Diagnosis and Management of Primary Aldosteronism

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Abstract

Primary aldosteronism (PA or Conn’s syndrome) is the most common secondary form of arterial hypertension, with an estimated prevalence ranging between 6% and 20% in patients with resistant hypertension. The use of aldosterone-renin ratio (ARR) for screening contributes to the increased diagnostic rate of this disease. Diagnosis of primary aldosteronism consists of an initial screening test and subsequent confirmatory tests. A prompt recognition of this disease and early institution of treatment is vital to protecting patients from aldosterone-related blood pressure control and attenuated cardiovascular events. Aldosterone-producing adenoma and bilateral adrenal hyperplasia (micronodular or macro-nodular) are the two main subtypes, constituting more than 90% of primary aldosteronism cases.

Aldosterone-producing adenoma (APA) is typically managed with laparoscopic adrenalectomy. Idiopathic hyperaldosteronism (IHA) is amenable to medical therapy with mineralocorticoid receptor antagonists. Adrenal image is not accurate for distinguishing between an APA and IHA. Adrenal venous sampling (AVS) is therefore essential for selecting the appropriate therapy for patients with a high probability of PA who require surgical treatment. Short-term treatment outcome is determined by factors such as pre-operative blood pressure level and hypertension duration, but evidence on long-term outcome and survival after therapy is still lacking.

The purpose of this review is to provide up-to-date information on the etiology as well as strategies for the subtype lateralization and the management of PA.

KEY WORDS: aldosteronism, adenoma, hyperplasia, hypertension

Introduction

Since Conn’s initial description of the primary aldosteronism (PA) more than 50 years ago, subsequent validation of laboratory renin and aldosterone assay in the 70 s has brought the identification of PA from qualitatively clinical-based decision-making to quantitatively laboratory-based diagnostic process, which increases dramatically the diagnostic yield (1). With the aid of plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio, which was first introduced by Hiramatsu in 1981, the screening of PA becomes more feasible and has greatly facilitated the estimation of disease prevalence though intense debate surrounds this important issue. There are wide variations of estimate regarding the prevalence of PA, ranging from 3-4% to nearly 20% (2). However, inconsistent diagnostic procedures, for instance, different cut-off values of aldosterone/renin ratio (ARR), various confirmatory and subtype differential tests, and different measure sensitivities also play a role in obscuring the accurate estimation of prevalence of PA. Aldosterone is produced in the zona glomerulosa of adrenal glands in response to...
renin-dependent angiotensin II stimulation, and further modified by other hormones such as adrenocorticotropic hormone (ACTH) and dopamine (3). Growing evidence has shown that high plasma aldosterone level leads to a risk of cardiovascular diseases (CVD), including fatal stroke and sudden cardiac death (4). In addition, long-term exposure to increased aldosterone levels resulted in renal and metabolic sequelae independent of the blood pressure level (5). A history of stroke, myocardial infarction and atrial fibrillation were 4-fold (12.9% vs 3.4%), 6-fold (4.0% vs 0.6%), and 12-fold (7.3% vs 0.6%) more common in patients with PA than essential hypertension, respectively (4).

Optimal BP control and specific management of aldosterone excess by either adrenalectomy or medical treatment with mineralocorticoid receptor (MR) antagonists are fundamental to the prevention of hypertension and cardiovascular events in patients with PA. From this perspective, a thorough understanding of the clinical presentations, the current diagnostic armamentarium for PA and its corresponding therapeutic choices is vital for early diagnosis and treatment.

Clinical Manifestations

The diagnosis of primary aldosteronism is usually made in patients who are in the third to sixth decade of life (6). Patients with marked hypokalaemia may present with muscle weakness and cramping, headaches, palpitations, polydipsia, polyuria, nocturia, or a combination of these. Polyuria and nocturia are attributed to the hypokalaemia-induced renal concentrating defect (6).

Hypokalemia is not as common as we would expect in PA patients (7). Kuo et al. found that the plasma level of potassium was lower than 3.3 mEq/L in only 18% of all patients with confirmed PA. However, in Taiwan, the Taiwan Primary Aldosteronism Investigator (TAIPAI) group identified that initial hypokalemia occurred in only 50% of cases, which reflects potential delayed or mistaken diagnosis of PA according to hypokalemia in usual practice (8). Because of a reset osmostat, the serum sodium concentration tends to be high-normal or slightly above the upper limit of normal. Autonomous aldosterone secretion in PA patients also antagonizes parathyroid hormone (PTH) secretion, and induces hypercalciuria by lowering serum calcium (9). Sonino and co-workers have recently demonstrated that psychiatric illnesses, such as generalized anxiety disorders, occurred more often in PA patients (10). Blood pressure may be normal in patients with well-documented PA. In normotensive patients, diastolic blood pressure and upright aldosterone correlated negatively with kalemia.

Subtypes of Primary Aldosteronism

The most common form of PA are idiopathic bilateral hyperplasia (IHA) and aldosterone-producing adenoma (APA), accounting for more than 90% of clinical cases (11). Unilateral adrenal hyperplasia is less commonly identified, but this diagnosis should be considered if lateralization test (e.g., adrenal venous sampling (AVS)) is positive but radiological and histological examination does not detect an adenoma. Approximately 1% of patients are shown to have aldosterone-producing carcinoma, and 10% of patients manifest initial metastasis (12).

There are three familial forms of PA, namely glucocorticoid-remediable aldosteronism (GRA), familial occurrence of adenoma or hyperplasia type II (FH-II) and FH-III. GRA, inherited in an autosomal dominant fashion, is caused by the presence of a chimeric gene originating from an unequal cross-over between the CYP11B1 and CYP11B2 genes, leading to ACTH-sensitive aldosterone production. The main features comprises increased level of hybrid steroid products (18-OH-cortisol and 18-oxo-cortisol), and suppressible with exogenous corticosteroid (13). FH-II is slightly more common than GRA, and could link to several chromosomal loci (7p22) with genetic heterogeneity. FH-III is a recently described clinical entity, and the culprit gene has been linked to KCNJ5, a cellular potassium channel located over zona glomerulosa cells (14).

Case Detection and Diagnosis

When to Screen Patient?

A consensus held by the endocrine society (15) indicates that testing should be performed in patients with the following features: [1] Joint National Commission stage 2 (systolic/diastolic > 160-179/100-109 mmHg) and stage 3 (> 180/110 mmHg) hypertension, [2] drug-resistant hypertension, [3] hypertension with spontaneous hypokalemia or diuretic-induced hypokalemia, [4] hypertension with adrenal incidentaloma, [5] hypertension and a family history of early-onset hypertension, or cerebrovascular accident at a young age (< 40 years old), and [6] patients with first-degree relatives diagnosed with PA. Whenever secondary hypertension is suspected, a diagnosis of PA should be executed.

How Is Diagnosis Obtained?

Aldosterone-Renin Ratio (ARR)

ARR is currently the most reliable and available means of screening for PA. Many studies have demon-
strated that ARR is superior to other laboratory markers (serum potassium, aldosterone concentration or renin alone) owing to its higher sensitivity (16). It should be performed in the morning, with serum potassium level restored to normal level (hypokalemia reduces aldosterone production), and without postural stimuli. An attempt to correct hypokalemia should be accompanied by accurate determination of serum potassium level.

How to Prepare for ARR Test?

Before making correct interpretation of the paired hormonal values, several issues should be considered. First, several medications can interfere with the ARR value. Most notably, mineralocorticoid antagonists (spironolactone and eplerenone) and amiloride will significantly compromise the test result (false negativity from stimulating more renin than aldosterone secretion), and should therefore be discontinued at least 6 weeks before testing (17). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB) can all result in a falsely negative ARR value due to their suppression of aldosterone secretion and enhancement of renin level. Direct renin inhibitor (aliskiren) is also reported to skew ARR interpretations (decreased when measured with PRA or increased direct renin concentration (DRC), then ARR will be false positive or false negative, respectively) (15). Other anti-hypertensive medications including β-adrenergic blockers, central α2-agonists (clonidine and methyl dopa) and diuretics (loop and thiazide) will suppress more the level of renin than that of aldosterone, leading to a false positive ARR result. Dihydropyridine calcium-channel blockers will elevate renin level, resulting in a falsely low ARR value (18). It is then prudent to discontinue these medications for 2-4 weeks before starting on the test. For controlling blood pressure during the drug washout period, it is preferable to use effect-neutral antihypertensive drugs, such as verapamil (slow-release form), hydralazine (combined with verapamil to avoid reflex tachycardia) and α1-antagonists (prazosin, doxazosin, and terazosin) (15).

In addition, several agents can also potentially introduce interpretation difficulties, such as products derived from licorice (e.g., chewing tobacco), nonsteroidal anti-inflammatory agents (NSAID), and oral contraceptives (15). Patients should be told to refrain from these medications before they receive ARR test.

There are hints that can assist in interpreting ARR results: a high PAC in a patient receiving drugs that should suppress PAC level suggests that this patient could have PA (19). From this viewpoint, knowledge of each drug’s tendency to divert ARR is of much importance.

How to Interpret ARR?

A lack of uniform assay method and diagnostic protocols in ARR determination creates a high variability in cut-off values among various investigation groups, ranging from 20 to 100 (using PAC in ng/dL and PRA in ng/mL/hr) (20). Several groups urge that elevated aldosterone level (> 15 ng/dL) is required for a positive ARR test to avoid bias from extremely low renin measurements, but the variability of assay between laboratories and different normal ranges of plasma aldosterone level constitute a major obstacle. Some investigators proposed that post-captopril ARR value was as sensitive as saline infusion for screening or confirmation, but the evidence is also insufficient (21). The TAIPAI group conducted a prospective study to compare the diagnostic yield of post-captopril ARR according to ARC and standard ARR, and a cut-off value of 35.5 was identified (22). Therefore, a cut-off value of ARR (according to PRA) of 35 (ng/dL per ng/mL/hr) with highest sensitivity and specificity is recommended for screening purpose (8).

Confirmatory Test for Identification of Primary Aldosteronism

What Tests Can Be Used for PA Confirmation?

An increased ARR is not diagnostic by itself, but points out that further testing is warranted. An accurate confirmatory test can spare the patients from subsequent invasive and costly examinations. However, the reference standard for diagnosis of PA has not been established to date. The tests include oral salt loading (OST) or intravenous salt infusion test (SIT), fludrocortisone stimulation test (FST), captopril or losartan challenge test (15), each with their proponents. In the following section, we will briefly introduce the procedure of each test (Table 1).

Oral Salt/Saline Loading Test (OST)

After a high sodium diet (salt tablet supplementation if needed) for 3 days (total 218 mmol of sodium, about 12.8 g NaCl given), a 24-hour urine specimen is collected (23). Urinary aldosterone excretion of more than 12 µg/day in this setting is consistent with insuppressible aldosterone secretion (15). The sensitivity and specificity of OST are around 96% and 93%, respectively (23).

Saline Infusion Test (SIT)

This is the most popular confirmatory test for
An overnight fasting is needed for preparation. Patients receive infusion of 2 liters of 0.9% saline over 4 hours and post-infusion plasma aldosterone level lower than 5 ng/dL excludes the diagnosis of PA, while that exceeding 10 ng/dL confirms the diagnosis (24).

**Fludrocortisone Stimulation Test (FST)**

In this test, fludrocortisone acetate is administered for 4 days (0.1 mg every 6 hours) in combination with sodium chloride tablet (2 g, thrice daily). At day 4, an upright plasma aldosterone level at 10 AM higher than 6 ng/dL confirms the diagnosis of PA (25).

**Captopril/Losartan Challenge Test (CST/LST)**

Patients are prescribed 50 mg captopril orally after sitting or standing for at least 1 hour. Blood sampling is performed for measuring serum renin, aldosterone, and cortisol before captopril and 1 or 2 hours after challenge. Normal suppression is defined as PAC < 15 ng/dL and ARR < 50 (15). Comparable sensitivity has been shown by some groups between SIT and CST. This test is not influenced by sodium intake, and is more suitable for patients with heart failure or other fluid overloading status (21).

The losartan challenge test (LST) is an alternative form of the captopril-based test, with the assumption that changes in ARR may be larger if ARB is used instead of ACE inhibitor (26).

### Table 1. Available confirmatory tests for diagnosis of primary aldosteronism

<table>
<thead>
<tr>
<th>Confirmatory test</th>
<th>Procedure</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral salt loading test (OST)</td>
<td>Preceding 3 days of high salt intake (6 g NaCl/day), as verified by 24-hour urine Na content (should &gt;200 mmol);</td>
<td>Urine aldosterone &gt; 12 µg/day</td>
</tr>
<tr>
<td>Saline infusion test (SIT)</td>
<td>2 liters of 0.9% saline infusion over 4 hours, when patients are recumbent;</td>
<td>PAC &gt; 10 ng/dL (277 pmol/L) confirms patients with PA</td>
</tr>
<tr>
<td>Fludrocortisone suppression test (FST)</td>
<td>Administration of fludrocortisone (0.1 mg 4 times a day) and NaCl tablets (2 g three times a day) for 4 days;</td>
<td>PAC &gt; 6 ng/dL confirms the diagnosis of PA</td>
</tr>
<tr>
<td>Captopril-suppression test (CST)</td>
<td>Administration of 50 mg captopril orally after sitting or standing for at least 1 hour;</td>
<td>ARC/PAC (ng/dL per ng/mL/hr) remained elevated more than 35.5 after captopril challenge confirms the diagnosis</td>
</tr>
<tr>
<td>Losartan-suppression test (LST)</td>
<td>Similar to CST, with losartan 50 mg given instead.</td>
<td>Interpretation similar to CST</td>
</tr>
</tbody>
</table>

Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.

**Subtyping of PA**

*Is There a Lateralization?*

To establish a lateralization is the most critical step to guide the further treatment of PA. Lateralization is to localize the aldosterone secreting activity on one side of the adrenal glands in preference to the other. Distinguishing between unilateral and bilateral adrenal disease is also vital, since prompt operation of unilateral adenoma results in normalization of hypokalemia and hypertension, but bilateral diseases are usually managed medically (27). Imaging cannot reliably visualize microadenoma or provide definite clues for lateralization. CT contributed to lateralization in about 50% of cases only, and this number decreased further to lower than 25% if APAs were smaller than 1 cm in diameter (15). This makes adrenal venous sampling (AVS) a procedure of choice for differentiating unilateral from bilateral forms of PA, despite its being expensive and invasive. The sensitivity and specificity of successful AVS (95% and 100%) for detecting unilateral disease are significantly better than those of adrenal CT (28).

AVS is a difficult procedure and usually required a dedicated doctor with experienced hands, since cannulating the smaller right adrenal vein, described as “the crux of AVS”, is technically demanding. According to a review of 47 reports, the success rate was 74%, but rose to 90-96% if angiographers were experienced (29). The addition of intraprocedural measurement of adrenal vein cortisol concentrations...
further facilitates the accuracy of catheter placement. Patients may be spared AVS if they are younger than 40 years old with solitary unilateral apparent adenoma on CT, with still high biochemical and clinical cure rates (28).

The aim of continuous cosyntropin infusion during AVS is to minimize stress-induced fluctuations in aldosterone secretion during sequential AVS, to maximize the gradient of cortisol between adrenal vein and IVC (to ensure optimal cannulation), and to stimulate the secretion of aldosterone from APAs (28). Dividing the right and left adrenal vein PAC by their respective cortisol level can neutralize the diluting interference of inferior phrenic vein or IVC, draining into the right and left adrenal vein, respectively. In the absence of cosyntropin infusion, a cortisol-corrected aldosterone lateralization ratio of more than 2:1 confirms unilateral disease (30). Some groups compared adrenal vein aldosterone-cortisol ratios to those in a simultaneously collected peripheral venous sample (cubital) or IVC. The acceptable cut-off points in this setting will be a unilateral hypersecretion (ratio of more than 2.5:1) with contralateral (ratio no higher than 1:1).

The TAIPAI experience confirmed the potential usefulness of dexamethasone suppression adrenocortical scintigraphy with CT (NP-59, I-131-6-beta)-usefulness of dexamethasone suppression (ratio no higher than 1:1).secretion (ratio of more than 2.5:1) with contralateral off points in this setting will be a unilateral hypersecretion (30). Some groups compared adrenal vein aldosterone-cortisol ratios to those in a simultaneously collected peripheral venous sample (cubital) or IVC. The acceptable cut-off points in this setting will be a unilateral hypersecretion (ratio of more than 2.5:1) with contralateral suppression (ratio no higher than 1:1).

The TAIPAI experience confirmed the potential usefulness of dexamethasone suppression adrenocortical scintigraphy with CT (NP-59, I-131-6-beta-iodomethyl-19-norcholesterol & NP59-SPECT/CT) (31). NP59-SPECT/CT is not only non-invasive but also avoids the adverse effects of intravenous contrast agents in conventional CT/MR, especially for elderly patients and patients with kidney diseases (32).

Testing for Familial Forms of PA – Familial Hyperaldosteronism Type I (GRA)

It is characterized by early-onset hypertension, usually severe, and refractory to conventional antihypertensive medications. The culprit is a chimeric gene duplication resulting from unequal crossing over between the promoter sequence of 11β-hydroxylase (CYP11B1), which is responsible for corticotrophin stimulation, and coding sequence of aldosterone synthase (CYP11B2), both on chromosome 8 (13). The result is ectopic expression of aldosterone synthase in adrenal zona fasciculate, which produces cortisol and mineralocorticoid regulation depending upon corticotropin. To diagnose this rare disorder, several methods are available, namely measurement of urinary 18-hydroxycortisol or 18-oxocortisol, dexamethasone suppression test, and genetic testing for chimeric gene. Genetic test was suggested for the following settings: patients with a family history of PA, patients with onset of PA at a younger age (< 20 years old), and patients with PA who have a family history of young stroke (32).

Testing for Familial Forms of PA – Familial Hyperaldosteronism Type II

FH-II is a genetically heterogeneous disorder. FH-II families can present clinically with APA or IHA, and are not distinguishable from patients with nonfamilial PA (15). The exact prevalence of FH-II is not known, but a high percentage of affected patients (7%) has been reported (33). The molecular basis of this syndrome is also unknown, but chromosomal region 7p22 has been implicated as an associated area. Further clinical testing is not available to date.

Testing for Familial Forms of PA – Familial Hyperaldosteronism Type III

FH-III is a particularly aggressive form of hyperaldosteronism, with medication-resistant hypertension (34). The genetic cause of this syndrome is attributed to KCNJ5, which encoded the potassium channel Kir 3.4. Recurrent somatic mutation of KCNJ5 results in increased sodium conductance and cell depolarization of adrenal zona glomerulosa cells in unselected patients of approximately 34%, with subsequent enhanced aldosterone production and cell proliferation (14). Clinically, patients present with severe hypertension and variable hypokalemia, with radiological bilateral massive adrenal hyperplasia. Treatment with bilateral adrenalectomy is frequent (34).

Aldosterone-Related Cardiovascular Events

Aldosterone-related detrimental effects are mediated through the activation of MR, which are widely expressed in endothelial cells, smooth muscle cells, cardiomyocytes, endothelial progenitor cells, (35) and neutrophils. Aldosterone exerts its actions on sodium and potassium handling through up-regulation of the activity of the distal tubule sodium epithelial channel. Aldosterone may possess more than direct endothelial effects. These include increased oxidative stress and collagen remodeling, triggering endothelial dysfunction, delayed endothelial recovery (35) and subsequent ventricular hypertrophy and myocardial as well as renal fibrosis. Regarding kidney damage, the possible hyperfiltration phenomenon may mask decreased kidney function, leading to underestimation of the burden of chronic kidney disease in PA patients (36). We have recently demonstrated that even a mild impairment of renal function may predict residual hypertension after unilateral adrenalectomy in PA patients. This indicates that subtle kidney impairment may be masked by
hypokalemia in these patients. Hypertension is cured by early PA can effectively improve hypertension and ameliorates the inflammatory reaction, and this effect may be independent of blood pressure reduction per se (38). Furthermore, patients with PA have a greater risk of developing left ventricular hypertrophy, myocardial fibrosis, and diastolic dysfunction than EH patients. Moreover, excessive aldosterone is known to induce endothelial dysfunction, increase arterial stiffness, and atherosclerosis. In research on vascular smooth muscle cells, aldosterone contributed to enhancement of collagen synthesis. Moreover, compared with EH patients, PA patients have shown to have increasing arterial stiffness measured by pulse wave velocity, and greater carotid intima-media thickness (39). In primary aldosteronism, escape of renin from suppression by excess aldosterone is associated with evidence of more severe target organ damage (e.g., kidney) and predicts intrarenal vascular injury, worse BP and renal outcomes after either surgical or medical treatment (40).

Treatment of PA

Treatment of PA is targeted to prevent the excess morbidity and mortality associated with hypertension, hypokalemia and aldosterone-associated organ damage. Blood pressure reduction should not be the only goal in managing PA patients, since mineralocorticoid receptors (MR) have been found in a variety of tissues including myocardium, brain and blood vessels. The treatment strategy should be chosen according to the subtyping and the underlying cause of PA. The general principle is that patients with unilateral PA (i.e., APA or unilateral adrenal hyperplasia) should be offered unilateral laparoscopic adrenalectomy (15). For patients with PA from bilateral adrenal disease, medical treatment with MR antagonist is the first-line treatment of choice (15). An algorithm of case detection, confirmation, differential subtyping testing, and management of PA according to the TAIPAI group experience is summarized in Fig. 1.

Unilateral Adrenalectomy for APA and Unilateral Hyperplasia

Unilateral adrenalectomy in patients with unilateral PA can effectively improve hypertension and hypokalemia in these patients. Hypertension is cured (defined as medication-free and blood pressure < 140/90 mmHg) in around half of the operated patients with APA. In the TAIPAI database, we found that patients with unilateral hyperaldosteronism receiving unilateral adrenalectomy displayed reversal of changes in myocardial structure (as evidenced in cardiac ultrasonographic findings) and of carotid intimal thickness (41, 42). The longitudinal changes of CysC-based GFR, proteinuria and the kidney-resistive index provide convincing evidence that the vasculotoxic effect of hyperaldosteronism can be mitigated after adrenalectomy but not through the use of conservative medical treatment (15). Laparoscopic adrenalectomy is the preferred surgical approach, and is associated with shorter hospitalization and lower morbidity compared with the conventional open approach. The surgical approach usually involves removal of the entire gland since APAs are commonly small and multiple, but laparoscopic partial adrenalectomy or enucleation has also been utilized by some, with shorter operative time but more blood loss, and infrequently, post-operative persistent hypertension (43).

Factors associated with resolution of hypertension in the post-operative period include having one or no first-degree relative with hypertension and pre-operative use of less than three types of antihypertensive agents (44). Other predictive factors like higher pre-operative serum creatinine level and longer duration of hypertension have also been found. The most common reasons for persistent post-operative hypertension are hypertension of unknown etiology, advanced age, and pre-operatively longer duration of hypertension (44). Blood pressure becomes normal or improves maximally within 1-6 months after unilateral adrenalectomy, but some reports indicate that this improvement period can lag up to one year (15).

Mineralocorticoid Receptor (MR) Antagonist

Bilateral adrenal diseases including IHA, bilateral APAs, and GRA are often managed medically with MR antagonists. However, no randomized placebo-controlled trials have evaluated the efficacy of each drug in the treatment of PA.

Spironolactone

This drug has been the treatment of choice for PA for more than four decades. The dosage is 12.5 mg to 25 mg per day initially and titrated upward to 400 mg per day if necessary to achieve normokalemia without potassium supplementation. The response of hypokalemia usually occurs promptly, but blood pressure response may take months to be fully achieved (23). Observational studies in patients with IHA have
Fig. 1. TAIPAI Algorithm for the screening, confirmation, differential sub-typing testing, and management of primary aldosteronism. Abbreviations: APA, aldosterone-producing adenoma; ARR, aldosterone/renin ratio; AVS, adrenal venous sampling; CCB, calcium channel blocker; HTN, hypertension; IHA, idiopathic hyperaldosteronism; MR, mineralocorticoid receptor; NP-59-SPECT/CT, I-131-6-beta-iodomethyl-19-norcholesterol single-photon emission computed tomography; PAC, plasma aldosterone concentration; RAAS, renin-angiotensin-aldosterone system; PA, primary aldosteronism; TSC guideline, 2010 guidelines of the Taiwan Society of Cardiology for the management of hypertension.

Units: Age, years; ARR, ng/dL per ng/mL/hr; PAC, ng/dL.
reported a mean reduction in systolic blood pressure of 25% and diastolic pressure of 22% with spironolactone dosage ranging from 50 mg to 400 mg per day (45). Most of the patients require as low as 25 to 50 mg per day after several months of therapy.

Side effects of spironolactone include mainly gynecomastia, decreased libido and erectile dysfunction in men or menstrual abnormality in women, a phenomenon stemming from concomitant sex steroid effect (11). The incidence is dose-related, with one study reporting an incidence of 5-10% at a dose of 25-50 mg per day for 6 months but increasing to 50% at a dose of more than 150 mg per day (46). In addition, spironolactone has several important drug-drug interactions. Spironolactone can increase the half-life of digoxin, and digoxin dosage adjustment should be considered when used simultaneously. Salicylate also interferes with tubular secretion of the active metabolite of spironolactone, decreasing its effectiveness.

**Eplerenone**

Eplerenone is a more selective MR antagonist, with minimal anti-androgen and progesterone agonist effects and lower incidence of adverse effects (15). The main structural modification leading to low androgenic and progesterone effect resides in the 9,11-epoxide group. It is approved for the treatment of essential hypertension and for heart failure after myocardial infarction (47). It is reasonable to start with a dosage of 25 mg twice daily (owing to the short half-life of eplerenone), and titrated upward for normokalemia and blood pressure effect. The maximal dosage for hypertension is 100 mg twice daily. Parthasarathy et al. reported a randomized study comparing eplerenone with spironolactone in treating PA patients, and spironolactone was found to outperform eplerenone with regard to anti-hypertensive efficacy (48). The contraindications of eplerenone are similar to those of spironolactone. Side effects include dizziness, headache, fatigue, diarrhea, abnormal liver enzyme, and hypertriglyceridemia (23). The contraindications of eplerenone include hyperkalemia (serum potassium > 5.5 mEq/L), clinically significant renal insufficiency (serum creatinine > 2.0 mg/dL in men and > 1.8 mg/dL in female), or combination therapy with other potassium-sparing diuretics.

**Other Pharmacologic Agents**

Amiloride and triamterene are also distal sodium epithelial channel antagonists, and amiloride in particular has been studied most extensively in PA patients. Amiloride can ameliorate both hypertension and hypokalemia and is well tolerated, without the notorious side effects of spironolactone, but is also devoid of the beneficial effects on endothelial function (49). However, the impact of its clinical use is still not elucidated.

**Conclusion**

PA has once been regarded as a rare disorder with very low prevalence among unselected hypertensive patients, but it is now realized that PA may constitute up to 10-20% of patients with hypertension. More importantly, the detrimental effect brought about by aldosterone in multiple tissues may go far beyond a pure complication from hypertension, and early treatment, surgically (adrenalectomy) or medically (spironolactone) will effectively relieve these adverse events and potentially restore organ injury. It is then important for physicians to recognize this disorder early and arrange proper diagnostic tests, with corresponding therapeutic modality instituted, to avoid missing curable hypertension in the primary care clinic.

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