REVIEW

Primary aldosteronism: Practical recommendations for treatment and follow-up

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Abstract Primary aldosteronism (PA) is the most common cause of secondary arterial hypertension. For unilateral cases, surgery offers the possibility of cure, with unilateral adrenalectomy being the treatment of choice, whereas bilateral forms of PA are treated mainly with mineralocorticoid receptor antagonists (MRA). The goals of treatment for PA due to either unilateral or bilateral adrenal disease include reversal of the adverse cardiovascular effects of hyperaldosteronism, normalization of serum potassium in patients with hypokalemia, and normalization of blood pressure. The Primary Aldosteronism Surgery Outcome group (PASO) published a study defining clinical and biochemical outcomes based on blood pressure and correction of hypokalemia and aldosterone to renin ratio (ARR) levels for patients undergoing total unilateral adrenalectomy for unilateral PA. In this review, we provide several practical recommendations for the medical and surgical management and follow-up of patients with PA.

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Hiperaldosteronismo primario: recomendaciones prácticas de tratamiento y seguimiento

Resumen El hiperaldosteronismo primario (HAP) es la causa más frecuente de hipertensión arterial secundaria. Para los casos unilaterales, la cirugía ofrece la posibilidad de curación, siendo la adrenalectomía unilateral el tratamiento de elección, mientras que las formas bilaterales de HAP se tratan principalmente con antagonistas del receptor de mineralocorticoides (ARM). Los objetivos del tratamiento del HAP debido a enfermedad suprarrenal unilateral o bilateral incluyen la reversión de los efectos cardiovasculares adversos del hiperaldosteronismo, la normalización del potasio sérico en pacientes con hipopotasemia y la normalización de...
Introduction

Primary aldosteronism (PA) is caused by excessive secretion of aldosterone from the adrenal glands, with subsequent changes in the renin–angiotensin system. In PA patients, there is a dysregulation in the aldosterone production, which is independent of renin and is not fully suppressed by volume and/or sodium loading, often despite hypokalemia. It has been largely demonstrated that patients with aldosterone excess have a higher risk of developing deleterious effects on the heart, vessels, brain, and kidney. The most important point is that several studies have demonstrated that both, surgery and mineralocorticoid receptor antagonist (MRA) partially revert the detrimental effect of aldosterone. Nevertheless, surgery is reported to be more effective than MRA. In this regards, Jing Y. meta-analysis found that patients with PA treated with MRA have a higher risk of cardiovascular events than those with essential hypertension (odds ratio (OR) 2.11; 95% CI: 1.88–2.38), but this increased risk is not observed in those treated with surgery. In this same line, they found that the risk of all-cause mortality was significantly lower in patients with treated PA [OR 0.86; 95% CI: 0.77–0.95] compared with essential hypertensive patients, but that this lower risk was only observed in PA treated surgically but not in those PA medically treated. A more recent meta-analysis found results along the same line, with results in favor of adrenalectomy. Nine studies with a total of 8473 PA ≥ 18 years were included, and it is found that there was a lower incidence of composite adverse primary outcomes in the adrenalectomy group (OR: 0.46 (95% CI: 0.38–0.56), P < 0.001) than in the group of medical treatment.

In this review, we provide practical recommendations for the treatment and follow-up after the medical and surgical treatment of patients with PA.

Treatment

Once a patient is diagnosed to have PA the goal of the treatment is the prevention of organ damage and not just the blood pressure (BP) and potassium control. The aim of the treatment should be also decreasing aldosterone production or efficiently blocking the mineralocorticoid receptor. As commented above, PA involves a variety of cardiovascular, renal, metabolic and bone complications related with this condition and in some cases relatively independent of BP increment. Although there has been controversy over whether adrenalectomy is superior to adequate medical treatment with regard to cardiovascular outcomes, recent evidence from observational studies lead to the benefit of surgical treatment in unilateral disease leading to less risk of atrial fibrillation and reduce number of non MRA anti-hypertensive medication after 1 year after adrenalectomy. Similarly, the SPAIN-ALDO registry results found that surgery improves biochemical control and reduces pill burden more commonly than MRA, and lead to hypertension cure or improvement in up to 83% of the patients. Moreover, the evidence of the presence of glucocorticoid co-secretion in aldosterone producing adenomas (APA) and bilateral hyperplasia associated with insulin resistance, higher body mass index, left ventricular hypertrophy (LVH) and impaired glucose tolerance may lead to a more favorable outcomes with surgical treatment as the co-secretion might be remove with the adrenalectomy. Subtype classification of PA is mandatory then, to identify PA types that can be treated surgically vs those that may be treated pharmacologically.

Surgical treatment

Laparoscopic adrenalectomy is recommended for patients with unilateral PA. This procedure has demonstrated benefits in terms of higher probability of BP cure, reduction in number of antihypertensive agents and resolution of hypokalemia.

Predictors of clinical outcomes following adrenalectomy include female sex, lower body mass index (BMI), younger age, short duration of hypertension, fewer antihypertensive medication and response to MRA treatment. In this regard, the SPAIN-ALDO group developed a predictive model of hypertension resolution after adrenalectomy in PA patients (SPAIN-ALDO score). According to this model (with an area under the receiver operating characteristic curve of 0.841), the group of patients with a higher probability of cure (80.4%) were those without type 2 diabetes, BMI < 30 kg/m², female sex, hypertension grade 1 and who use two or fewer antihypertensives. Another SPAIN-ALDO study focused on evaluating the impact of obesity on the characteristics of PA, and the association between obesity and renin–aldosterone–angiotensin (RAAS) components, found that obesity implicates a lower rate of hypertension cure after adrenalectomy.

Before intervention BP and potassium need to be in an appropriate control and medication used must be withdrawn immediately before the surgery. However, after
surgical resection of the APA, the contralateral adrenal gland may not immediately resume normal function, leading to the development of postoperative hypoaldosteronism with hyperkalaemia. Maintaining MRA treatment until the day before surgery may be associated with a lower risk of postoperative hyperkalaemia during the first month after surgery and less need of potassium supplementation before. Hypoaldosteronism may persist in a very small percentage of patients requiring use of fludrocortisone. In addition, the prevalence of unilateral PA with cortisol co-secretion is 4–77.6% and these co-secreting adenomas suppress contralateral adrenal cortisol secretion as a result, postoperative steroid treatment may be needed. Therefore, the dexamethasone (1 mg) suppression test is recommended before surgery in all patients with adenoma in computed tomography (CT) and a cutoff > 1.8 implies cortisol secretion and subsequently higher risk of adrenal insufficiency post-surgery.

There is no consensus of when to assess the effectivity of surgery, plasma aldosterone concentration (PAC) usually decreases early post-surgery but it could take more than a month to recover function of the contralateral adrenal gland and therefore the possibility to assess the aldosterone–renin function. In 2017 the Primary Aldosteronism Surgery Outcome group (PASO) published a study defining clinical and biochemical outcomes based on blood pressure and correction of hypokalaemia and aldosterone to renin ratio (ARR) levels for patients undergoing total unilateral adrenalectomy for unilateral PA (Table 1). Different studies reported ARR and hypokalaemia normalization in 90–100% of the patients and hypertension resolution in 30–50%.

**Medical therapy**

Medical treatment is indicated in patients with bilateral PA, in patients with unilateral PA who denies surgical approach and prior to adrenalectomy (Table 2).

**Mineralocorticoid receptor antagonist (MRA):** this therapeutic group is the first line therapy in PA. They may

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### Table 1 Definitions of clinical and biochemical success of unilateral total adrenalectomy as defined by the Primary Aldosteronism Surgery Outcome group (PASO).

<table>
<thead>
<tr>
<th>Clinical success</th>
<th>Biochemical success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>Normal BP without antihypertensive medication.</td>
</tr>
<tr>
<td></td>
<td>Correction of hypokalaemia (if present before surgery) and normalization of the aldosterone to renin ratio; in patients with an elevated aldosterone to renin ratio after surgery, aldosterone secretion should be suppressed in a confirmatory test.</td>
</tr>
<tr>
<td>Partial</td>
<td>The same BP as before surgery with less antihypertensive medication or reduction in BP with the same or less antihypertensive medication.</td>
</tr>
<tr>
<td></td>
<td>Correction of hypokalaemia (if present before surgery) and an elevated aldosterone to renin ratio with one or both of the following (compared with pre-surgery): ≥ 50% decrease in baseline plasma aldosterone concentration; or abnormal but improved post-surgery confirmatory test result.</td>
</tr>
<tr>
<td>Absent</td>
<td>Unchanged or increased BP with the same or increase in antihypertensive medication.</td>
</tr>
<tr>
<td></td>
<td>Persistent hypokalaemia (if present before surgery) or persistent elevated aldosterone to renin ratio, or both, without suppression of aldosterone secretion with a postoperative confirmatory test.</td>
</tr>
</tbody>
</table>

*BP: Blood pressure.*

### Table 2 Option of medical treatment for primary aldosteronism.

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>MR selectivity</th>
<th>Total daily dose</th>
<th>Biochemical success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>Steroidal MRA</td>
<td>Nonselective</td>
<td>25–400 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Once daily</td>
</tr>
<tr>
<td>Epleronona</td>
<td>Steroidal MRA</td>
<td>Selective</td>
<td>50–600 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2–3 times daily</td>
</tr>
<tr>
<td>Amiloride/trimaterene ENaC inhibitor</td>
<td>Steroidal MRA</td>
<td>Mild nonselective</td>
<td>2.5–75/50–300 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parenteral use</td>
</tr>
<tr>
<td>Canrenone</td>
<td>Steroidal MRA</td>
<td>Mild nonselective</td>
<td>10–20 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Once daily</td>
</tr>
<tr>
<td>Finerenone</td>
<td>Nonsteroidal MRA</td>
<td>Selective</td>
<td>2.5–5 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Once daily</td>
</tr>
<tr>
<td>Esaxerenone</td>
<td>Steroidal MRA</td>
<td>Selective</td>
<td>2.5–5 mg/day</td>
</tr>
</tbody>
</table>

MR: mineralocorticoid receptor; MRA: mineralocorticoid receptor antagonist.
achieve reductions in systolic and diastolic BP of 25% and 22% respectively.17

- **Spironolactone**: this MRA is a steroidal nonselective and competitive antagonist. At high dose spironolactone has antiandrogen effect because of its affinity for the androgen receptor and its progesterone receptor agonist effect. These effects may cause side effects in men treated with doses > 150 mg/day of spironolactone, including breast engorgement up to true gynecomastia, decreased libido, erectile dysfunction in 52% of patients. In premenopausal women menstrual irregularity have been described also with breast tenderness. It is also important to consider the use of contraception while using this drug due to the risk of feminization of a male fetus during first trimester of pregnancy (FDA category C).18

Spironolactone has a long-lasting effect of 24–58 h allowing once per day or even every other day administration. Because this drug is metabolized in the liver into long-acting active compounds. Once started it takes 3–4 weeks to achieve maximum effect on BP thus, spironolactone dose titration should be accomplished every 4–8 weeks. Concomitant drug intake with food increases absorption of this drug. Although total daily dose recommended are from 25 to 150 mg/day, doses as high as 400 mg/day has been reported in patients with PA.19

- **Eplerenone**: This MRA is a selective steroidal competitive drug, weaker than spironolactone, with 40–50% of MRA potency. This drug has a half-life of 3 h with no active metabolites unlike spironolactone so twice daily administration is needed. Doses from 25 mg twice daily to 300 mg twice daily may be required. If needed eplerenone can be administered 3 times a day. To consider, eplerenone is metabolized by cytochrome P450 3A4 and can interact with other drugs that use CYP3A4. On the other hand, no reproductive disorders or teratogenic effects have been detected in animals or humans (FDA category B).20

The dose of MRA is usually titrated to normokalaemia, normotension but there is no way of knowing if all the mineral reducts are being blocked. Plasma renin activity might constitute an additional marker to evaluate successful aldosterone blockade. There is evidence that patients in whom plasma renin gets unsuppressed, showed an identical cardiovascular risk profile as the essential hypertensive patients.21 However, there are some aspects that may influence in renin elevation independently to PA as dietary sodium load may rise suppress renin or compliance to treatment. Several other MRAs have been studied. Canrenone is an active spironolactone metabolite with lower antiandrogenic activity. Potassium canrenoate is the only MRA available for parenteral use.22 EsaXerena is a nonsteroidal MRA available in Japan with greater decrease in systolic blood pressure when compared to spironolactone and these effects were maintained at 52 weeks.16

When MRA are contraindicated or not well tolerated amiloride and triamterene can be used although these diuretics do not block MRA receptor.22

**Amiloride**: epithelial sodium channel blocker. It is not as effective as MRA. It is used at doses between 2.5 and 20 mg/day and should be taken fasting. This drug is well tolerated, and the most common side effect is hyperkalaemia, so concomitant medications should be taken in consideration as well as renal insufficiency. Other side effects include nausea, diarrhea, headache muscle clumps.

**Triamterene**: even with less blood pressure effect than amiloride, its potassium sparing properties are comparable. It is available in 50- and 100-mg capsules, with a maximum dose of 300 mg/day. Side effects are similar to amiloride: hyperkalaemia, headache, nausea, muscle clumps.

**Low salt diet**: PA physiopathology implies impaired renal sodium retention and potassium excretion. It’s been published than patients with PA have reduced salt taste with greater intake than (10 g/day) than patient with same grade essential hypertension.23 Limiting dietary sodium intake reduce intravascular volume and blood pressure and increase renin plasma levels. Thus, low salt diet should be recommended to patients with PA.

**Finerenone**: non-steroidal MRA with high selectivity for mineralocorticoid receptor and low affinity for androgen and progesterone receptors. This drug has modest effect on blood pressure and less risk of hyperkalaemia. Finerenone has been approved for adults with chronic renal disease and type 2 diabetes to reduce the decline of glomerular filtration, cardiovascular death and hospitalization for heart failure. It has not been studied in PA yet.

**Follow-up**

**Follow-up after medical treatment**

Since the goals of treatment for PA due to either unilateral or bilateral adrenal disease include reversal of the adverse cardiovascular effects of hyperaldosteronism, normalization of serum potassium in patients with hypokalaemia, and normalization of BP, these are the primary data to monitor (Fig. 1).

For nonsurgical candidates, MRAs appear to be effective in controlling BP and protecting target organs regardless of effects on BP.17 The goals of medical therapy are correction of hypokalaemia, restoration of normal BP, and reversal of the vascular, cardiac, and renal effects of hyperaldosteronism. Serum potassium, creatinine, and BP should be monitored frequently during the first four to six weeks of medical treatment, especially in patients with renal insufficiency or diabetes mellitus. Compared with patients with essential hypertension, the initiation of MRA treatment in patients with PA results in a decrease in the glomerular filtration rate in the first weeks and months of treatment that afterwards remains stable, and a restoration of normal albuminuria.14 This occurs because the antagonism of aldosterone excess normalizes the increased renal plasma flow and glomerular hyperfiltration and unmasks the already present structural renal damage induced by PA.15 The American Heart Association recommends measuring renal function and serum potassium levels on days 3 and 7 after the start of MRA treatment, following up at least monthly thereafter for the first 3 months.16 Furthermore, with each medication change, it is important to monitor the effect on both BP
and serum potassium. Subsequently, the clinical course and circumstances dictate the frequency of monitoring.

Moreover, in PA patients on MRA therapy, it is also important to monitor plasma renin with the goal of non-suppressed levels. Hundermer et al. reported that, independent of BP changes, the group of PA patients whose plasma renin activity was increased by MRAs to ≥ 1 μg/L/h had a cardiovascular event rate similar to that of essential hypertensive patients, whereas PA patients whose renin activity remained suppressed (< 1 μg/L/h) on MRAs had significantly more cardiovascular events compared with essential hypertensive patients. Furthermore, Yoshida et al. reported that PA patients with active renin concentration levels < 5 pg/mL after MRA treatment may indicate that salt sensitivity has not adequately improved, while the group with an increased active renin concentration levels of ≥ 5 pg/mL showed improved salt sensitivity, based on a correlation analysis of estimated daily salt intake with serum active renin concentrations before and after MRA treatment. Thus, patients with suppressed plasma renin levels after MRA treatment should be educated about strict dietary salt restriction and, if possible, the MRA dose should be increased. Therefore, these reports suggest that suppressed plasma renin activity or low serum renin concentrations after MRA treatment might be related to poor cardiovascular outcomes. Contrary to these studies, Nomura et al. retrospectively showed that PA patients with high change in plasma renin activity after MRA treatment had a significantly higher cardiovascular disease risk than the group with intermediate change in plasma renin activity. Therefore, future studies are needed to clarify the implications of changes in plasma renin after MRA treatment in PA patients.

On the other hand, MRA treatment in PA patients is expected to have other benefits in addition to lowering BP and increasing serum potassium. Previous studies have shown that PA patients have poorer physical and mental quality of life (QOL) compared to healthy controls, and that MRAs improve their QOL.

Finally, regarding the adverse effects of MRA treatment, in the case of spironolactone treatment, it is well known to be associated with a number of sex hormone related side effects due to androgen receptor antagonist and progesterone receptor agonist activities, such as gynecomastia and erectile dysfunction in men and menstrual irregularities in women, which should be monitored. However, the development of gynecomastia in patients on spironolactone therapy is reversible and dose-related. Eplerenone is a more selective MRA than spironolactone and is associated with fewer side effects; however, compared to spironolactone, eplerenone is a less effective antihypertensive agent.

**Follow-up after surgical treatment**

Surgical treatment of unilateral PA should correct the excessive aldosterone secretion. Persistence of PA after adrenalectomy suggests an incorrect initial diagnosis, with the patient having bilateral rather than unilateral PA. To define remission, persistent or recurrent disease after surgery, specific clinical and biochemical data are needed.

Regarding the follow-up interval, the first assessment of the postoperative outcome with at least BP and plasma potassium is recommended to perform within the first 3 months after surgery to adjust antihypertensive drugs and correct hypokalemia (due to possible persistence of hyperaldosteronism) or hyperkalemia (due to possible hypokaldosteronism) if necessary. The final outcome with measurement of BP, plasma potassium, aldosterone concentration, and plasma renin concentration or activity is recommended to be assessed at 6–12 months after adrenalectomy and re-evaluated at annual intervals indefinitely including a minimum assessment of BP and potassium concentration to rule out persistence or recurrence of PA. In addition, renal function should be monitored since most patients with longstanding PA have some degree of renal failure that is masked by glomerular hyperfiltration associated with aldosterone excess and effective PA treatment with either surgery or MRA will unmask the underlying chronic kidney disease.

**Conclusion**

PA is the most frequent cause of secondary hypertension. For unilateral cases, unilateral adrenalectomy is considered the treatment of choice, whereas bilateral forms of PA are treated mainly with MRA. The goals of treatment for PA include reversal of the adverse cardiovascular effects of hyperaldosteronism, normalization of serum potassium in patients with hypokalemia, and normalization of BP.

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Informed consent statement

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Conflicts of interest

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References


