PROGRESS IN PRIMARY ALDOSTERONISM

Mineralocorticoid antagonist treatment for aldosterone-producing adenoma

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Abstract

Mineralocorticoid receptor antagonists have been used in patients with aldosterone-producing adenomas (APAs) as a test designed to predict the blood pressure (BP) outcome of surgery. They are commonly used in patients undergoing adrenalectomy to reduce BP and increase plasma potassium levels during the preoperative period. A small number of studies have compared the effects of surgery and mineralocorticoid antagonists either on BP, on serum potassium levels, or on the incidence of cardiovascular and renal outcomes in patients with primary aldosteronism with or without an APA; these studies found no difference between the two therapeutic options. Mineralocorticoid receptor antagonists can be used as a maintenance treatment for patients with APAs, who are judged to be poor operative risks or who do not want to undergo surgery.

European Journal of Endocrinology
(2015) **172**, R125–R129

Introduction

Mineralocorticoid receptor antagonists (MRAs) are drugs that competitively bind to the mineralocorticoid receptor and block its activation by mineralocorticoids such as aldosterone. They are used as potassium-sparing diuretics and antihypertensive agents in various conditions with primary aldosteronism (PA) or secondary hyperaldosteronism, including hypertension, cardiac

failure, and edematous states. Herein, we review the clinical use of MRAs in patients with aldosterone-producing adenomas (APAs). MRAs may be used in such patients to reduce blood pressure (BP) and increase serum potassium levels during the preoperative period for patients undergoing adrenalectomy or alternatively as a maintenance treatment for patients who are judged

Invited Author's profile

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to be poor operative risks or who decline surgery. Spironolactone has also been used in the short term as a test to predict the BP outcome of adrenalectomy.

Available MRAs

Two MRAs are currently available, spironolactone (Aldactone) (and in a few countries its active metabolite canrenone) and eplerenone (Inspra) (1, 2). They are steroidal, competitive MRAs.

Spironolactone

Spironolactone, approved in 1959, is cited in the World Health Organization model list of essential medicines and is universally available. Potassium canrenoate, a spironolactone metabolite, is available in a small number of countries as tablets or for i.v. administration. As can be expected for a drug developed in 1950s, the pharmacokinetics and pharmacodynamics of spironolactone have not been studied in detail. Its absolute bioavailability in humans has not been determined. Spironolactone is rapidly metabolized in the liver into a number of metabolites including 7 α -methyl-spironolactone and canrenone. Unchanged spironolactone, 7 α -methyl-spironolactone, and canrenone all have anti-mineralocorticoid activities and their mean half-lives in normal subjects are 1.4, 13.8, and 16.5 h respectively (3, 4). The onset of action of spironolactone is delayed with the peak response occurring several days after the first dose, possibly because, during continuous treatment, active metabolites reach steady-state plasma concentrations only slowly (4). Moreover, increased natriuresis and decreased kaliuresis persist several days after discontinuation of spironolactone. In a report of five patients with low renin hypertension given 300–400 mg spironolactone daily for 5–8 weeks, plasma renin activity remained higher than the pre-spironolactone values 13–36 weeks after discontinuation of the drug (5). Although this observation has not been replicated, the effects of spironolactone on sodium and potassium homeostasis are commonly believed to be long-lasting. Spherical, laminated inclusions of 2–20 μ m, surrounded by a clear halo, have been detected in the adrenal cortex of patients undergoing adrenalectomy following prolonged treatment with spironolactone. Although they have been called ‘spironolactone bodies’, they have also been described in diverse organs following treatment with various compounds. Thus, they cannot be regarded as specific to spironolactone or to the adrenal

cortex (6). Nevertheless, guidelines for the management of PA recommend discontinuing spironolactone at least 4 weeks before assaying plasma renin and aldosterone for the diagnosis of the condition and, indeed, extend this recommendation to eplerenone (7). Spironolactone has been given once daily at doses ranging from 1 to 4 mg/kg body weight per day in patients with essential hypertension or with APAs, but there is little evidence that doses >50 mg/day lead to a greater reduction in BP (8). Spironolactone is associated with various sex-steroid-related adverse effects, mainly breast tenderness, menstrual abnormalities, decreased libido, and impotence, with an incidence rate of 6.9% at doses of 50 mg/day or less and exceeding 50% at doses of 150 mg/day or more (9).

Eplerenone

Eplerenone, an antagonist more selective than spironolactone for the mineralocorticoid receptor, was approved by the Food and Drug Administration in 2002, more than 40 years after the approval for spironolactone (10). It is mostly used to improve the survival of stable patients with left ventricular systolic dysfunction and clinical evidence of congestive heart failure after an acute myocardial infarction (11, 12). It is also used as an alternative to spironolactone in patients with essential hypertension or APAs (13). Eplerenone differs from spironolactone in that its affinity for the progesterone and androgen receptors is 500-fold lower, no active metabolites have been identified, and its elimination half-life (4–6 h) is shorter (4, 11). Eplerenone is given at doses of 25–50 mg/day to patients with cardiac failure (11, 12), and at doses of 50–100 mg once or twice daily to patients with essential hypertension (13, 14). It has been tested in patients with PA at doses from 50 to 300 mg/day in one or two daily doses (see below for details) (15, 16). In patients with essential hypertension, there were no differences in side effects between eplerenone and placebo (14).

Additional MRAs

Drospirenone is a steroidal MRA that is structurally related to 17 α -spironolactone and has anti-mineralocorticoid and anti-androgenic activities. It can reduce BP significantly, but it has progestin effects and, indeed, was developed for hormone therapy in postmenopausal women (15) and as a contraceptive pill (16).

Novel non-steroidal MRAs are at preclinical and early developmental stages (17).

Amiloride

Amiloride is not an MRA but an antagonist of the renal epithelial sodium channel. It is an alternative to MRAs, because it reduces BP and increases the serum potassium concentration. Amiloride given at doses of 20–40 mg daily had a similar antihypertensive efficacy as 50–100 g spironolactone daily in patients with low renin hypertension (18).

MRAs in the management of PA and APA

Treatment objectives in patients with PA are to reduce BP, correct hypokalemia, and to prevent or reverse any cardiovascular or renal alterations caused by the excess of aldosterone. Retrospective case–control studies found that the cardiovascular and renal consequences of hypertension were more severe in patients with PA than in patients with essential hypertension and similar levels of office BP (19, 20). Consequently, treatment objectives include correction for aldosterone hypersecretion or for the excess stimulation of mineralocorticoid receptors (21). In patients with lateralized aldosterone hypersecretion, this goal can be achieved by adrenalectomy and probably by the long-term prescription of MRAs (22), and MRAs provide a specific treatment for PA in patients who are not candidates for surgery.

Effect of MRAs on BP and kalemia

Spironolactone and eplerenone have been directly compared in patients with PA. In an open randomized trial, Karagiannis *et al.* (23) compared spironolactone (50–400 mg daily) with eplerenone (50–200 mg daily) in two groups of 17 patients with idiopathic PA. After 16 weeks of monotherapy, the decrease from baseline in systolic BP was marginally greater in the eplerenone group (29 ± 3 mmHg) than in the spironolactone group (27 ± 4 mmHg) (reported to be significant at $P < 0.05$). In a double-blind randomized cooperative trial, Parthasarathy *et al.* (24) compared spironolactone (75–225 mg once daily) with eplerenone (100–300 mg once daily) in patients with PA. The numbers of patients with idiopathic PA and those with APA were not reported. Fifty-seven of the 71 patients randomized to spironolactone and 44 of the 70 patients randomized to eplerenone completed the study. After 16 weeks, the reductions from baseline

in systolic BP were 27 ± 2 mmHg for spironolactone and 10 ± 2 mmHg for eplerenone ($P < 0.001$), and in diastolic BP, 13 ± 1 mmHg for spironolactone and 6 ± 1 mmHg for eplerenone. The trial reported by Parthasarathy *et al.* (24) had a higher statistical power and a better design than that reported by Karagiannis *et al.* (23). Consistent with findings in patients with essential hypertension (13) or cardiac failure (25), eplerenone seems to be less effective but better tolerated than spironolactone in patients with PA. The Endocrine Society clinical practice guidelines recommend spironolactone as the primary agent for the management of PA, with eplerenone as an alternative (7).

Use of MRAs to predict the outcome of adrenalectomy

It has been suggested that preoperative normalization of BP on monotherapy with high-dose spironolactone may distinguish patients with PA from those with secondary aldosteronism and patients with APAs from those with idiopathic PA (for review, see reference (26)). However, this has not been confirmed in series published since 2000 and including at least 50 consecutive patients (26, 27).

MRAs in the perioperative period

MRAs or potassium chloride is commonly prescribed to hypokalemic patients with APAs to increase kalemia before surgery. Adrenalectomy *per se* may also decrease serum potassium concentrations. Owing to the risk of hypokalemia-induced arrhythmia during anesthesia (28), all patients undergoing adrenalectomy should be given MRAs before surgery. In the trial reported by Parthasarathy *et al.* (24) serum potassium level was modestly higher on 75–225 mg spironolactone than on 100–300 mg eplerenone (3.94 vs 3.83 mmol/l, $P < 0.001$). Preoperative treatment with MRAs does not seem to increase the incidence of hypoaldosteronism or hyperkalemia after surgery (29). After surgery, MRAs should be withdrawn in the first postoperative day to avoid hyperkalemia (7).

MRAs vs surgery

The administration of MRAs is a pathophysiological treatment for patients with idiopathic PA, whereas adrenalectomy is the etiological treatment for patients with APAs. However, studies that compared spironolactone with surgery in patients with APAs found no difference between the two options for the control of either BP or serum potassium concentrations (30). As discussed earlier, patients with PA are more likely to have

cardiovascular complications than patients with essential hypertension, consistent with aldosterone excess having an etiological role independent of BP (19, 20, 31). Studies with long-term follow-up suggest that spironolactone induces a regression of left ventricular hypertrophy (32). A prospective long-term study compared patients with unilateral PA receiving spironolactone or undergoing adrenalectomy and patients with essential hypertension. The incidence of a composite endpoint (myocardial infarction, coronary revascularization, stroke, and sustained arrhythmia) did not differ between PA patients treated with spironolactone and those treated by surgery, or between patients with PA and patients with essential hypertension (22). The rate of correction of glomerular hyperfiltration and microalbuminuria has been found to be similar in patients with PA given MRAs and those undergoing adrenalectomy (31, 33). Another study reported that the quality of life is lower in patients with unilateral PA than in the general population, and that administration of spironolactone or amiloride improves the quality-of-life scores after 6 months; however, the improvement was slower and smaller on medication than following surgery (34). In view of these results, spironolactone can be considered to be the best first treatment for APAs. However, a cost-benefit analysis showed that adrenalectomy is more cost effective than lifelong treatment with MRAs if life expectancy exceeds 25 years (35).

Can MRAs cure PA?

Spontaneous remissions of PA have been reported, mostly in patients with idiopathic PA who did not undergo surgery (36, 37). Yoneda *et al.* (38) reported the case of a 41-year-old patient with lateralized PA who did not undergo surgery because of severe cardiac hypertrophy. He was treated with spironolactone. Fifteen years later, aldosterone levels were determined in the peripheral and adrenal veins because the patient wished to undergo adrenalectomy, but PA was no longer present. Nevertheless, in the vast majority of cases, MRAs do not reduce the production of aldosterone by the adrenals and do not cure PA.

Perspectives

MRAs are indicated for patients with idiopathic PA and are an effective option for patients with APAs. The limitations include the constraints of a lifelong treatment, the high prevalence of adverse events on spironolactone, and the limited efficacy and high cost of eplerenone. New potent

and highly selective MRAs could improve tolerability and reduce costs. If such agents become available, APA carriers could be offered a trial with MRAs before coming to a decision about adrenalectomy. The use of MRAs as a treatment for APAs would facilitate the management of PA, as it would limit the efforts needed to differentiate unilateral from bilateral forms of PA.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

Funding

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 14 July 2014

Revised version received 7 October 2014

Accepted 14 October 2014