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Treatment of Familial Hyperaldosteronism Type I: Only Partial Suppression of Adrenocorticotropin Required to Correct Hypertension

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ABSTRACT

In familial hyperaldosteronism type I, inheritance of a hybrid 11β-hydroxylase/aldosterone synthase gene leads to ACTH-regulated overproduction of aldosterone (causing hypertension) and of "hybrid" steroids, 18-hydroxy- and 18-oxo-cortisol. To determine whether complete suppression of the hybrid gene is necessary to normalize blood pressure, we sought evidence of persisting expression in eight patients who were rendered normotensive for 1.3–4.5 yr by glucocorticoid treatment. At the time of the study, six patients were receiving dexamethasone (0.125–0.25 mg/day) and two patients were taking prednisolone (2.5 or 5 mg/day). Urinary 18-oxo-cortisol levels during treatment demonstrated close correlation with mean "day curve" (blood collected every 2 h for 24 h) cortisol ($r = 0.74$), consistent with regulation by ACTH. Although urinary 18-oxo-cortisol levels were lower during than before treatment (mean 12.6 ± 2.4 SEM *vs.* 35.0 ± 5.6 nmol/mmol creatinine; $P < 0.01$), they remained above normal (0.8–5.2 nmol/mmol creatinine) in all eight patients. Although mean upright plasma potassium levels during treatment were higher, aldosterone levels lower, PRA levels higher, and aldosterone to PRA ratios lower than before treatment, PRA levels were uncorrected (<13 pmol/L·min) and aldosterone to PRA ratios were uncorrected (>65) during treatment in four patients. For each of the eight patients, day curve aldosterone levels during treatment correlated more tightly with cortisol (mean r for the eight patients, 0.87 ± 0.05 SEM) than with PRA (mean $r = 0.36 \pm 0.10$ SEM). Hence, control of hypertension by glucocorticoid treatment was associated, in all patients, with only partial suppression of ACTH-regulated hybrid steroid and aldosterone production. Normalization of urinary hybrid steroid levels and abolition of ACTH-regulated aldosterone production is not a requisite for hypertension control and, if used as a treatment goal, may unnecessarily increase the risk of Cushingoid side effects. (*J Clin Endocrinol Metab* **85:** 3313–3318, 2000)

FAMILIAL hyperaldosteronism type I (FH-I; glucocorticoid-remediable aldosteronism) is caused by the inheritance of a "hybrid" gene, composed of regulatory sequences derived from the 11β-hydroxylase gene and coding sequences derived from the aldosterone synthase gene (1). Expression of the gene is regulated by ACTH by virtue of its 11β-hydroxylase regulatory sequences, but the gene codes for an enzyme with aldosterone synthase activity, which catalyzes the final steps of aldosterone biosynthesis (1). As a result, aldosterone production in FH-I is regulated by ACTH rather than by angiotensin II (AII), and there is overproduction of aldosterone, which leads to the development of hypertension (2–6).

Whereas expression of the wild-type aldosterone synthase gene is normally confined to zona glomerulosa, *in situ* hybridization analysis in nontumorous adrenal tissue removed from a patient with FH-I has indicated that the hybrid gene is expressed throughout all adrenocortical layers (7). The resulting aberrant expression of aldosterone synthase activity in zona fasciculata, where 11-deoxy-cortisol and cortisol are available as substrates, is thought to explain the excessive, ACTH-regulated production of so-called "hybrid steroids," 18-hydroxy and 18-oxo-cortisol, associated with this condition (1, 8, 9).

In patients with FH-I, treatment with glucocorticoids, by suppressing ACTH, suppresses hybrid gene expression, which results in amelioration of hyperaldosteronism and hypertension (2, 5) and lowering of hybrid steroid levels (10, 11). The aim of the current study was to determine the degree of hybrid gene suppression required and, in particular, to ascertain whether complete suppression of the hybrid gene is necessary to normalize blood pressure in the medium- to long-term management of patients with FH-I. To do this, we sought evidence of persisting hybrid gene expression among patients who had been rendered normotensive for at least 1 yr by glucocorticoid treatment.

Subjects and Methods

Diagnosis of FH-I and clinical characteristics of study subjects (Table 1)

The study involved eight hypertensive patients (three females and five males; mean age, 38.0 ± 5.9 yr SEM; range, 14–60) with FH-I. All patients provided informed consent to their undergoing the studies described here. In all subjects, the diagnosis of FH-I was confirmed by demonstrating the presence of the hybrid gene in peripheral blood leucocyte DNA by a "long-PCR"-based method (12).

At the time of the baseline study, before commencing glucocorticoid treatment, three patients were receiving medication (patient 5, enalapril and felodipine; patient 6, lisinopril, felodipine, and labetolol; and patient 8, slow-release verapamil and hydralazine) as treatment for previously documented hypertension. Blood pressure levels on these medications were 172/105, 140/100, and 162/112, respectively. Antihypertensive

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TABLE 1. Clinical, treatment, and echocardiographic characteristics of eight subjects with FH-I rendered normotensive by glucocorticoid treatment

Patient number	Sex	Age HT detected (yr)	Age FH-I diagnosed (yr)	Yr on GC	Current GC type and dose	Yr on this GC dose	LVMI on GC (g/mm^2)
1	M	27	42	3.8	Dex 0.25 mg/day	2.3	65.2
2	F	24	51	1.3	Dex 0.125 mg/day	0.6	83.9
3	M	14	14	1.3	Dex 0.25 mg/day	0.5	81.9
4	F	13	60	1.8	Pred 5 mg/day	0.9	77.1
5	M	13	45	4.5	Dex 0.25 mg/day	3.8	106.2
6	M	11	45	1.5	Dex 0.25 mg/day	0.8	93.4
7	F	14	14	3.5	Pred 2.5 mg/day	2.1	62.7
8	M	17	33	3.8	Dex 0.25 mg/day	1.5	81.8
Mean ± SEM		16.6 ± 2.0	38.0 ± 5.9	2.7 ± 0.5		1.6 ± 0.4	81.5 ± 5.0

HT, Hypertension; GC, glucocorticoid treatment; Dex, dexamethasone; Pred, prednisolone.

medications had been withheld in three others (patient 1, metoprolol and hydrochlorothiazide/triamterene; and patients 2 and 4, hydrochlorothiazide/amiloride) for 1–8 weeks before the baseline study, by which time their blood pressures were 140/96, 162/104, and 156/100, respectively. The two remaining patients (patients 3 and 7, both aged 14 yr) had only recently been found to be hypertensive (blood pressures 186/90 and 150/100, respectively) and had not yet been commenced on antihypertensive treatment. The mean age at detection of hypertension was 16.6 ± 2.0 yr (range, 11–27). Patients were referred, diagnosed as having FH-I, and commenced on glucocorticoid treatment after an interval of 0.13–47 yr following detection of hypertension. During this interval, the maximum number of antihypertensive medications that each patient was known to have been prescribed at any one time ranged from zero to four (mean, 1.5 ± 0.5 medications). Among the five subjects (patients 2, 3, 6, 7, and 8) for whom it was possible to obtain information regarding blood pressure levels before commencement of any form of antihypertensive medication, systolic blood pressures ranged from 150–250 mm Hg (mean, 195 ± 21 mm Hg) and diastolic readings ranged from 92–140 mm Hg (mean 110 ± 9 mm Hg). One 60-yr-old female patient (patient 4) had suffered three separate cerebrovascular accidents (at ages 32, 35, and 60 yr) before referral.

At the time of re-study, during glucocorticoid treatment, six patients were receiving dexamethasone in doses of either 0.125 or 0.25 mg/day, and two were taking prednisolone in doses of either 2.5 or 5 mg/day. Treatment was administrated either in single (morning or evening) or twice daily doses. Patients had been receiving their current dose of glucocorticoid medication continuously for periods ranging from 0.5–3.8 yr (mean, 1.6 ± 0.4), having previously been on higher doses (dexamethasone, 0.25 -0.75 mg/day). In total, subjects had received continuous glucocorticoid treatment for periods ranging from 1.3–4.5 yr (mean, 2.5 ± 0.4 yr). All had been rendered normotensive, without the need for additional antihypertensive medication, within 2 months of commencement of glucocorticoids, and had remained normotensive up until the time of re-study, with blood pressures consistently within the normal range for age and sex (13), when measured by medical or nursing staff within the Hypertension Unit using a mercury sphygmomanometer and by the patients themselves using a validated home blood pressure device. All demonstrated normal systolic left ventricular function and a normal left ventricular mass index (LVMI) when measured by echocardiography within 2 months of the re-study period, with LVMI values ranging from 65.2–106.2 g/m^2 among the five males and from 62.7–83.9 g/m^2 among the three females [upper limit of normal range 134 g/m^2 for men and 110 g/m^2 for women (14)]. These LVMI values were either lower (five subjects) or only slightly higher (one subject; 62.7 *vs.* 60.4 g/mm^2) than those measured 0.8–3.5 yr before the current study in the six subjects who had undergone previous echocardiographic examination by a similar technique while receiving glucocorticoid treatment. In each of the four subjects (patients 2, 3, 4, and 5) who had undergone echocardiography before commencement of glucocorticoid treatment, LVMI values had fallen by the time of the restudy period (in the two male patients, from 94.3 to 81.9 g/m^2 and from 112.0 to 106.2 g/m^2, respectively; in the two female patients, from 95.2 to 83.9 g/m^2 and from 116.4 to 77.1 g/m^2, respectively). In all cases, echocardiography was performed according to a strict protocol by either one of only two selected technicians skilled in LVMI measurement, and results were analyzed according to a strict protocol by either one of only two cardiologists with a particular expertise in this technique.

Biochemical studies

In all subjects, both before and during glucocorticoid treatment, levels of plasma potassium, plasma aldosterone, PRA, and aldosterone to PRA ratios were measured in blood collected without stasis at 1000 h after 2–4 h of upright posture, and levels of 18-oxo-cortisol (corrected for creatinine excretion) were measured in a 24-h urine collection.

Hormone "day-curve" studies were performed on the same day as the above studies on three patients before and on all eight subjects during glucocorticoid treatment. For each day-curve study, a cannula was inserted into a forearm vein in the cubital fossa for blood sampling. Blood (15 mL) was collected every 2-h for 24 h from 1000 h to 1000 h for measurement of plasma aldosterone, PRA, potassium, and plasma cortisol. Posture was unrestricted until midnight, after which subjects remained recumbent until 0800 h and then assumed an upright posture until the completion of the day-curve at 1000 h. A day-curve study was also performed on a 45-yr-old female with "essential" hypertension on no regular medications, and results are presented for comparison. In this latter individual, despite an extensive diagnostic workup (including renal isotope scanning, renal artery duplex ultrasonography, plasma aldosterone to PRA ratio testing, measurement of 24-h urinary catecholamine levels, and analysis of circadian plasma cortisol levels), no cause for the hypertension was found.

Assays

Plasma aldosterone was measured by RIA (Coat-A-Count ^{125}I-Aldosterone RIA Kit; Diagnostic Products, Los Angeles, CA), in a modification of the method of Mayes *et al.* (15), with intra- and interassay coefficients of variation of 4.0% and 6.0%, respectively, and a lower detection limit of 69 pmol/L. PRA was measured by RIA (Gamma Coat [^{125}I] Plasma Renin Activity RIA Kit; INCSTAR Corp., Stillwater, MN) of generated angiotensin I in a modification of the method of Haber *et al.* (16), with intra- and interassay coefficients of variation of 4.3% and 7.2%, respectively, and a lower detection limit of 1.3 pmol/L·min. Plasma cortisol was measured either by RIA (Quanticoat ^{125}I-Cortisol RIA Kit; Kallestad Diagnostics, Chaska, MN; intra- and interassay coefficients of variation; 4.5% and 9.6%, respectively; lower detection limit, 28 nmol/L) or by fluorescence polarization immunoassay (TDX Cortisol FPIA Kit; Abbott Laboratories, Abbott Park, IL; intra- and interassay coefficients of variation ,4.4% and 2.6%, respectively; lower limit of detection, 35 nmol/L). Urinary 18-oxo-cortisol levels were determined by RIA, using a method described previously (9).

Data analysis

Group data are presented as mean ± SEM, unless otherwise indicated. Wilcoxon's matched pairs test was used to compare data obtained prior with those obtained during glucocorticoid treatment. For each day-curve study, Spearman rank correlation coefficients were determined for correlations between aldosterone and cortisol levels as a reflection of ACTH-dominated aldosterone regulation, and between aldosterone and

PRA levels as a reflection of AII-dominated regulation of aldosterone. Correlations were also sought within the group between urinary 18-oxo-cortisol levels, measured during glucocorticoid treatment, and mean day-curve levels of plasma cortisol, plasma aldosterone or PRA (collected in each patient on the same day as the urine collection), as a means of seeking evidence for regulation of 18-oxo-cortisol production by either ACTH and/or AII.

Results

Plasma potassium, plasma aldosterone, PRA, and aldosterone to PRA ratio results are shown in Table 2. Plasma potassium levels rose in response to treatment (from 3.6 ± 0.2 to 4.0 ± 0.1 mmol/L, $P < 0.05$) in all patients, and the three patients who were hypokalemic (plasma potassium, <3.5 mmol/L) before treatment were rendered normokalemic. Upright plasma aldosterone levels were all within the wide normal range (140 -1100 pmol/L) before commencement of glucocorticoid treatment and fell in all patients, except one, in response to treatment, with mean levels for the group falling significantly (from 480 ± 38 to 260 ± 41 pmol/L, $P < 0.05$).

Before treatment, PRA levels were suppressed (<13 pmol/L·min) in all patients, except one. Levels rose in response to treatment in six of the eight patients, with mean levels for the group rising significantly (from 4.0 ± 1.6 to 11.1 ± 3.1 pmol/L.min, $P < 0.05$). Aldosterone to renin ratios, elevated above the normal range (11–65) in all patients, except two, before treatment, fell in seven patients, with mean levels for the group falling from 236 ± 58 to 58 ± 20 ($P < 0.05$). However, in four patients, PRA levels remained suppressed and aldosterone to PRA ratios remained elevated during treatment, despite normalization of blood pressure levels.

In all patients, 24-h urinary 18-oxo-cortisol levels were elevated (>5.2 nmol/mmol creatinine) before treatment and fell in response to treatment (from 35.0 ± 5.6 to 12.6 ± 2.4 nmol/mmol creatinine, $P < 0.05$, Table 3). However, levels remained above normal in all patients during glucocorticoid treatment, despite normalization of blood pressure levels.

Among this group of patients, when studied during glucocorticoid treatment, urinary 18-oxo-cortisol levels demonstrated a significant correlation ($r = 0.74$, $P < 0.05$) with mean day-curve plasma cortisol levels. The correlation coefficient for urinary 18-oxo-cortisol *vs.* mean day-curve plasma aldosterone levels was lower and did not reach statistical significance [$r = 0.55$, not significant (NS)]. There was no demonstrable correlation between urinary 18-oxo-cortisol levels with mean day-curve PRA levels in this group of treated patients ($r = -0.12$, NS).

The three patients (patients 2, 3, and 4) who underwent day-curve studies before commencement of glucocorticoid treatment demonstrated tight correlation of day-curve plasma aldosterone with cortisol levels ($r = 0.69$, $P < 0.01$; $r = 0.99$, $P < 0.001$; and $r = -0.97$, $P < 0.001$) but not with PRA levels ($r = 0.11$, -0.02 and 0.39, respectively, all NS). All eight patients underwent day-curve studies during glucocorticoid treatment (Table 3). In each case, plasma aldosterone levels showed closer correlation with cortisol levels ($r = 0.87 \pm 0.05$) than with PRA levels ($r = 0.36 \pm 0.10$). Seven of the eight r values for aldosterone *vs.* cortisol were statistically significant ($P < 0.001$ in each case), compared with only three for PRA ($P < 0.05$ in two cases and $P < 0.01$ in one case). By contrast, a 45-yr-old female patient with essential hypertension demonstrated significant correlations between plasma aldosterone and both PRA ($r = 0.83$, $P < 0.001$) and cortisol ($r = 0.71$, $P < 0.01$) levels, with the correlation coefficient for aldosterone *vs.* PRA being higher than that for aldosterone *vs.* cortisol.

Discussion

To our knowledge, long-term follow-up studies designed to assess the optimum dose of glucocorticoids in patients with FH-I, and the degree of hybrid gene suppression necessary to maintain long-term hypertension control, have not been previously reported. In recently published reviews, dexamethasone doses in the order of 0.5–2.0 mg daily have been recommended for the treatment of hypertension due to FH-I (17–19). We have previously reported that long-term treatment with dexamethasone in doses as low as 0.5 and 0.75 mg daily are sufficient in some patients to cause marked, continuous suppression of ACTH (20). This was presumably associated with complete suppression of hybrid gene-induced aldosterone production because PRA levels in these

TABLE 2. Levels of plasma potassium, plasma aldosterone, PRA, and aldosterone/PRA ratios, before and after commencement of glucocorticoids, in patients with FH-I rendered normotensive by glucocorticoid treatment

Patient number	Plasma potassium (mmol/L) (3.5–5.0)[a]		Plasma aldosterone (pmol/L) (140–1100)[a]		PRA (pmol/L · min) (13–50)[a]		Aldosterone/PRA ratio (11–65)[a]	
	Pre GC	On GC	Pre GC	On GC	Pre GC	On GC	Pre GC	On GC
1	4.2	4.3	555	155	1.3	1.3	431.4	120.8
2	2.7	3.6	594	386	1.3	5.1	461.6	75.0
3	3.5	3.7	361	208	2.6	1.3	140.2	161.8
4	3.4	3.8	613	194	14.1	16.7	43.3	11.6
5	4.3	4.5	463	469	1.3	21.9	360.2	21.4
6	3.9	4.2	519	133	3.9	15.4	134.5	8.6
7	3.5	3.8	327	255	1.3	5.1	254.5	49.6
8	3.1	3.7	408	277	6.4	21.9	63.4	12.7
Mean ± SEM	3.6 ± 0.2	4.0 ± 0.1	480 ± 38	260 ± 41	4.0 ± 1.6	11.1 ± 3.1	236.2 ± 58.4	57.7 ± 20.3
P value[b]	<0.05		<0.05		<0.05		<0.05	

GC, Glucocorticoid treatment; Pre GC, prior to commencement of GC; On GC, after at least 1 yr on GC.
All levels were measured in blood collected at 1000 h after at least 2 h or upright posture.
[a] Figures in parentheses indicate normal ranges.
[b] P value for comparison of Pre GC and On GC means.

TABLE 3. Urinary 18-oxo-cortisol levels before and after commencement of glucocorticoids and results of plasma hormone day-curve studies during treatment, in patients with FH-I rendered normotensive by glucocorticoid treatment

Patient number	Urinary 18-oxo-cortisol (nmol/mmol creatinine) (0.8–5.2)[a]		Aldo, PRA and cortisol day curve studies during GC[b]						
	Pre GC	On GC	Mean aldo (pmol/L)	Mean PRA (pmol/L·min)	Mean cortisol (nmol/L)	Aldo *vs.* cortisol		Aldo *vs.* PRA	
						r	P[c]	r	P[c]
1	33.1	16.4	319	3.5	163	0.88	<0.001	0.60	<0.05
2	39.2	11.4	479	2.8	238	0.89	<0.001	0.06	NS
3	39.5	8.2	182	3.6	73	0.95	<0.001	−0.06	NS
4	24.4	9.2	309	22.0	116	0.49	NS	0.32	NS
5	44.7	12.9	426	14.9	149	0.97	<0.001	0.25	NS
6	17.6	5.3	371	16.6	92	0.90	<0.001	0.74	<0.01
7	16.6	10.2	331	4.5	110	0.95	<0.001	0.62	<0.05
8	64.5	27.5	509	20.8	137	0.89	<0.001	0.37	NS
Mean ± SEM	35.0 ± 5.6	12.6 ± 2.4	366 ± 37	11.1 ± 2.9	135 ± 18	0.87 ± 0.05		0.36 ± 0.10	
P value[d]	<0.05					<0.05			

GC, Glucocorticoid treatment; Pre GC, before commencement of GC; On GC, after at least one year on GC; NS, not significant.

[a] Normal range shown in *parentheses*.

[b] For the day-curve studies, blood sampling was performed every 2 h for 24 h from 1000 h to 1000 h. Mean levels of plasma aldosterone (Aldo), PRA and plasma cortisol, and the correlation coefficients (r) for Aldo *vs.* PRA levels and for Aldo *vs.* cortisol levels, were determined for each day-curve study.

[c] P value corresponding to each r value.

[d] P value for comparison between mean Pre GC and On GC urinary 18-oxo-cortisol levels, and between mean Aldo *vs.* cortisol and Aldo *vs.* PRA correlation coefficients.

patients were in the high normal or frankly elevated range, and circadian plasma aldosterone levels usually demonstrated tight correlation with PRA but not cortisol levels, consistent with the AII-regulated wild-type aldosterone synthase genes dominating over the suppressed ACTH-regulated hybrid gene in terms of aldosterone production. This was in contrast to findings in untreated patients or patients on lower doses of glucocorticoids causing only partial ACTH suppression, in which aldosterone levels usually correlated tightly with cortisol but not PRA levels, suggesting dominance of the hybrid gene over the wild-type genes (20). These observations suggest that currently recommended glucocorticoid doses would be likely, in most patients, to cause complete suppression of ACTH and hybrid gene expression. Whereas an argument exists for attempting complete suppression of abnormally regulated aldosterone production in patients with FH-I (see below), this approach would also be expected to render patients at significant risk of Cushingoid side effects. Indeed, occasional reports (21) of glucocorticoid-induced side effects in treated patients have caused some investigators to express caution in the use of glucocorticoids (22, 23) and, in the case of affected children, to favor the use of other agents (such as amiloride) to avoid the growth-retarding effects of glucocorticoid treatment in this age group (24).

In the current study of eight patients with genetically proven FH-I, glucocorticoid doses of 0.125–0.25 mg dexamethasone daily or 2.5–5 mg prednisolone daily were sufficient to maintain normal blood pressure throughout 0.5–3.8 yr of follow-up without the need for additional antihypertensive medication. Adequacy of hypertension control was supported by the demonstration of normal and stable (or falling) LVMI values on echocardiography.

Glucocorticoid treatment was associated with significant rises in mean plasma potassium and PRA levels and significant falls in mean plasma aldosterone, aldosterone to PRA ratio (Table 2), and urinary 18-oxo-cortisol levels (Table 3), suggesting that hybrid gene expression was, at least partially, suppressed by treatment at these doses. Despite being normotensive, however, four of the eight patients demonstrated persisting biochemical evidence of primary aldosteronism, with PRA levels that were suppressed below the normal range and aldosterone to PRA ratios that were elevated, consistent with continuing expression of the hybrid gene. None were receiving concomitant β-adrenergic blocking medications to explain these biochemical findings. The coexistence of a second form of primary aldosteronism in these patients, while not able be excluded with certainty from our results, would be very unlikely.

The demonstration in the current study of a significant correlation of urinary 18-oxo-cortisol levels with mean day-curve plasma cortisol levels during treatment is consistent with these steroids being ACTH regulated, as has been reported previously (25). We have previously shown that when patients with FH-I are given dexamethasone in a sufficient dose (0.5 mg 6 hourly) to cause complete suppression of ACTH, urinary levels of 18-oxo-cortisol suppress to within the normal range during 4 days of glucocorticoid administration (11). In the current study, 18-oxo-cortisol levels during treatment with lower doses of glucocorticoids were elevated in every patient, providing further evidence that ACTH production and hybrid gene expression were not completely suppressed in these patients, despite the fact that they had been rendered normotensive.

During treatment, whereas seven of the eight patients demonstrated statistically significant correlations between day-curve aldosterone and cortisol levels, only two patients showed significant correlations between aldosterone and PRA levels. In all patients, day-curve plasma aldosterone levels demonstrated tighter correlation with cortisol than with PRA levels, suggesting dominance of the hybrid gene over the wild-type genes in terms of aldosterone production.

By contrast, in a day-curve study performed on a single subject with essential hypertension, circadian aldosterone levels correlated significantly with both PRA and cortisol levels, but demonstrated tighter correlation with PRA than with cortisol. In keeping with these latter findings, expression of the wild-type aldosterone synthase gene has been shown *in vitro* to be sensitive to both AII and ACTH, but with greater sensitivity to AII than to ACTH (26).

Several groups of investigators have reported that in untreated FH-I the severity of hypertension varies markedly from one individual to another (27–29). Some affected individuals have remained normotensive well into adulthood (30). These observations, and those of the current study, lead us to propose that the degree of hybrid gene suppression required to render hypertensive subjects normotensive will, likewise, vary from individual to individual and will be dependent on interactions with environment and other genetic factors.

Mounting evidence suggests that aldosterone may have direct effects on the myocardium and vasculature, independent of its effect on blood pressure. Excessive levels of aldosterone, in the presence of salt, are thought to promote cardiac and vascular hypertrophy, remodeling and fibrosis, and to thereby contribute to the development of diastolic ventricular dysfunction in primary aldosteronism and to the pathophysiology of congestive cardiac failure (31–33). These deleterious effects can be ameliorated by spironolactone and do not seem to involve hemodynamic factors (34, 35). It could be debated, therefore, that the goal of treatment in FH-I should be to suppress all excessive aldosterone production and not just that proportion required to maintain blood pressure levels in the elevated range. Although the absence of left ventricular hypertrophy or evidence of cardiac dysfunction on echocardiography in all of our eight treated patients would tend to argue against this view, we nevertheless intend to follow such individuals over a much longer period, with carefully performed serial measurements of cardiac and vascular morphology and function, to more fully address this issue.

Because all of the study subjects demonstrated satisfactory hypertension control, it was possible to examine the clinical use of certain biochemical parameters in terms of their ability to guide the selection of appropriate glucocorticoid doses in patients with FH-I. Although the measurement of isolated, timed (for example, mid-morning) plasma cortisol levels would seem an ideal candidate for this purpose, a meaningful comparison of levels among subjects in the current study was not possible because of nonuniformity of glucocorticoid dosing regimens (which included morning only, evening only, or twice daily glucocorticoid administration). Analysis of mean day-curve cortisol levels would help to address this issue, but would be more difficult to achieve in clinical practice. A more practical approach might be to measure 24-h urinary-free cortisol levels. Although this was not undertaken in the current study, the reasonable uniformity (a 3-fold range) of mean day-curve plasma cortisol levels among our subjects does raise the possibility that an optimal "therapeutic window" for 24-h urinary cortisol levels might be definable. In none of our treated normotensive subjects were upright PRA levels elevated above the upper end of the normal range or urinary 18-oxo-cortisol levels lowered to within the normal range, and none demonstrated tighter correlation of day-curve plasma aldosterone with PRA rather than cortisol levels [unlike in subjects receiving higher doses of glucocorticoids (11, 36)]. Avoidance of these potential outcomes of glucocorticoid treatment, therefore, may help to prevent overtreatment in individuals with FH-I.

Based on the findings of the current study for adults with FH-I, we propose commencement of treatment with dexamethasone at a dose of 0.125 mg daily or prednisolone at 2.5 mg daily. Our usual practice is to advise once daily, evening dosing to most effectively cover the morning period when ACTH production normally peaks, and thereby optimize efficiency of hybrid gene suppression induced by treatment. The maintenance treatment dose (which in most cases would not be expected to exceed 0.25 mg dexamethasone or 5 mg prednisolone daily) should be the minimum required to maintain normotension and a normal LVMI on echocardiography. Frank elevation of PRA levels or normalization of urinary 18-oxo-cortisol levels (where assays for this hormone are available) may indicate the need to reduce treatment. As a further guard against the risk of Cushingoid side effects, we perform periodic day-curve studies to assess the relative status of ACTH- and AII-regulated aldosterone production and measurement of bone mineral density by dual-energy x-ray absorptiometry on all patients receiving glucocorticoid treatment.

Although the risk of adverse glucocorticoid side effects would be small at the doses recommended above, an argument exists for avoiding glucocorticoids altogether and opting instead for treatment with aldosterone antagonists such as spironolactone or amiloride. These latter agents are not without their own problems, however. Injudicious use may result in hyperkalemia, which may reach dangerous levels, particularly in patients with compromised renal function. The use of spironolactone may result in gynecomastia and menstrual irregularities and should be avoided during the period of sexual maturation in children because of its antagonist action on sex steroid receptors. Therapeutic trials involving the administration of eplerenone, a new, more selective aldosterone receptor antagonist, in children with FH-I are currently being conducted to address this issue.

In conclusion, in the current study of eight patients with FH-I, satisfactory control of hypertension by glucocorticoid treatment was associated, in all patients, with only partial suppression of ACTH-regulated hybrid steroid and aldosterone production. These findings suggest that normalization of urinary hybrid steroid levels and abolition of ACTH-regulated aldosterone production is not required for hypertension control and, if used as a treatment goal, may unnecessarily increase the risk of Cushingoid side effects.

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