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Consensus

SFE/SFHTA/AFCE consensus on primary aldosteronism, part 7: Medical treatment of primary aldosteronism

Consensus hyperaldostéronisme primaire SFE/SFHTA, groupe 7 : traitement médical de l'hyperaldostéronisme primaire

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Abstract

Spironolactone, which is a potent mineralocorticoid receptor antagonist, represents the first line medical treatment of primary aldosteronism (PA). As spironolactone is also an antagonist of the androgen and progesterone receptor, it may present side effects, especially in male patients. In case of intolerance to spironolactone, amiloride may be used to control hypokaliemia and we suggest that eplerenone, which is a more selective but less powerful antagonist of the mineralocorticoid receptor, be used in case of intolerance to spironolactone and insufficient control of hypertension by amiloride. Specific calcic inhibitors and thiazide diuretics may be used as second or third line therapy. Medical treatment of bilateral forms of PA seem to be as efficient as surgical treatment of lateralized PA for the control of hypertension and the prevention of cardiovascular and renal morbidities. This allows to propose medical treatment of PA to patients with lateralized forms of PA who refuse surgery or to patients with PA who do not want to be explored by adrenal venous sampling to determine whether they have a bilateral or lateralized form.

Keywords: Spironolactone; Amiloride; Eplerenone; Calcic inhibitor; Thiazide diuretic; Primary aldosteronism; Hypertension; Cardiovascular morbidity

Résumé

La spironolactone, antagoniste du récepteur minéralocorticoïde, est le médicament à proposer en première intention dans le traitement médical de l'hyperaldostéronisme primaire (HAP). Comme la spironolactone est également antagoniste du récepteur des androgènes et de la progestérone, elle a des effets indésirables en particulier chez l'homme. En cas d'intolérance à la spironolactone, l'amiloride permet un bon contrôle de l'hypokaliémie et nous suggérons que l'éplérénone, antagoniste plus sélectif du récepteur minéralocorticoïde, soit utilisée lorsqu'il existe une intolérance à la spironolactone et/ou une efficacité antihypertensive insuffisante de l'amiloride. En deuxième ou troisième ligne nous suggérons d'utiliser certains inhibiteurs calciques et ou thiazidique. Le traitement médical de l'HAP semble avoir une efficacité comparable au traitement chirurgical des formes latéralisées d'HAP, sur le plan des résultats tensionnels et du retentissement cardiovasculaire et rénal. De ce fait, le traitement médical de l'HAP peut être proposé aux patients porteurs d'un HAP latéralisé qui refuseraient la chirurgie ou aux patients porteurs d'un HAP qui refuseraient la réalisation d'un cathétérisme veineux surrénalien nécessaire pour déterminer si leur HAP est latéralisé ou non.

Mots clés : Spironolactone ; Amiloride ; Éplérenone ; Inhibiteur calcique ; Diurétique thiazidique ; Hyperaldostéronisme primaire ; Hypertension ; Morbidité cardiovasculaire

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R 6.1: spironolactone treatment is recommended in non-lateralized PA, and in lateralized PA for patients not wishing or unable to undergo surgery. (Strong, evidence +++)

R 6.2: in case of spironolactone intolerance, amiloride may be used as replacement or in association with low-dose spironolactone. (Strong, evidence +++)

R 6.3: in case of non-controlled hypokalemia with spironolactone intolerance, amiloride should be preferred to long-course potassium supplementation. (Strong, evidence +)

R 6.4: eplerenone may be used in case of spironolactone intolerance when amiloride proves ineffective. (Strong, evidence+)

R 6.5: in second or third line, calcium channel blockers or thiazide diuretics may be used. (Strong, evidence +)

1. Introduction

When primary aldosteronism (PA) is lateralized or results from a Conn's adenoma, laparoscopic unilateral adrenalectomy may be proposed (see section 6). In non-lateralized PA, adrenalectomy is consensually not indicated, although one study reported some benefit [1]. Medical treatment is thus widely preferred in this situation, and also offers an alternative in lateralized forms.

2. Spironolactone

Spironolactone has been the reference medical treatment for PA for more than 45 years. The literature testifies to its efficacy with respect not only to hypertension but also to protection of several target organs.

2.1. Action mechanism and pharmacology

2.1.1. Action mechanism

Spironolactone is a competitive antagonist of both aldosterone and androgen receptors and behaves as a weak agonist of the progesterone receptor. Spironolactone inhibits sodium reabsorption in the baso-lateral membrane of the principal cells of the renal collecting duct, directly by inhibiting Na/K ATPase and indirectly by inhibiting ENac, the epithelial sodium channel. The resultant potassium retention makes spironolactone a potassium-sparing diuretic. As androgen receptor antagonist and progesterone receptor agonist, spironolactone induces adverse sexual effects in both males and females.

2.1.2. Metabolism

Spironolactone has a long half-life of more than 12 hours in healthy subjects, and up to 24 hours in case of heart failure and 58 hours in case of cirrhosis of the liver. It generates 2 active metabolites, 7 α-thiomethyl-SL and canrenone, responsible for its prolonged pharmacological action.

2.1.3. Side-effects

Spironolactone enhances testosterone aromatization into estradiol, reduces testicular testosterone production, and displaces testosterone from SHBG (sex-hormone binding globulin), thus increasing its clearance. It acts as an anti-androgen by binding to androgen receptors, and as a progesterone receptor agonist.

Despite a clearly demonstrated dose–response relation for spironolactone side-effects, a significant incidence of adverse effects is found as of 25–50 mg/day. One study reported 7% incidence of gynecomastia at 6 months for doses < 50 mg/day and 52% incidence for > 150 mg/day [2].

The exact rate of menstrual disorder in premenopausal women is not known.

2.2. Efficacy of spironolactone on PA-associated hypertension and hypokalemia

Funder et al. reported mean reductions in systolic and diastolic blood pressure of 25% and 22% respectively in response to spironolactone 50–400 mg/day for 1–96 months in 7 studies totaling 122 patients [3].

Sartori et al. compared time to blood pressure normalization (< 140/90 mmHg) between 3 groups of patients: idiopathic hyperaldosteronism ($n = 58$), hypertension associated with aldosterone elevation without PA criteria ($n = 91$), and essential hypertension ($n = 160$). Spironolactone (25–200 mg/day) was administered only in idiopathic hyperaldosteronism, and provided 41% BP normalization, compared to 38% and 54% respectively in the other 2 groups. Patients with elevated aldosterone plasma levels develop resistant hypertension, even in the absence of clinically diagnosed primary aldosteronism, and have to be more agressively and specifically (anti-aldosterone treatment) targeted [4].

Ghose et al. reported a retrospective analysis of 24 patients with secreting adenoma treated medically for at least 5