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Response of hypertension to conventional antihypertensive treatment and/or steroidogenesis inhibitors in Cushing's syndrome

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Abstract. Fallo F, Paoletta A, Tona F, Boscaro M, Sonino N (Division of Endocrinology, Institute of Semeiotica Medica, University of Padova, Padova, Italy). Response of hypertension to conventional antihypertensive treatment and/or steroidogenesis inhibitors in Cushing's syndrome. *Journal of Internal Medicine* 1993; 234: 595–598.

Objectives. To evaluate the effect of conventional antihypertensive drugs and/or inhibitors of steroid production in the management of hypertension in Cushing's syndrome.
Design. A retrospective open clinical study with pre- and post-treatment assessment.
Setting. A university hospital, where patients were initially admitted and then followed-up in an ambulatory clinic over a period of 6 years.
Subjects. Forty consecutive hypertensive patients with Cushing's syndrome.
Interventions. Patients were divided into two groups according to the different management of hypertension. The first group (group 1) of 28 patients included those treated with antihypertensive drugs at full dose (diuretics, calcium antagonists, angiotensin converting enzyme [ACE] inhibitors, as single agents or in combination). The second group (group 2) of 12 patients received ketoconazole alone.
Main outcome measures. Blood pressure variations compared to pre-treatment levels.
Results. Blood pressure normalization was obtained in four of the 28 patients of group 1. In 12 of the remaining patients, ketoconazole, an inhibitor of steroid production, was subsequently added and this normalized blood pressure in all but the one in whom cortisol was not decreased. In the 12 patients of group 2, ketoconazole alone lowered blood pressure within normal limits in all but one who had long-standing hypertension.
Conclusions. In hypertensive patients with Cushing's syndrome, conventional antihypertensive therapy is mostly ineffective. Blood pressure response is satisfactory only after the restoration of normal cortisol levels, indicating the need for a specific treatment for hypertension in this disorder.

Key words: antihypertensive drugs, Cushing's syndrome, hypertension, ketoconazole.

Introduction

Hypertension is a common feature of Cushing's syndrome and may be the reason for the initial consultation [1]. No specific mechanism in the pathogenesis of blood pressure elevation has been identified, accounting for the empiric pattern of treatment with conventional antihypertensive drugs employed for patients awaiting definitive treatment [2]. The pathogenetic mechanisms of hypertension in this condition should be considered multifactorial, resulting from cortisol action in many metabolic processes, neural activity and other endocrine systems involved in the regulation of body fluids, electrolyte composition and arterial tone. The aim of this study is to assess retrospectively the effect of conventional antihypertensive drugs and/or inhibitors of adrenocortical biosynthesis in a group of patients with Cushing's syndrome.

Patients and methods

Forty consecutive hypertensive patients with Cushing's syndrome (32 with pituitary-dependent

Table 1 Details of patients with Cushing's syndrome and hypertension ($n = 40$). In group 1 ($n = 28$) all patients received antihypertensive drugs (AHD) initially. In 12, ketoconazole was subsequently added (AHD+KC). Group 2 ($n = 12$) received KC only as treatment

	Group 1		Group 2
	AHD ($n = 28/28$)	AHD+KC ($n = 12/28$)	KC ($n = 12$)
Age (years)	40±2	38±3	39±2
Sex (f/m)	23/5	9/3	10/2
S/D BP (mmHg)	167±3/105±2	170±4/111±3	161±3/103±2
Urinary cortisol (μg 24 h^{-1})	517±62	547±91	476±91
Duration of disease before treatment (months)	7±4	13±5	9±3
Duration of therapy (months)	6±1	10±2	7±2
Patients with BP normalization	4	11	11
S/D BP on treatment	135±2/85±2 ($n = 4$)	133±2/83±1 ($n = 11$)	130±1/82±2 ($n = 11$)

S/D BP, systolic/diastolic blood pressure.
Results are given as mean±SEM; intergroup differences by Student's *t*-test were not significant ($P > 0.05$) for all parameters.

bilateral adrenal hyperplasia, five with an adrenal adenoma, one with an adrenal carcinoma and two with ectopic adrenocorticotrophic hormone [ACTH] production) admitted to our institution during the last 6 years were evaluated in a retrospective study. The diagnosis was based on standard criteria [3] and proved at surgery in all cases. The duration of disease and the duration of therapy were obtained from the patient's history and a detailed review of medical records. All patients had been classified at diagnosis as hypertensive at stage I or II according to the World Health Organization's (WHO) classification. None of the patients had any other disease. In all patients medical therapy with antihypertensive drugs or with steroidogenesis inhibitors alone was initiated after 2 weeks of wash-out of previous drugs, and preceded definitive treatment (by pituitary or adrenal surgery). These 40 patients were divided in two groups according to the type of therapy. A first group of 28 patients (group 1) included all those initially treated with a single antihypertensive agent (diuretics or calcium antagonists or ACE inhibitors) at full dose and then, in case of lack of hypertension control at the 2 months follow-up (i.e. supine diastolic blood pressure $\geqslant 95$ mmHg), with a combination of at least two of the same drugs. Twelve of these patients showing hypertension resistant to two-drug therapy were subsequently given ketoconazole, an inhibitor of steroid production (400–800 mg day^{-1}) as a palliative treatment for hypercortisolism. A second group (group 2) of 12 subjects were treated with ketoconazole alone at the same doses (Table 1). Each treatment (i.e. antihypertensive drugs, antihypertensive drugs+ketoconazole, ketoconazole) was given for at least 4 months (range 4–30 months).

The groups were similar for age and sex and had no statistical difference for duration of disease, duration of treatment, basal blood pressure and urinary cortisol levels (Table 1). Also, the body mass index (BMI; normal range; 19–24.9) was similar in group 1 (30.2 ± 1.2; $n = 28$) and its subset (29.4 ± 1.2; $n = 12$) and in group 2 (31.2 ± 2; $n = 12$).

Results are expressed as mean±SEM. Inter-group comparisons were calculated by using Student's *t*-test for unpaired data. Non-parametric tests were also performed and yielded similar results. A $P < 0.05$ was considered significant.

Results

Blood pressure normalization was obtained in four (one with a diuretic and one with a calcium antagonist as single agents, two with a combination of diuretics and ACE inhibitors) of 28 patients belonging to group 1 (Table 1). Of the 12 patients of group 1 with hypertension resistant to combined antihypertensive drugs in whom ketoconazole was subsequently added, a parallel normalization of blood pressure and urinary cortisol occurred in 11. In the patient with an adrenal carcinoma, both blood pressure and cortisol levels did not normalize with the addition of ketoconazole. Tolerable side-effects occurred in three of the 28 patients during administration of antihypertensive therapy (leg

oedema in two and skin flushes in one, during calcium antagonist administration).

In group 2, ketoconazole alone lowered blood pressure within normal limits in 11 out of 12 patients, and normalized cortisol in all. Side-effects from ketoconazole included dyspepsia in one patient and transient liver function abnormalities in one.

Urinary cortisol was not correlated with blood pressure levels in basal conditions and no relationship was found between the hypotensive response and pre-treatment urinary cortisol levels.

The outcome of blood pressure values after hypercortisolism therapy in the remaining 12 patients of group 1 with resistant hypertension, not treated with ketoconazole, was normalization in eight out of nine of those cured by surgery. Hypertension persisted in the three in whom cortisol overproduction was not corrected by surgery.

Discussion

The ideal objective of treatment in Cushing's syndrome is to permanently remove the overproduction of cortisol which is due to either an adrenal tumour or to bilateral hyperplasia secondary to abnormal stimulation by ACTH of pituitary or ectopic origin. Successful pituitary or adrenal surgery is known to reverse both metabolic derangement and elevated blood pressure in this condition [4]. In patients with Cushing's syndrome awaiting surgery or in whom surgery is not feasible, inhibitors of adrenal steroidogenesis and glucocorticoid antagonists also have the potential to correct the syndrome and control hypertension as well, at least for short periods [2, 5, 6]. Our results show that secondary hypertension of Cushing's syndrome is not satisfactorily ameliorated by the use of conventional antihypertensive therapy. To our knowledge, very few reports have been published on the effects of antihypertensive drugs in patients with Cushing's syndrome. As renin substrate and plasma renin activity are known to be increased by glucocorticoids, the predominance of an angiotensinogenic component in inducing hypertension in hypercortisolism has been suggested [7]. However, either infusion of the competitive angiotensin II antagonist saralasin or short-term administration of the ACE inhibitor captopril do not produce a consistent fall of blood pressure levels [8, 9] in most patients. Our data with prolonged treatments with ACE inhibitors or other antihypertensive agents, alone or in combination, confirm a poor control of hypertension in Cushing's syndrome. The cause of blood pressure normalization in a few patients treated with these drugs is unclear, because age, duration of hypertension, urinary cortisol and blood pressure levels were not different from those of patients with hypertension resistant to therapy. Conversely, the addition of steroid production inhibitor ketoconazole to conventional antihypertensive drugs in a subset of patients normalized blood pressure in all but one patient in whom cortisol was not decreased. In the second group of patients, ketoconazole alone lowered cortisol levels within normal limits in all, and blood pressure to normal in all but one. This was a patient with hypertension preceding overt Cushing's syndrome of at least 3 years. In such cases, lack of hypertension control could ensue from irreversible vascular lesions which are a result of long-standing hypertensive disease. As previously reported, ketoconazole treatment is generally well tolerated, but patients should be watched closely for excessive inhibition of enzyme activities (adrenal insufficiency, impaired testicular function, gynaecomastia) and for liver toxicity [5, 10].

Our data with steroidogenesis inhibitors indicate that restoration of normal cortisol is the *conditio sine qua non* to obtain a satisfactory blood pressure control in patients with Cushing's syndrome. This also means that a specific treatment is indicated for this type of hypertension.

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