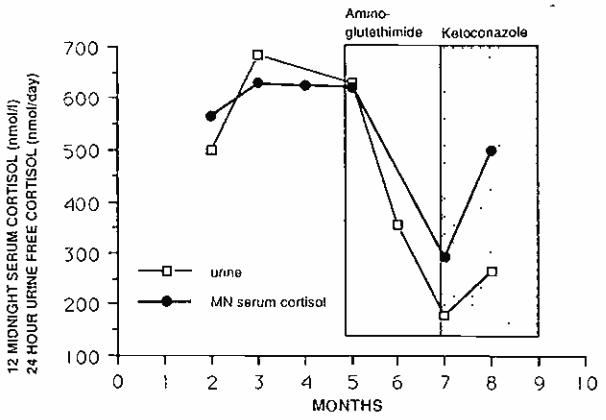
Fig 1 - Serum cortisol and 24-hour urine free cortisol before and after treatment with aminoglutethimide and ketoconazole



cant side-effects from the drugs other than the occasional feeling of malaise.

In conclusion, aminoglutethimide and ketoconazole had brought about symptomatic alleviation and biochemical improvement of the disease in our patient under study.

DISCUSSION

Surgery as the definitive treatment of Cushing's syndrome from adrenal adenoma is well established. Excellent cure rates have been documented consistently. However, bilateral adrenalectomy often leads to a need for life-long mineralocorticoid and glucocorticoid replacement therapy. In addition, some patients with Cushing's syndrome may not be fit for surgery; such was the case with our patient. Also, some patients refuse surgery. An alternative, non-surgical approach may become necessary under such circumstances.

Aminoglutethimide was first introduced in 1960 as an anticonvulsant, but was subsequently withheld in 1966 because of its side-effect of inhibition of steroid biosynthesis in the adrenals. This is due to the impaired conversion of cholesterol to 5-pregnenolone. This 'side-effect' of aminoglutethimide was precisely the pharmacological action exploited by subsequent investigators in the management of hypercortisolism. Schteingart et al[3] were the first to report on the use of aminoglutethimide in a patient with Cushing's syndrome due to metastatic adrenal carcinoma.

The literature on the use of aminoglutethimide in the treatment of Cushing's syndrome is limited, and there is no report on its use in Oriental patients. Mishin et al[4] in 1976 reviewed 66 patients with Cushing's syndrome who were treated with aminoglutethimide, and found that 50% of them showed significant biochemical and clinical improvement. Particularly impressive was the high rate of successful palliation of Cushing's syndrome due to malignant causes. They concluded that aminoglutethimide has a place in controlling the signs and symptoms of adrenocorticoid excess in patients with Cushing's syndrome due to malignancy and is an effective preoperative therapy for patients with adrenal adenomata and bilateral hyperplasia.

Thaven et al[5] in 1985 showed that aminoglutethimide at a dose of 0.5 to 1.0 gm a day produced clinical improvement and reduction in the level of cortisol. The side-effects reported were largely mild and reversible (skin rashes, sedation, headache, myalgia, upper gastrointestinal symptoms). Our patient did not have these side-effects. His symptoms, hypertension, myopathy and biochemical profile improved dramatically with aminoglutethimide at a dose of 0.75 gm/day.

Ketoconazole is an imidazole compound which was initially used as an orally-administered, broad-spectrum anti-fungal agent. It was later discovered that ketoconazole also reversibly inhibited the synthesis of testicular and adrenal steroids in humans[6,7]. This 'adverse effect' of ketoconazole was later exploited by some investigators in the treatment of Cushing's syndrome[6,8]. Sonino et al[8] studied the effects of ketoconazole at 800 mg/day for 30 days, followed by 600 mg/day for a minimum of 2 months in 5 patients with severe recurrent hypercortisolism from pituitary-dependent Cushing's disease. All patients rapidly improved clinically after starting ketoconazole treatment, by 4 to 6 weeks they had regained their normal appearance with regression of symptoms. Both urinary and serum cortisol levels rapidly decreased to within normal limits even after the dose was lowered to 600 mg/day.

Angeli and Frairia[7,9] reported observations in the ketoconazole treatment of 5 women with Cushing's disease. Each patient received 800 mg/day for 4 months, then 3 patients received a reduced dose of 600 mg/day. A slight decrease in cortisol secretion was observed after 2 weeks of ketoconazole treatment, clearly reduced after 1 to 2 months, and highly reduced by the third month. All 5 patients improved clinically, menstruated normally, and experienced improvement in psychiatric symptoms.

In our patient, there appeared to be a slight increase in the plasma cortisol and urinary free cortisol levels after he was switched from aminoglutethimide to ketoconazole. This can be explained by the fact that he was initially started on a dose of ketoconazole (400 mg/day) which was lower than that recommended by the aforementioned studies. However, he remained symptomatically well, and the blood pressure remained well controlled. Paola Loli et al in 1986 showed that while a low dose (400 mg/day) treatment was effective, the achievement and maintenance of normal or near-normal urinary cortisol levels required higher doses of ketoconazole. Hence, in our patient, the dose of ketoconazole was subsequently increased to 600 mg/day.

There is as yet no published data that we know of on the combination of aminoglutethimide and ketoconazole, although such a combination might theoretically be beneficial since aminoglutethimide and ketoconazole inhibit adrenal steroid synthesis via different biochemical pathways[6,7].

CONCLUSION

If left untreated, Cushing's syndrome is associated with much morbidity and even mortality. While surgery remains the mainstay of treatment of Cushing's syndrome, there are situations in which surgery is either refused by the patient or is not feasible. In such cases, the use of aminoglutethimide or ketoconazole may be considered. The experience with our patient showed that definite clinical improvement and biochemical control of Cushing's syndrome are possible with aminoglutethimide 0.75 gm/day or ketoconazole 0.6 gm/day, with minimal side-effects. This concurs with the international experience. We conclude that aminoglutethimide or ketoconazole (or perhaps their combination) offers a viable non-surgical alternative to the treatment of Cushing's syndrome.

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