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EFFECT OF HYPERCORTISOLISM CONTROL ON HIGH BLOOD PRESSURE IN CUSHING'S SYNDROME*

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Abstract Many hypertensive patients affected by endogenous Cushing's syndrome (CS) persist with high blood pressure (HBP) despite good control of cortisol excess. We assessed the effect of preoperative ketoconazole administration and of definitive treatment of CS on arterial hypertension and analysed the factors involved in the persistence of hypertension. We assessed retrospectively 71 patients with CS and HBP (60 women, 11 men; 50 pituitary, 21 adrenal) successfully treated by surgery and/or radiotherapy; 19 of them received ketoconazole (KNZ) before surgery. After treatment, patients were divided into those with persistent high blood pressure (PHBP) and those with normal blood pressure (NBP). As possible predictive factors for PHBP we analysed age, duration and family history of HBP, pre-treatment 24 hour urinary free cortisol (24h-UFC) and body mass index (BMI). HBP normalized in 53 out of 71 patients (74.6%), regardless of the origin of Cushing's syndrome. PHBP patients were older (p=0.003), had longer duration (p=0.007) and higher systolic blood pressure before treatment (p=0.046) than NBP patients. Thirteen out of 19 patients (68.4%) treated with ketoconazole, normalized their hypertension and remained normotensive after successful surgery. Five patients became normotensive only after surgery. In conclusion: a) blood pressure levels normalized in most patients after remission of CS; b) ketoconazole was effective for the control of HBP, and seems to be a good indicator of post-surgical outcome, and c) higher age at presentation, longer duration of hypertension and higher systolic blood pressure figures before treatment negatively influence normalization of blood pressure after resolution of Cushing's syndrome.

Key words: Cushing's syndrome, endocrine hypertension, ketoconazole therapy

Resumen ***Efecto del control del hipercortisolismo sobre la hipertensión arterial en el síndrome de Cushing.*** Muchos pacientes con síndrome de Cushing (SC) permanecen hipertensos a pesar del control del exceso glucocorticoideo. Investigamos el efecto de la administración de ketoconazol (KNZ) y del tratamiento definitivo del SC sobre la hipertensión arterial (HTA), analizando su relación con diversos factores. Evaluamos 71 pacientes con SC e HTA (60 mujeres, 11 varones; 50 pituitarios, 21 adrenales) exitosamente tratados por cirugía y/o radioterapia; 19 de ellos recibieron KNZ antes de cirugía. Luego del tratamiento, fueron divididos en pacientes con HTA persistente (HTAP) y normal (HTAN). Como posibles factores predictivos de HTAP se analizaron edad, duración, historia familiar de HTA, cortisol libre urinario de 24 hs pre-tratamiento e índice de masa corporal. La HTA normalizó en 53/71 pacientes (74.6%) independientemente del origen del síndrome de Cushing. Los pacientes con HTAP fueron de mayor edad (p=0.003), con mayor duración previa (p=0.007) y valores mayores de presión arterial sistólica antes de tratamiento (p=0.046) que aquellos con HTAN. Trece de 19 pacientes (68.4 %) tratados con ketoconazol normalizaron su tensión arterial y se mantuvieron normotensos luego de cirugía exitosa. Cinco pacientes se tornaron normotensos solo después de cirugía. En conclusión: a) la HTA se normalizó en la mayoría de pacientes luego de remisión del SC, b) el ketoconazol fue efectivo para el control tensional y aparenta ser indicador de la evolución pos-quirúrgica, y c) mayor edad, duración más prolongada de la HTA y valores más altos de presión sistólica influencian negativamente la normalización de la presión arterial luego de resolución del síndrome de Cushing.

Palabras clave: síndrome de Cushing, hipertensión endocrina, ketoconazol

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Cardiovascular disease in particular hypertension, is a major factor of morbidity and mortality in patients with Cushing's syndrome, more than 70% of whom have high blood pressure at diagnosis[1-3]. In the present work, we assessed the effect of specific therapy for hypercortisolism on arterial hypertension of Cushing's patients in order to: a) establish the prevalence of patients who normalize blood pressure after control of cortisol excess, b) consider the evolution depending on the pituitary or adrenal origin of Cushing's syndrome, c) evaluate the response of HBP to ketoconazole before surgery and compare it to that obtained after surgery and/or pituitary radiotherapy, and d) analyse the potential risk factors for persistence of HBP after resolution of hypercortisolism.

Materials and Methods

One hundred and fifty one (70.9%) out of 213 patients with Cushing's syndrome, admitted to our institution from 1978 to 2003 that were assessed retrospectively, had hypertension. From that group we selected 71 patients that fulfilled the following criteria: presence of HBP at diagnosis of CS, and the complete remission of hypercortisolism after treatment of pituitary or benign adrenal Cushing's syndrome. All patients achieved normalization of cortisol levels after one or more diverse therapeutic methods. Pituitary surgery was performed in 50 patients with CS of pituitary aetiology (Cushing's disease); in 11 of them an additional approach such as radiotherapy and/or bilateral adrenalectomy was required. Stereotactic radiosurgery with gamma-knife was indicated in 2 patients with CS of pituitary aetiology. A unilateral adenoma was removed in the 21 patients with CS of adrenal origin. Patients with adrenal carcinoma, ectopic corticotropin production, or with persistent HBP but with a follow-up shorter than 24 months, were excluded. In addition, the response of blood pressure to ketoconazole treatment (dose range: 200-1000 mg/d, mean: 650 mg/d) was analysed in a subgroup of 19 patients who were treated with this drug prior to surgery.

High blood pressure was defined as systolic (SBP) = 140 mm Hg and/or diastolic (DBP) = 90 mm Hg blood pressures, measured at least three times in three different days, in subjects without any anti-hypertensive treatment. Patients were classified in three stages: stage 1, SBD 140-159 mm Hg and/or DBP 90-99 mm Hg; stage 2, SBD 160-179 mm Hg and/or DBP 100-109 mm Hg and stage 3, SBP = 180 mm Hg and/or DBP = 110 mm Hg[4]. The diagnosis of Cushing's syndrome was based on standard criteria which included: 1 mg dexamethasone suppression test[5] and/or 24 h-UFC and/or nocturnal UFC levels[6] and/or 24 h-urinary 17 hydroxycorticoids[7]; cortisol was measured by using a commercial kit (*DPC*, California) after extraction with dichloromethane. Etiologic diagnosis was based on 8 mg dexamethasone suppression test and/or metopirone test and/or plasma ACTH level[8, 9]. Abdominal computed tomography and/or pituitary magnetic resonance imaging completed the evaluation of localization. Pathological findings after surgery confirmed the diagnosis throughout. Criteria to define remission of hypercortisolism after definitive treatment were the finding of 24 h-UFC excretion and/or early morning serum cortisol concentration below the normal range (<20 µg/24 hs and <5.0 µg/dl, respectively), and/or suppression of serum cortisol below 2.0 µg/dl after low-dose dexamethasone test, immediately after surgery or during the follow up in patients treated with radiotherapy.

As possible predictive factors for HBP persistence we analysed age, duration of HBP at diagnosis, family history of HBP, pre-treatment 24-UFC and BMI, before therapy and after patients became normotensive, or at least two years later in those who remained hypertensive. As other major cardiovascular risk factors we assessed glucose levels, renal function and lipid profile. Comparisons were made between patients with pituitary Cushing's syndrome and those having an adrenal adenoma. For the whole group, patients were classified after definitive treatment in those with: a) persistent high blood pressure (PHBP) if they remained with high blood pressure figures in at least three separate controls after 24 months of follow-up, and b) normal blood pressure (NBP)[4]. Because of the long recruitment period of the study, different antihypertensive therapy regimens were administrated to achieve normotension including dietary sodium restriction and antihypertensive drugs such as angiotensin-converting enzyme inhibitors, and/or calcium channel antagonists, and/or beta-blockers, and/or spironolactone, in diverse dosages; these different regimens were not substantially different between the subgroups compared in the study. Statistical analysis was performed by Wilcoxon's test for unpaired data and Fisher's test. Odds ratios (OR) and confidence intervals (CI = 95%) were determined to establish probabilities for risk factors. Values for qualitative variables are reported as means ± SD; $p < 0.05$ was considered significant.

Results

Seventy-one patients (60 women and 11 men) with proven Cushing's syndrome were evaluated. Out of the total, 50 had a pituitary adenoma and 21 an adrenal adenoma. Mean age at diagnosis for the whole group was 37.4 ± 12.8 years (range: 13-75). Mean duration of HBP before treatment was 41.5 ± 49.7 months, BMI 30.7 ± 8.2 kg/m^2 and 24-UFC 470.28 ± 432.97 µg/24 hours. Pretreatment SBP was 154 ± 19.7 mm Hg and DBP 98.7 ± 10.2 mm Hg. Pretreatment cholesterol levels were 234 ± 43.8 mg/dl (n= 38), creatinine 1.2 ± 1.3 mg/dl (n= 30) and glycemia 110 ± 61 mg/dl (n= 52); 10 subjects had fasting plasma glucose levels upper than 126 mg/dl.

Post-treatment follow-up was longer than 24 months for patients with persistent HBP (range: 24-264). Average follow-up was 48.7 ± 52.3 months for the whole group.

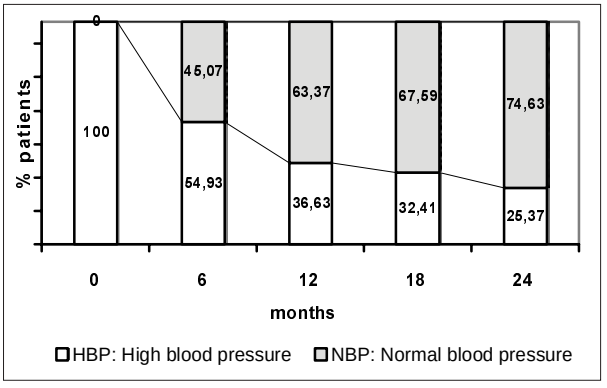

Fig. 1.– Evolution of blood pressure after remission of hypercortisolism

According to blood pressure figures, 24/71 patients were classified as stage 1, 26/71 as stage 2 and 21/71 as stage 3[4], before any treatment. After definitive reso-lution of hypercortisolism, 53 out of 71 patients (74.6%) normalized their blood pressure with no need for any anti-hypertensive therapy. The period required for normali-zation of blood pressure was variable, with a mean of 6.6 ± 6.5 months (60.4% in the first 6 months, 24.5% in 6 to 12 months, 5.7% in 12 to 18 months and 9.4% in 18 to 24 months) after definitive therapy (Fig. 1). Out of the remaining 19 patients with persistent HBP, ten of them continued in their previous stage while nine patients were able to decrease the dose and number of antihypertensive medications, so they were reclassified into a minor stage after resolution of hypercortisolism.

In the analysis of patients with pituitary and adrenal origin of Cushing's syndrome, no differences were found in age, previous duration of HBP, SBP, DBP or 24 h-UFC levels, either before or after treatment (Table 1). In Table 2, a comparison between data from PHBP and NBP subgroups is shown. Mean age at diagnosis and both, preoperative HBP duration and SBP, were significantly higher in PHBP than in NBP (p =0.003, 0.007 and 0.041, respectively). Moreover, age over 35 years old and duration of hypertension longer than 24 months before diagnosis, were significantly related to the persistence of HBP (OR= 6.72, CI= 1.56-33.3, p=0.006; OR= 5.69, CI= 1.53-22.4, p=0.006, respectively). Although BMI decrease was higher in NBP as compared to PHBP group (9.2% vs. 3.5%) after definitive treatment, this difference was not statistically significant (p = 0.08). However, BMI reached after cure correlated with postoperative systolic blood pressure (r= 0.27, p=0.023). Pretreatment BMI, DBP, frequency of family history of HBP, glycemia, cholesterol, urea and creatinine levels were similar in both groups, whereas pretreatment 24h-UFC levels were higher in NBP (Table 2).

For the whole group, there was a significant positive correlation between age and post-treatment systolic and diastolic blood pressure (r = 0.44, p < 0.001 and r = 0.33, p < 0.005, respectively). There was also a positive and significant correlation between preoperative HBP duration and postoperative systolic blood pressure (r = 0.33, p< 0.005); however, there was no correlation between pretreatment 24 h-UFC and blood pressure evolution after therapy. Glycemia decreased significantly (<0.001) after successful treatment and all patients normalized blood glucose.

Nineteen patients treated with ketoconazole before surgery showed a significant decrease in 24 h-UFC levels from 501.1 ± 386.6 to 72.5 ± 65.9 µg/24 hs (p< 0.0001) in a mean time of 58 ± 39.8 days, accompanied by a significant reduction in systolic and diastolic blood pressure values (Table 3). High blood pressure levels normalized under treatment in 13/19 patients (68.4%): in 8 it was reached with KNZ alone, whereas in the remaining 5 anti-hypertensive therapy was reduced in 4 and withdrawn in 1 when KNZ therapy was added. Time required to normalize blood pressure with ketoconazole (64.2 ± 78.9 days; range: 5-240) significantly correlated with 24 h-UFC figures at that moment (r = 0.79, p=0.002) and with time elapsed to recover normal 24 h-UFC levels under treatment (r = 0.82, p=0.001). All these patients continued with normal blood pressure after definitive treatment.

Six patients remained hypertensive under ketoco-nazole therapy despite normalization of 24 h-UFC levels.

TABLE 1.– *Comparison of findings in patients with Cushing´s syndrome of pituitary vs. adrenal origin*

	N	Adrenal	N	Pituitary
Age (years)	21	37.0 ± 12.6	50	37.5 ± 13.0
HBP duration (months)	21	33.7 ± 34.5	48	44.9 ± 55.0
Pre-BMI (kg/m^2)	21	28.5 ± 6.4	50	31.7 ± 8.7
Post-BMI	20	25.7 ± 4.7	47	29.4 ± 7.8
Pre-UFC (µg//24 hs)	20	406.9 ± 310.5	39	443.5 ± 396.01
NBP (%)	21	77.3	50	71.5
Pre-SBP (mm Hg)	21	155.5 ± 16.1	50	153.2 ± 21.1
Pre-DBP (mm Hg)	21	98.3 ± 7.3	50	98.9 ± 11.3
Post-SBP (mm Hg)	21	121.9 ± 14.8	50	127.0 ± 20.2
Post-DBP (mm Hg)	21	78.8 ± 10.5	50	79.7 ± 10.1

HBP, high blood pressure; BMI, body mass index before (Pre) and after (Post) treatment; Pre-UFC, pretreatment urinary free cortisol. NBP, normal blood pressure; SBP, systolic blood pressure before (Pre) and after (Post) treatment; DBP, diastolic blood pressure before (Pre) and after (Post) treatment. Values presented are means ± SD. No significant differences were found for any of the parameters studied.

TABLE 2.– *Analysis of findings in patients with persistent high blood pressure (PHBP) and normal blood pressure (NBP) after remission of Cushing's syndrome*

	N	PHBP	N	NBP
Age (years)	18	45.7 ± 13.2	53	34.5 ± 11.5**
Duration of HBP (months)	17	78.4 ± 76.8	52	29.4 ± 28.9**
Pre- BMI (kg/m^2)	18	31.5 ± 6.9	53	30.5 ± 8.6
Post- BMI (kg/m^2)	17	30.5 ± 7.5	50	27.6 ± 7.0
Pre- UFC (µg/24 hs)	13	428 ± 603	46	431 ± 276*
Pre-SBP (mm Hg)	18	163.3 ± 25.0	53	150.7 ± 16.6*
Pre-DBP (mm Hg)	18	99.7 ± 10.9	53	98.4 ± 10.0
Post-SBP (mm Hg)	18	151.4 ± 14.3	53	116.7 ± 9.8***
Post-DBP (mm Hg)	18	91.1 ± 8.3	53	75.5 ± 7.2***
Pre-glycemia (mg/dl)	14	122.8 ± 76.9	38	105.6 ± 54.8
Pre-cholesterol (mg/dl)	10	243.4 ± 47.6	28	230.06 ± 42.7
Pre-creatinina (mg/dl)	10	0.94 ± 0.19	20	0.95 ± 0.27
Post-glycemia (mg/dl)	10	86.3 ± 17.6	29	90.8 ± 28.8

*HBP, high blood pressure; BMI, body mass index before (Pre) and after (Post) treatment; Pre-UFC, pretreatment urinary free cortisol. SBP, systolic blood pressure before (Pre) and after (Post) treatment. DBP, diastolic blood pressure before (Pre) and after (Post) treatment. Values represented are means ± SD; statistical comparisons were done by Wilcoxon's test. *p<0.05 **p<0.01, ***p<0.001.*

TABLE 3.– *Blood pressure response after normalization of UFC levels under ketoconazole (KNZ) treatment and after surgery*

	Baseline (n=19)	Under KNZ (n=19)	Post surgery (n=19)
SBP (mm Hg)	154.0 ±19.8	124.7 ± 14.0****	125.9 ± 18.8****
DBP(mm Hg)	98.8 ± 10.2	82.6 ± 14.6****	79.7 ± 10.1****

*SBP, systolic blood pressure; DBP, diastolic blood pressure; KNZ, ketoconazole. Values represented are means ± SD; **** p<0.0001 (KNZ vs. Baseline and Post surgery vs. Baseline); there were no significant differences between KNZ and Post surgery.*

Five of them, who had been hypertensive for less than 3 years and received KNZ for short periods (1 to 5 months), achieved normotension only after surgery; one patient with a history of HBP longer than 11 years remained hypertensive under ketoconazole and after definitive treatment.

Discussion

Hypertension occurs in at least 70% of patients presenting endogenous Cushing's syndrome and in 20% of those receiving pharmacological doses of glucocorticoids[10]. Oral cortisol is known to increase blood pressure in a dose dependent fashion: at doses of 40 mg/day there is no apparent changes in blood pressure, whereas at doses of more than 80 mg/day, significant increases in systolic and diastolic blood pressure occur within 24 hours, with a peak response usually observed on day 4 or 5 of treatment[11].

Pathogenic mechanisms involved in hypertension induced by endogenous hypercortisolism are considered multifactorial, including increased mineralocorticoid action and renin substrate production, inhibitory activity on vasodilatory systems, enhanced cardiovascular response to vasoactive substances and a direct effect of ACTH on vascular tone[12-15]. In addition, glucocorticoid excess can accelerate the development of atherosclerosis, by promoting direct endothelial cell injury and by inducing hyperlipidemia and glucose intolerance, both factors that contribute to damage blood vessels[16,17,18].

ACTH enhances blood pressure by regulating the production of cortisol in the adrenal glands. In addition, ACTH seems to enhance cortisol effect on vascular tone through inhibition of peripheral conversion of cortisol to cortisone in the kidney. Downregulation of the expression

of 11-β-hydroxysteroid dehydrogenase in the endothelial vascular cells, induced by ACTH, is another mechanism that could favour cortisol action on vessels[14, 15]. As previously reported by others[19], no differences in blood pressure figures or in its response to treatment could be disclosed in our study between patients with ACTH-dependent and ACTH-independent Cushing's syndrome. Moreover, our findings are in contrast with those of Zacharieva et al[20] who described a high rate of normotension in cured adrenal CS, probably associated to a shorter duration of hypertension than in pituitary CS. Therefore, it seems unlikely that corticotropin excess could play a role in hypertension in our patients, although we excluded patients with ectopic ACTH syndrome in whom corticotropin levels are frequently higher.

The results of the present study showed that 74.6 % of patients with remission of Cushing's syndrome normalized their hypertension. In addition, in most cases of persistent HBP it was possible to reduce the number and doses of antihypertensive drugs required to control HBP levels. The persistence of hypertension has been described in many cases of patients with remission of Cushing's syndrome, in spite of hypercortisolism normalization. The rate of persistent hypertension in our group of patients is similar to that reported in other series[21, 22]. Some reports have been published on the evolution of hypertension in treated adult Cushing patients. In three of these studies, patient population comprised either a mix of different adrenal pathologies[23, 24], or only Cushing adrenal adenomas[22]. Fallo et al[21] have specifically addressed this issue in a group of 54 patients with ACTH-dependent and ACTH-independent Cushing's syndrome in the usual epidemiological proportion. They concluded that only duration of HBP appeared to be related to persistent hypertension following successful surgery in Cushing's syndrome. In our study, we found that persistence of hypertension after remission of CS was significantly associated not only with duration longer than 24 months, but also with age over 35 years old. On the other side, a series involving 31 young patients (less than 20 years old) with Cushing's syndrome reported barely 5.5% of persistent high systolic blood pressure one year after surgical cure[25]. Age, (probably due to a higher probability of coexistence with essential hypertension), preoperative HBP duration and higher figures of preoperative SBP, may induce the development of permanent vessel changes leading to irreversible hypertension. In our series, pretreatment values of UFC seemed not to influence evolution, since they were higher in NBP than in PHBP patients, suggesting that sustained hypercortisolism is more important than isolated cortisol values in determining the final outcome of BP.

Colao et al[17] reported that clinical and metabolic features of active Cushing's syndrome persist and maintain the cardiovascular risk associated to cortisol excess, even after 5 years' remission of CS, suggesting that the accumulation of visceral obesity and insulin resistance, rather than generalized obesity, might be responsible for the persistence of a high cardiovascular risk in these patients. In this study, metabolic parameters although lower than that observed during the active phase of Cushing's syndrome, persisted significantly higher than controls after normalization of circulating cortisol levels. Although in our work we found a higher decrease of BMI in the NBP group after treatment, this difference failed to reach statistical significance. BMI reduction after cure seems to influence the decrease of systolic blood pressure. By contrast, we found that glycemia decreased significantly after successful treatment and all patients reached normal blood glucose levels.

Time required to normalize blood pressure is another crucial issue to consider keeping or stopping antihypertensive therapy. In the follow-up of our patients we established that 45 out of 53 (84.9%) patients of NBP group normalized blood pressure during the first year after definitive treatment. The remaining 15.1% became normotensive during the second year, showing that HBP normalization may take longer than one year, so adequate long-term follow-up is essential to evaluate the final response.

Ketoconazole may be used in patients with Cushing's syndrome mainly as preparation for surgery, awaiting the results of pituitary irradiation, or in patients who are not candidates for surgical treatment[26]. Our data confirm and extend previous observations from Sonino et al[27] who assessed 21 patients with Cushing's syndrome and HBP treated with ketoconazole, showing that anti-hypertensive medication could be reduced in 13 and discontinued in 7, within 2 weeks. Fallo et al[28] found that KNZ therapy was better than conventional anti-hypertensive therapy to control blood pressure levels in 12 patients with Cushing's syndrome. We found that 13 out of 19 (68.4%) patients who received KNZ therapy before surgery normalized HBP, with no need for other drugs in at least half of them. Time required to normalize blood pressure was shorter in patients who more rapidly normalized 24-UFC levels, and in those with lower 24h-UFC values. Five patients achieved normal values only after surgery but they had been treated with ketoconazole only for short periods, which may explain the different influence of both treatments on HBP.

Interestingly, the effect of successful surgical treatment of Cushing's syndrome on HBP closely correlated with previous response to ketoconazole treatment, which thus appears to be a reliable predictor of the late result of definitive therapy on arterial hypertension.

In conclusion: a) the cure of Cushing's syndrome brought about HBP normalization in 74.6% of our patients in less than 2 years; b) the evolution of blood pressure levels was unrelated to the pituitary or adrenal origin of

cortisol excess; c) age at presentation and preoperative HBP duration seem to affect adversely the normalization of HBP levels after treatment; and d) response of HBP to ketoconazole therapy seems to be a good indicator of late post-surgical blood pressure control.

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