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Abstract—Primary aldosteronism is a specifically treatable and potentially curable form of secondary hypertension. The aldosterone/plasma renin activity ratio (ARR) is routinely used as a screening test. Antihypertensive therapy can interfere with the interpretation of this parameter, but a correct washout period can be potentially harmful. We have investigated the effects of therapy with atenolol, amlodipine, doxazosin, fosinopril, and irbesartan on the ARR in a group of 230 patients with suspected primary aldosteronism. The percent change from control of ARR in patients taking amlodipine was −17%±32; atenolol, 62%±82; doxazosin, −5%±26; fosinopril, −30%±24; and irbesartan, −43%±27. The ARR change induced by atenolol was significantly higher compared with that induced by all other drugs ($P<0.0001$), and the ARR change induced by irbesartan was significantly lower than that induced by doxazosin ($P<0.0001$). One of 55 patients from the group taking amlodipine (1.8%) and 4/17 of the patients taking irbesartan (23.5%) gave a false-negative ARR (<50). None of the patients of the groups taking fosinopril, doxazosin, and atenolol displayed a false-negative ARR. Doxazosin and fosinopril can be used in hypertensive patients who need to undergo aldosterone and PRA measurement for the diagnosis of primary aldosteronism; amlodipine gave a very small percentage of false-negative diagnoses. β-Blockers also do not interfere with the diagnosis of primary aldosteronism, but they can be responsible for an increased rate of false-positive ARRs. The high rate of false-negative diagnoses in patients undergoing irbesartan treatment requires confirmation in a higher number of patients. **(*Hypertension*. 2002;40:897-902.)**

Key Words: aldosterone ■ renin ■ antihypertensive therapy ■ plasma

Primary aldosteronism (PA) is a common form of endocrine hypertension, characterized by inappropriate production of aldosterone in the absence of activation of the renin-angiotensin cascade. Recent studies have reported a much higher prevalence of this disease than that previously accepted when it was believed that (1) PA accounted for <1% of hypertensive patients and (2) hypokalemia was necessary to start the investigation for the diagnosis of PA.[1,2] However, increasing evidence indicates that the prevalence could be up to 12% of hypertensive patients, with most of the PA patients being normokalaemic.[3–7] Therefore, PA could be the most common identifiable, specifically treatable, and potentially curable form of hypertension, and the diagnostic work-up to identify PA will be increasingly used by physicians.

Because of the demonstration that the plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio (ARR) is the most reliable method of screening for PA,[8] this test became widely used in hypertensive clinics.[8–11] PAC and the PRA measurements must be performed in patients in washout from all hypertensive drugs to avoid false-positive and false-negative results. In particular, β-blockers and clonidine can raise the ARR by decreasing, to a greater extent, the PRA compared with the PAC.[12–14] Conversely, diuretics (including spironolactone), ACE inhibitors (ACE-Is), dihydropyridine calcium channel blockers (CCBs), and angiotensin II receptor blockers (ARBs) tend to reduce ARR.[9,15–18] Few data are available on α-blockers; however, both prazosin and doxazosin do not appear to have a significant effect on ARR.[19–21] In fact, it is commonly believed that doxazosin has no effect on ARR.[9,10] Because PA often causes severe hypertension, it is potentially harmful to stop all medication for the 3 weeks necessary for a correct washout period. To date, few studies have been performed to evaluate the effect of different drug therapies on the screening test for PA: Gallay et al[22] published recently a prospective study in which the ARR was evaluated in a group of 90 patients with poorly controlled hypertension without discontinuation of the therapy. This study described 15 patients with the ARR >100 (aldosterone expressed in nanograms per deciliter and PRA in nanograms per milliliter per hour), all of which were confirmed as having PA; this demonstrates that an ARR cutoff of 100 is highly specific, even with multidrug therapies, but does not provide information on the sensitivity

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and specificity of the more widely used ARR cutoff (between 20 and 50) during drug therapy.

The role of single antihypertensive agents in modifying the ARR, and thus in interfering with the screening of PA, has never been investigated in a large group of patients. The ARR performed during the washout period is considered the gold-standard screening test, but it is often not possible to withdraw all medication in a patient with severe hypertension who is taking ≥3 classes of drugs.

To evaluate if antihypertensive therapy could interfere with the diagnosis of PA—in particular by reducing the sensitivity of the most common screening test, the ARR—in the present study, we investigated the effect of single-drug therapy on the ARR compared with the same parameter measured after a 1-month washout period. In particular, we evaluated the effect of an ACE-I (fosinopril), ARB (irbesartan), dihydropiridine CCB (amlodipine), β-blocker (atenolol), and α-blocker (doxazosin) on the ARR in a population of hypertensive patients referred to our unit.

Methods

Selection of the Patients

This study was approved by a local ethics review committee, and all subjects gave informed consent.

Patients were recruited from a group of 6967 patients referred to our Hypertension Unit between 1995 and 2001. We usually perform a washout period of 3 to 4 weeks in all patients for whom it is possible, to allow us to perform a correct screening of secondary hypertension without the confounding interference of antihypertensive therapy. Severe hypertensives taking ≥3 classes of drugs were excluded from the study because it could be harmful to perform a correct washout period; 2160 hypertensives were then included in this study (Figure 1).

After 1 month of washout from all previous therapies, samples of blood were taken to measure PRA and PAC in the upright position between 8:00 and 10:00AM. Patients with an ARR >50 and aldosterone >15 ng/dL were randomized into 4 groups according to the type of therapy with a single antihypertensive drug (fosinopril, 20 mg/day; atenolol, 100 mg/day; doxazosin, 8 mg/day; and amlodipine, 10 mg/day); after August 1998, a fifth group of patients taking irbesartan (300 mg/day) was included. Each drug was prescribed for at least 2 months. The ARR cutoff of 50 is used in our unit for PA screening, because we found in a previous study that in our hands, this ratio is associated with 100% sensitivity and high specificity (90%).[23]

Patients with serum potassium levels <3.6 mmol/L repeated the ARR after correction of the hypokalemia. The 230 patients with ARR >50 at the end of the washout period were considered in the final analysis: all of them underwent an intravenous saline load (2 L of 0.9% NaCl infused in 4 hours) as a confirmatory test for the diagnosis of PA, which was confirmed in 154 patients.[11,24]

A CT scan and/or adrenal venous sampling were performed to differentiate between PA owing to aldosterone-producing adenoma and PA owing to bilateral adrenal hyperplasia, resulting in 35 aldosterone-producing adenoma and 119 bilateral adrenal hyperplasia; however, because only some of the patients (65%) underwent adrenal venous sampling, the proportion of the 2 subgroups of patients with PA could be different, owing to an underestimation of aldosterone-producing adenoma by the CT scan.[25]

Biochemical Measurements

PRA and PAC were measured as previously described.[26] Briefly, PAC and PRA were determined by radioimmunoassay with kits purchased from Sorin Biomedical Diagnostics. The measurement of PRA was based on the radioimmunoassay quantification of angiotensin I enzymatically generated by renin from its substrate angiotensinogen. The PRA samples were incubated for 90 minutes for angiotensin I generation. The intra- and interassay coefficients of variation (CVs) for PRA were 5.4% and 9.1%, respectively; the normal range is 0.4 to 3.0 ng/mL per hour supine and 1.5 to 6.0 ng/mL per hour upright. The intra- and interassay CVs for aldosterone were 7.9% and 9.6%, respectively; the normal range is 2 to 12 ng/dL supine and 5 to 30 ng/dL upright.

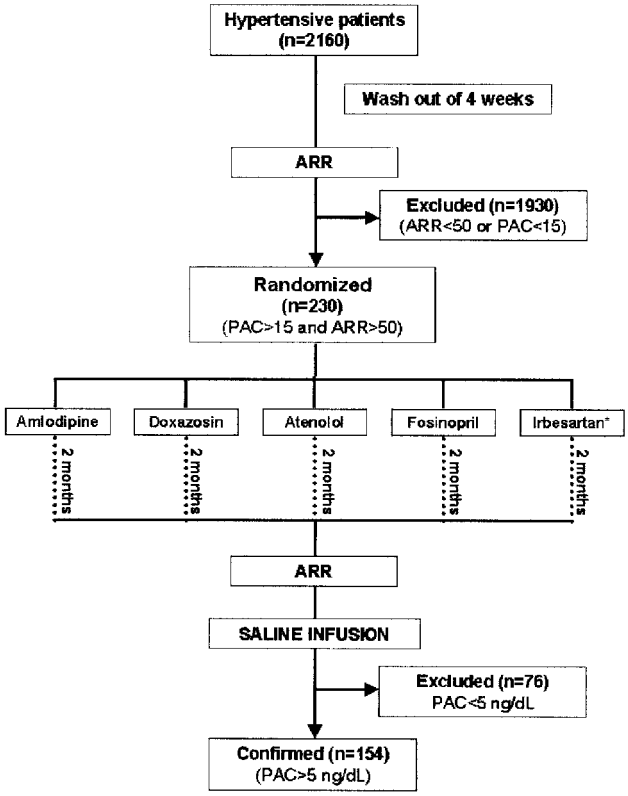

Figure 1. Design of the study. *Irbesartan was introduced into the randomization 3 years after the beginning of the study.

Long polymerase chain reaction for the chimeric gene was performed as described previously[27] in all patients with PA to exclude the possibility of glucocorticoid-remediable aldosteronism.

Statistical Analysis

Data are expressed as mean±SD. ANOVA and Bonferroni post-hoc test for multiple comparisons were performed to estimate differences between groups. A paired *t* test was performed to check for any differences between placebo and posttreatment period. All parameters that were not normally distributed were tested with a Wilcoxon test. A value of $P<0.05$ was considered statistically significant.

Results

Two hundred thirty patients of the 2160 recruited (10.6%) displayed an ARR after the washout period >50; among them, 154 (7%) had a confirmed PA and 76 were essential hypertensives (Figure 1). Twenty-eight patients (18%) had plasma potassium levels <3.6 mmol/L. During the single drug therapy period, 55 patients were taking amlodipine, 55 doxazosin, 51 atenolol, 52 fosinopril, and 17 irbesartan. The clinical and biochemical parameters of these patients are summarized in Tables 1 and 2. The groups of patients did not differ for any of the evaluated parameters after the washout period; the different therapy groups all showed a significant reduction in the systolic and diastolic blood pressure levels after therapy compared with

TABLE 1. Clinical and Biochemical Characteristics of the 230 Patients Included in the Study

Parameters	Amlodipine (n=55)	Doxazosin (n=55)	Atenolol (n=51)	Fosinopril (n=52)	Irbesartan (n=17)
s-K^+, mEq/L	3.98±0.5	4.01±0.6	4.04±0.5	4.02±0.4	3.99±0.5
BMI, kg/m^2	26.4±2.9	25.8±2.8	26.2±2.6	25.9±3.1	26.1±2.7
Age, y	55.5±7.6	56.3±7.3	54.9±6.9	56.1±7.1	55.8±7.2
Washout					
SBP, mm Hg	172±18	169±16	170±19	164±15	172±17
DBP, mm Hg	105±8	105±9	104±8	102±6	102±9
Therapy					
SBP, mm Hg	152±11*†	157±13†	160±17†	154±13†	157±14†
DBP, mm Hg	96±8†	99±8†	99±7†	96±7†	96±9†

Values are mean±SD. The groups of patients did not differ for any of the evaluated parameters after the washout period. s-K^+ indicates serum potassium levels; BMI, body mass index; SBP, systolic blood pressure; DBP diastolic blood pressure; washout, after 4 weeks washout from previous therapy; and therapy, after 2 months of single-drug therapy.

*SBP after amlodipine was significantly lower than SBP after atenolol (P=0.03).

†SBP and DBP levels after therapy were significantly lower compared with levels at the washout (P<0.001).

the washout (P<0.001). No differences in blood pressure reduction were observed among the different groups except for a bigger reduction of the systolic blood pressure in the amlodipine group compared with the atenolol group (P=0.03).

TABLE 2. Hormonal Parameters Before and After Therapy

Drugs/Parameters	Washout	After Therapy	P
Fosinopril			
ARR	176.2±92	121.7±65.2	<0.0001
PRA	0.2±0.09	0.29±0.2	0.0016
PAC	31.2±12.9	26.4±13.2	<0.0001
Δ% ARR		−30±24	
Atenolol			
ARR	179.1±138.3	249.4±152.9	<0.0001
PRA	0.23±0.09	0.13±0.08	<0.0001
PAC	33.3±13.7	28.3±14.9	<0.0001
Δ% ARR		62±82	
Doxazosin			
ARR	142.0±86.9	132.7±86.9	0.03
PRA	0.23±0.08	0.3±0.5	0.21
PAC	27.8±9.9	26.5±11.6	0.01
Δ% ARR		−5±26	
Amlodipine			
ARR	173.9±113.4	134.5±86.2	0.0002
PRA	0.2±0.1	0.23±0.1	0.02
PAC	29.2±11.7	24.9±9.7	<0.0001
Δ% ARR		−17±32	
Irbesartan			
ARR	167.2±87	104.5±84.7	0.0001
PRA	0.18±0.08	0.26±0.16	0.016
PAC	27.3±16.9	23.0±17.5	0.0036
Δ% ARR		−43±27	

Values are mean±SD.

Δ% ARR indicates percentage change from control of ARR after therapy.

Fosinopril induced a statistically significant increase of PRA (P=0.0016) and a decrease of PAC and ARR (P<0.0001 for both parameters) (Table 2); atenolol induced a statistically significant decrease of PRA and PAC and an increase of ARR (P<0.0001 for all parameters); and doxazosin did not induce modification of PRA and induced a significant decrease of PAC and ARR (P=0.01 and P=0.03, respectively). Amlodipine induced an increase of PRA (P=0.02) and a significant decrease of PAC and ARR (P<0.001). Finally, irbesartan induced an increase of PRA (P=0.016) and a reduction of PAC (P=0.0036), resulting in a significant reduction of ARR (P=0.0001) (Table 2).

The percent change from control of the ARR in patients taking amlodipine was −16.98%±32.3; in patients taking atenolol, 62%±82; in patients taking doxazosin, −5%±26; in patients taking fosinopril, −30%±24; and in patients taking irbesartan, −43%±27 (Table 2 and Figure 2). The ARR change induced by atenolol was significantly different from that induced by all the other drugs (P<0.0001). Furthermore, the ARR change induced by irbesartan was significantly different from that induced by doxazosin (P<0.0001).

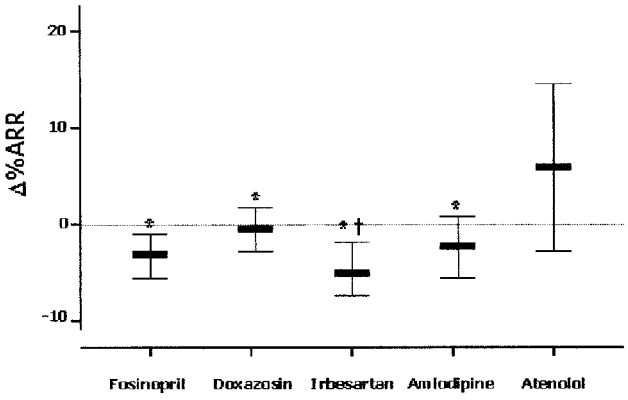

Figure 2. Percentage change from control of the ARR (PAC/PRA) after 2-month therapy with single drugs. *P<0.05 vs atenolol; †P<0.05 vs doxazosin.

On of 55 patients from the group taking amlodipine (1.8%) and 4/17 of the patients taking irbesartan (23.5%) gave a false-negative ARR (<50) compared with the washout period. None of the patients of the groups taking fosinopril, doxazosin, and atenolol displayed a false-negative ARR compared with the washout period.

Considering only the patients with confirmed PA, 1/40 (2.5%) of the patients taking amlodipine and 4/11 (36%) taking irbesartan would be misdiagnosed as essential hypertensives. This means a reduction in the sensitivity for the patients under amlodipine treatment from 100% to 98% and for patients under irbesartan treatment from 100% to 76%.

Discussion

Increasing evidence indicates that PA is much more prevalent than previously believed, making this disease the most frequent cause of secondary hypertension. The fact that PA can be specifically treated and potentially cured makes the diagnosis a particular challenge for the clinician. Because PA often presents as moderate to severe hypertension, patients are usually screened when they are already undergoing antihypertensive therapy. The known effect of the different antihypertensive drugs on ARR, led to the suggestion that ARR should be measured after at least 2 to 3 weeks of washout from previous potentially interfering therapy. This strategy is not always feasible, however, most notably for the severe hypertensive patient.

We designed a study to investigate the effect of different therapies on the ARR to determine which of these can be used by the clinician to avoid interference with the diagnosis of PA. We performed only one determination of the ARR as inclusion/exclusion criteria: in our experience and in that of others, this test is highly sensitive and specific.[3,4,7–11,23] This test is also highly reproducible and is marginally affected by posture.[8,28] A recent study by Montori et al[29] did not confirm this finding; however, PRA and PAC were measured after 30 minutes of ambulation. Under these conditions, PAC levels can increase owing to a reduction in the hepatic clearance of the hormone; the levels of PRA can take longer to rise, resulting in an increase of ARR. Nonetheless, we cannot exclude the possibility of missing some patients with PA using a single ARR determination; in contrast, an inclusion of excess patients would be corrected with the confirmatory test. The diagnosis was confirmed by intravenous saline load: this method has been described as reliable and specific for the diagnosis of PA.[11,24] Some groups use the fludrocortisone suppression test to confirm the diagnosis. Although the fludrocortisone suppression test is more "physiological," it requires hospitalization of the patients. Therefore, many investigators use the intravenous saline load and, to date, no study has shown that fludrocortisone suppression test is preferable to intravenous saline load.[6,11,26]

Our study confirms that PA is very frequent in patients referred to a hypertension unit.[3–7] This prevalence can be higher than the real prevalence of PA in a population of hypertensive patients, owing to the selection of the patients that have to be referred to a clinic. In contrast, in our selected population, the prevalence of PA could have been even higher if resistant hypertensives would not have been excluded from the study.

These data also confirm the opinion that normokalemia is a frequent feature in PA patients, as reported previously.[3–5,10,11] We excluded thiazide diuretics and spironolactone from the study because our unpublished observations and those of others have demonstrated that thiazide diuretics and spironolactone can be responsible for a reduction of ARR and therefore a missed diagnosis of PA.[9,15] Our data demonstrate that doxazosin and fosinopril do not interfere with the final diagnosis of PA. The effect of doxazosin on the ARR is very small, as also observed after acute and chronic usage.[20,21] In contrast, the effect of fosinopril on ARR is more evident but does not result in any false diagnosis of essential hypertension in patients with PA. This is in agreement with the proposal that ACE-Is can be used to confirm the diagnosis of PA.[30,31] Previous studies have shown that ACE-Is, such as enalapril, are effective in reducing blood pressure and aldosterone secretion in patients with PA.[32] This could be owing to the inhibition of angiotensin II generation, to which IHA patients display enhanced sensitivity.[33] However, despite the fact we did not have any PA misdiagnosed as essential hypertension in our sample of patients, we cannot exclude the possibility of a very small proportion of false-negatives with this therapy, considering the known effect of ACE-Is in increasing the PRA and reducing the aldosterone levels.[9,15,16]

The CCB amlodipine produced a reduction in ARR; this effect is probably owing to a reflex sympathetic stimulation, to natriuretic effects, and/or to inhibition of aldosterone secretion.[9,17,34,35] In fact, calcium ions have been proposed to be the final common intracellular messenger of most aldosterone secretagogues, including angiotensin II, corticotrophin, and potassium.[36] This reduction caused a small percentage of false-negative diagnoses in our population, in agreement with a previous report that indicated that sporadic masking of PA under dihydropyridine CCB usage.[18] Atenolol caused an increase in the ARR even in our selected population; this is in agreement with its known effect on the PRA and aldosterone.[12,13] In fact, a reduction of the PRA greater than that of the PAC, resulting in an increase of the ARR, has been described previously.[12,13,37] This effect could theoretically be responsible for an increased frequency of falsely elevated ARR in a general population. In our work, this cannot be confirmed because we studied only patients that showed an increased ARR in washout. Finally, ARB causes a greater increase of the ARR both in EH and in PA and therefore gives a high rate of false negatives in patients taking this drug. However, these results have to be taken cautiously because in our population only a small amount of patients were undergoing therapy with this type of drug. The observed effect could be because compared with the ACE-I, ARB causes a more complete blockade of the renin-angiotensin system, resulting in an increase production of renin that decreases the ARR.

Taken together our data indicate that α-blockers, such as doxazosin, and ACE-inhibitors, such as fosinopril, can be used in patients for whom anti-hypertensive treatment cannot be stopped and need to undergo aldosterone and PRA measurement for the diagnosis of PA: in fact, these 2 classes

of drugs do not interfere significantly with PA diagnosis. Amlodipine, a dihydropyridine CCB, gave a very small percentage of false-negative diagnoses for PA, suggesting that it could be used if strictly necessary to control blood pressure. β-Blockers also do not interfere with the diagnosis of PA, but because they could be responsible for an increased rate of false-positive ARR and therefore of an increased necessity for the confirmatory PA test, should be avoided before ARR measurement. The high rate of false-negative diagnoses in patients undergoing irbesartan treatment requires confirmation in a higher number of patients; however, our data suggest that ARB should be avoided in hypertensive patients before the diagnosis of PA is excluded. Because of the study design, we cannot rule out the possibility of a higher false-negative rate for single-drug therapies lasting more than 2 months or for patients taking a combination of different drugs.

In conclusion, our study demonstrates that doxazosin and fosinopril can be used in patients in whom the diagnosis of PA has not been excluded, thus avoiding the washout period before the measurement of ARR.

Perspectives

Recent studies from all continents indicate that PA prevalence is much higher than previously believed. PA can be specifically treated, in the case of bilateral adrenal hyperplasia, and potentially cured, in the case of aldosterone-producing adenoma. The present study shows that clinicians can perform a correct screening test for the diagnosis of PA even without the washout period previously suggested in this situation. The use of an α-blocker (such as doxazosin), ACE-I (such as fosinopril), and, with some caution, dihydropyridine CCB (such as amlodipine) allows a reduction of blood pressure levels without interfering with the screening test. These data could allow more clinicians to search for PA even in patients for whom the withdrawal from antihypertensive therapy would be dangerous. Greater attention to this secondary form of hypertension would allow the determination of its true prevalence and provide an opportunity for treatment or cure to a greater number of patients.

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