

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
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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.

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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.

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Mots clés : Spironolactone ; Amiloride ; Éplérénone ; 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 aggressively 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

years with either spironolactone 100–200 mg/day or amiloride 20–40 mg/day; treatment details were not provided, and spironolactone and amiloride treatment were not distinguished. At last follow-up, four patients were receiving only potassium-sparing diuretics, thirteen a potassium-sparing diuretic plus another class (not specified), six received 3 anti-hypertensive drug classes, and one patient 4. Blood pressure fell from 175/106 to 129/79 mmHg and kalemia increased from 3.0 to 4.3 mmol/L. The adrenal mass showed no malignant progression; 5 subjects showed increased adrenal size [5].

Elevated aldosterone-to-renin ratio (ARR) is predictive of spironolactone response. In 1999, Lim et al. followed up, for a mean of 12.9 months, 28 patients diagnosed with PA on the basis of aldosterone-to-renin elevation without suppression on saline infusion or fludrocortisone test and no evidence of adenoma on abdominal CT. At baseline, patients were taking a mean of 2.1 drugs; diastolic blood pressure was above 90 mmHg in 16 of the 28 (57%). Adding spironolactone 25–50 mg/day allowed the mean number of associated drugs to be reduced to 0.7; only 1 patient had to interrupt spironolactone for poor tolerance; systolic and diastolic blood pressure diminished in all patients but 1. In 13 out of 27 patients (48%), spironolactone was administered as monotherapy [6].

2.3. *The particular case of PA remission after long-course spironolactone*

A retrospective analysis of 34 patients diagnosed with PA 3–15 years previously found that medical treatment lowered ARR and plasma aldosterone concentration to below pathological thresholds in 26 cases (76%). Surprisingly, 12 of the 34 patients were taking no anti-aldosterone treatment; other drugs (1–5 per patient) were not specified. The most strongly predictive factors for this “cure” were elevated baseline kalemia, prolonged hypertensive treatment, and female gender [7].

Yoneda et al. (2012) likewise reported normalization of blood pressure, plasma aldosterone and plasma renin in a patient with a secreting left adrenal mass treated for 5 years with spironolactone; the improvement was lasting, with persistence of the adrenal mass but resolution of all signs of secretion, as shown by absence of lateralization on adrenal vein sampling [8].

In a German retrospective series of 37 idiopathic hyperaldosteronism patients, there was a single case of complete remission (normalization of blood pressure, kalemia, aldosterone/renin ratio [ARR] and suppression test results) at 5.8 ± 0.7 years' treatment by mineralocorticoid receptor antagonist, and one case of partial remission (biological and hormonal normalization but persistent hypertension); these 2 patients were treated by spironolactone at 100 mg/day for 6 years and at 75 mg/day for 8 years, respectively [9].

2.4. *Efficacy of spironolactone against hypertension impact on target organs*

In 2005, Milliez et al. demonstrated that PA patients with hypertension were more exposed to atrial fibrillation, myocardial infarction and stroke than other patients with comparable

hypertension. Mineralocorticoid receptor antagonists can thus be expected to reduce impact on target organs; this was shown for spironolactone for cardiac and renal effects and for eplerenone for cardiac and vascular effects [10].

2.4.1. *Cardiac impact*

The above-mentioned case report by Yoneda et al. showed not only clinical and biological normalization under medical treatment but also lasting regression of left ventricle hypertrophy [8]. In 2013, Ori et al. reported a series of 48 patients (24 PA, 24 low-renin hypertension), 39 of whom (81%) presented with left ventricular hypertrophy. All received low-dose spironolactone (33 ± 14 mg/day at 1 year and 29 ± 12 mg/day at 3 years). At 1 year, left ventricle mass had significantly diminished in 44 patients (92%) and normalized in 16 of the 39 patients with initial hypertrophy (41%); at 3 years, left ventricular mass had continued to diminish and was normal in 57% of cases. There was no correlation between changes in left ventricular mass and in blood pressure [11].

Catena et al. compared the effects of adrenalectomy ($n=24$) and spironolactone ($n=30$) on left ventricular mass in 54 PA patients followed up for a mean of 6.4 years. Blood pressure was comparable between groups at follow-up: 135/82 and 137/82 mmHg. During the first year, left ventricular mass had decreased significantly in the adrenalectomy but not the spironolactone group; at last follow-up, however, the values were the same. Diastolic function was only slightly improved. In both groups, reduction in left ventricle mass correlated directly with change in blood pressure and with baseline aldosterone level [12,13].

2.4.2. *Renal impact*

Catena et al. studied renal function in 56 PA patients. At baseline, patients with renin levels > 2.5 pg/mL had higher blood pressure, kalemia and albuminuria but lower creatinine clearance; patients with plasma aldosterone > 225 pg/mL had lower kalemia and greater creatinine clearance. Creatinine clearance correlated positively with plasma aldosterone and negatively with renin. Twenty-five of the 30 patients with adrenal adenoma underwent adrenalectomy; 2 of the other 5 had bilateral adenoma and 3 refused surgery. Patients were treated surgically or medically with 50–300 mg/day spironolactone; at a mean of 6.2 years' prospective follow-up, hypertension proved more difficult to control and the reduction in albuminuria was slighter in those with higher baseline renin levels [14]. Non-suppressed renin in PA thus seems predictive of poorer control of hypertension and more severe renal involvement.

In 54 PA patients with renal cysts, cyst progression had ceased at a mean of 6.2 years' ultrasound follow-up, due, according to the authors, to low kalemia [15].

In 2012, Fourkotiis reported results in 2 cohorts: 29 patients with recently diagnosed PA, followed up for 1 year after treatment initiation, and 119 PA patients assessed at a mean of 5.3 and 6.8 years after treatment initiation. In a separate transverse population, renal function was assessed according to treatment by adrenalectomy ($n=86$), spironolactone ($n=65$) or eplerenone ($n=18$). In the first cohort, glomerular filtration rate and urinary

albumin/creatinine ratio diminished rapidly after treatment initiation but remained unchanged in the second cohort (in which hypertension was well-controlled). The transverse population showed no differences in glomerular filtration rate or urinary albumin/creatinine ratio according to treatment, but kalemia was lower and the number of associated drugs greater with eplerenone [16]. This study thus suggests comparable efficacy between surgical and medical treatment of PA in terms of renal impact.

3. Eplerenone

3.1. Action mechanism and pharmacology

3.1.1. Action mechanism

Eplerenone has no active metabolites. Its half-life is 3–4 hours, necessitating twice-daily administration. It is metabolized in the liver by CYP 3A4, a member of cytochrome P450, and drugs impacting CYP 3A4 function can thus affect concentration. It exerts a weaker but much more selective inhibitory action than spironolactone, with 60% of spironolactone's mineralocorticoid receptor antagonism but 500-fold lower affinity for sex steroid receptors [17]. Tolerance is better, and cost higher. In case of moderate liver involvement, no dose adaptation is required, but eplerenone should thus be used with caution in case of severe liver disease, safety and efficacy not having been determined.

3.1.2. Side-effects

Lower affinity for sex steroid receptors explains why eplerenone has far fewer side-effects than spironolactone [17]. In the EPHEsus study, in 6500 patients with left ventricular dysfunction following myocardial infarction, incidence of gynecomastia and impotence were equivalent under eplerenone or placebo: 1% and 1.1%, respectively [18].

3.2. Efficacy of eplerenone on PA-associated hypertension and hypokalemia

In 2011, Parthasarathy et al. compared 2 groups of patients with biologically diagnosed PA, receiving 1 week's placebo therapy and then randomized between 16 weeks' spironolactone 75–225 mg/day or eplerenone 100–300 mg/day under double-blind. Diastolic blood pressure fell less under eplerenone than spironolactone (–5.6 vs. –12.5 mm Hg), but there were more frequent side-effects under spironolactone (21.2% vs. 4.5% gynecomastia in males, and 21.1% vs. 0% mastodynia in females). The rate of adrenal adenoma was not specified, and only biological criteria of PA were required for inclusion, without systematic radiological assessment [19].

The 2008 study by Karagiannis et al., using the PROBE method, showed very different results, with comparable efficacy for spironolactone and eplerenone. Thirty-four idiopathic hyperaldosteronism patients received 2 weeks' placebo followed by 24 weeks' spironolactone or eplerenone, both 25 mg twice-daily. The main endpoint was blood pressure < 140/90 mm Hg

after 16 weeks' monotherapy, with dosage gradually increased up to 400 and 200 mg/day for spironolactone and eplerenone, respectively. Blood pressure normalized in 13/17 and 14/17 patients, respectively (NS), but systolic pressure fell more rapidly under eplerenone. Kalemia normalized (> 3.5 mmol/L) in all patients by week 4. Moderate hyperkalemia was observed in 2 patients under spironolactone 400 mg/day and 3 under eplerenone 150 mg/day. In 2 patients, painful bilateral gynecomastia under spironolactone 400 mg/day at week 16 regressed under eplerenone 150 mg/day, without loss of control of hypertension [20].

3.3. Efficacy of eplerenone against PA impact on target organs

Pitt et al., in the “4E-LVH” study of 202 patients, showed that eplerenone 200 mg/day was as effective as enalapril 40 mg/day in reducing left ventricular mass and controlling hypertension, and that associating 200 mg eplerenone to 10 mg enalapril was more effective than eplerenone alone; but their population was composed of essential hypertension patients with left ventricle hypertrophy rather than hypertension patients with PA.

Pitt et al. compared eplerenone versus atenolol in a double-blind trial in 16 hypertension patients followed up for 1 year. For comparable blood pressure control, arterial rigid resistance increased under atenolol whereas it improved under eplerenone. Collagen/elastin ratio and inflammation markers were reduced in the eplerenone but not the atenolol group. However, once again, this study included only patients with essential hypertension, and not those with PA-associated hypertension [21].

4. Amiloride

The effect of amiloride (10–40 mg/day for 6 months) was assessed by Griffing in 12 PA patients (4 with adenoma, 8 with idiopathic hyperaldosteronism). Kalemia increased by 0.96 mmol/L and blood pressure fell by 22/10 mm Hg, but complementary medication was needed in most cases to normalize blood pressure. There was no correlation between treatment response and aldosterone concentration or presence of unilateral adenoma [22].

Triamterene–hydrochlorothiazide association also proved effective on hypertension and kalemia in a series of PA reported by Ganguly and Weinberger in 1981 [23].

5. Dihydropyridinic calcium channel blockers

Some dihydropyridinic calcium channel blockers are mineralocorticoid receptor (MR) antagonists, and moreover block MR co-activator recruitment and inhibit aldosterone-induced gene expression. The efficacy of calcium channel blockers to counteract aldosterone effect varies from molecule to molecule, nimodipine, felodipine and nitrendipine being the strongest and amlodipine the weakest; diltiazem and verapamil have no effect on mineralocorticoid receptors [24].

6. Aldosterone synthase inhibitors

Aldosterone and cortisol are produced by conversion of cholesterol in the adrenal cortex. The final stages of conversion involve cytochrome P450 aldosterone synthase and 11 β -hydroxylase enzymes encoded by the CYP11B2 and CYP11B1 genes, respectively. Selective aldosterone synthase inhibitors efficiently reduce aldosterone levels. Amar et al. (2013) compared the antihypertensive and biological effects of an aldosterone synthase inhibitor (LCI699) and a mineralocorticoid receptor antagonist (eplerenone) in 14 PA patients, with the following protocol: placebo for 2 weeks, LCI699 for the following 2 weeks and placebo again for 1 week, then eplerenone (associated to the patient's previous anti-hypertensive treatment) for 30 days (at 50 mg twice daily, increased to 100 mg twice daily in 12 patients). Ambulatory systolic blood pressure decreased more strongly under eplerenone than LCI699 ($\Delta = 5.34$ mmHg; $P = 0.027$), kalemia increased more strongly (4.3 vs. 3.9 mmol/L; $P = 0.009$), as did renin concentration (+131% vs. +39%; $P = 0.023$). Aldosterone levels fell by 75% under the aldosterone synthase inhibitor and increased by 89% under the mineralocorticoid receptor antagonist. The aldosterone synthase inhibitor thus reduced target organ exposure to aldosterone [25].

7. Cyanodihydropyridines

Cyanodihydropyridines were developed recently, and show excellent mineralocorticoid receptor antagonism, without calcium channel blockade. They are presently at the animal trial phase, and no human phase I study has yet been reported [26].

8. Comparison of efficacy between surgical and medical management of PA

This section will review studies comparing medical and surgical treatment in terms of the various impacts of PA: blood pressure, kalemia, and cardiovascular, renal and metabolic effects. It is important to state first that prospective randomized comparative studies designed to address this issue are still lacking. These would obviously need to be conducted in a population of patients with a form of lateralized PA (Conn's adenoma or unilateral hyperplasia), whereas most of the published studies compare surgery in lateralized PA versus medical treatment in bilateral PA (idiopathic hyperaldosteronism).

8.1. Hypertension

Two non-randomized prospective studies reported that medical treatment of idiopathic hyperaldosteronism was less effective against hypertension than surgical treatment of aldosterone-producing adenoma [27,28], while two other studies reported comparable efficacy [12,29].

8.2. Hypokalemia

Two studies reported that medical treatment of idiopathic hyperaldosteronism was as effective against hypokalemia as surgical treatment of aldosterone-producing adenoma [28,29].

8.3. Arterial rigidity

Surgery reduced arterial rigidity in most cases of aldosterone-producing adenoma, unlike spironolactone in idiopathic hyperaldosteronism [28].

8.4. Left ventricle hypertrophy, stroke

Two observational [30,31] and 1 prospective study [27] reported that spironolactone treatment of idiopathic hyperaldosteronism was less effective in reducing left ventricular hypertrophy than surgical treatment of aldosterone-producing adenoma. However, 3 prospective studies found the two treatments equally effective, although results with spironolactone were more progressive [12,27,32].

No significant difference was found between the two forms of treatment in reducing the risk of acute ischemic stroke [32].

8.5. Renal function

It should be borne in mind that the renal impact of PA begins with an increase in glomerular filtration rate and urinary albumin excretion, progressing toward kidney failure in the long term. PA treatment can thus be expected to reduce glomerular filtration and urinary albumin in the short term and, of course, protect kidney function in the long term.

Results suggest comparable efficacy between medical and surgical treatment: in 3 prospective studies [14,33,34] both provided comparable reduction in glomerular filtration rate, urinary albumin, resistance index and pulsatility; similar results were found in a case-control study [35] and a retrospective study [16], in which both provided similar reduction in glomerular filtration and urinary albumin. In two other prospective studies [36,37], medical and surgical treatment both reduced glomerular filtration and urinary albumin, but results were not compared between the two.

In contrast, a prospective study [38] at 1 year's follow-up reported that surgery, but not spironolactone, reduced glomerular filtration, urinary albumin and resistance index.

A recent meta-analysis [39], however, found reduced glomerular filtration rate with both treatments.

8.6. Metabolic markers

Two studies showed that aldosterone-producing adenoma surgery improved insulin sensitivity on hyperinsulinic–euglycemic clamp [29] or insulin resistance on homeostasis-model assessment (HOMA) [31], but that spironolactone did not produce these effects in idiopathic hyperaldosteronism.

9. Conclusion

Keeping in mind the above limitations (comparisons made with differing forms of PA), medical and surgical treatment can be said to show comparable efficacy in terms of hypertension, hypokalemia and the cardiac and renal impact of PA. This has important implications for choice of treatment strategy (medical or surgical) in lateralized PA.

Disclosure of interest

A. Pechère participated in Servier, Daiiky sankyo, Takeda, and Menarini advisory boards.

D. Herpin has nothing to disclose. H. Lefebvre received travel & research grants and/or payments for lectures from AstraZeneca, MSD, Novo-Nordisk, Novartis, Ipsen, Sanofi, Sandoz & Pfizer laboratories.

Appendix A. Precautions in medical treatment of PA

Interactions and particular situations

Drug associations and interactions

Amiloride and spironolactone: There have been few clinical trials of two associated potassium-raising drugs. One, in healthy volunteers, associated amiloride 5 mg and spironolactone 25 mg for 4 weeks, and found a slight rise in kalemia of 0.4 mmol/L.

Indomethacin increases hyperkalemia risk when associated to spironolactone. This is said to be due to hypoaldosteronism-hyporeninism, with diminished 24-hour potassium excretion, thought to be caused by a proximal and distal renal tubule impact of indomethacin [40].

NSAIDs, aspirin: Aspirin, indomethacin and mefenamic acid weaken the diuretic effect of spironolactone by blocking renal tubule secretion of canrenone, a major active metabolite of spironolactone.

A prospective cohort study analyzed drug interactions in 445 non-hospitalized patients aged over 75 years in Brazil. Spironolactone interaction rate was 17%, inducing hyperkalemia. Concomitant angiotensin-II receptor antagonists (captopril, enalapril, losartan), reduced glomerular filtration rate and comorbidities such as type-2 diabetes or hypertension were risk factors of hyperkalemia.

Digoxin: Spironolactone reduces clearance and increases serum concentration and half-life of digoxin. A important confounding factor is possible interference between spironolactone and/or its metabolites and the digoxin assay method: the former may reduce or increase serum levels, complicating surveillance [41]. Reassuringly, spironolactone and digoxin were co-prescribed in a large-scale clinical trial in heart failure, in which 75% of the 822 patients allocated to spironolactone received concomitant digoxin [42,43], with surveillance of signs and symptoms of digitalis toxicity, and of digoxinemia.

Abiraterone: Spironolactone may reduce the effect of abiraterone, which is prescribed in prostate cancer. Cancer progression was reported in an 80 year-old patient receiving spironolactone for heart failure. After 1 week's spironolactone,

prostate-specific antigen levels had doubled; interrupting spironolactone brought levels back to baseline within 2 weeks [44]. In vitro, spironolactone seems to enhance mutated androgen receptor expression in patients receiving abiraterone for castration-resistant prostate cancer [45].

Carbenoxolone: Associating spironolactone and carbenoxolone may reduce the efficacy of both drugs.

Eplerenone:

Strong CYP3A4 inhibitors: There is strong pharmacologic interaction between eplerenone and powerful CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, nelfinavir, atazanavir, clarithromycin, telithromycin, nefazadone and nicardipine [46]. Simultaneous administration of any of these with eplerenone may considerably increase serum eplerenone concentration.

Weak-to-moderate CYP3A4 inhibitors: Macrolides (erythromycin), saquinavir, amiodarone, diltiazem, verapamil and fluconazole reduce eplerenone metabolism, increasing the area under the curve up to 2-fold.

Recommendation: Eplerenone dose should not exceed 25 mg when associated to weak-to-moderate CYP3A4 inhibitors.

CYP3A4 inducers: Millepertuis, rifampicin, carbamazepine, phenytoin and phenobarbital, which are all strong CYP3A4 inducers, administered simultaneously with eplerenone, reduce the area under the curve for eplerenone by up to 30%, leading to treatment failure. Concomitant administration of trimethoprim, which is also a strong inducer of CYP3A4, with eplerenone increases hyperkalemia risk. Surveillance of kalemia and renal function is therefore required, especially in elderly patients and those with kidney failure [47].

Angiotensin converting enzyme inhibitors and angiotensin-II receptor antagonists: Caution should be taken in simultaneously associating eplerenone to angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists due to hyperkalemia risk in case of kidney failure, for example in elderly patients. Close surveillance of kalemia and renal function is recommended.

Alpha-blockers (e.g., prazosin, alfuzosin): Associating alpha-blockers to eplerenone may increase the hypotensive effect and/or induce orthostatic hypotension. Clinical control of orthostatic hypotension is recommended when alpha-blockers are associated to eplerenone.

Tricyclic antidepressants, neuroleptics, amifostine, baclofen: There is a risk of increased antihypertensive effect and orthostatic hypotension when these drugs are associated to eplerenone.

Glucocorticoids, tetracosactide: Simultaneous administration of glucocorticoids or tetracosactide with eplerenone may probably reduce the antihypertensive effect by salt and water retention.

Digoxin: Area under the curve for digoxin increases by 16% (90% CI: 4%–30%) when administered concomitantly with eplerenone, requiring caution if digoxin levels are near the upper therapeutic limit.

Warfarin: Caution is recommended if warfarin levels are near the upper therapeutic limit.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may cause acute kidney failure by direct impact on glomerular filtration, especially in at-risk patients (elderly and/or dehydrated). Patients receiving associated eplerenone and NSAIDs need to be well-hydrated and renal function should be checked before treatment initiation.

Lithium: There have been no studies of drug interaction between lithium and eplerenone. However, lithium toxicity has been reported in patients receiving lithium concomitantly to diuretics or angiotensin converting enzyme inhibitors. Associating lithium to eplerenone should be avoided; if the association is unavoidable, plasma lithium concentrations should be closely monitored.

Cyclosporine, tacrolimus: Cyclosporine and tacrolimus may impair renal function and increase hyperkalemia risk; association to eplerenone should be avoided; if the association is unavoidable, kalemia and renal function should be closely monitored.

Particular situations

Kidney failure:

In kidney failure, angiotensin converting enzyme inhibitors, angiotensin-II and renin antagonists and heparin, including low molecular weight heparin, may induce hyperkalemia if associated to spironolactone or eplerenone.

Pregnancy

PA is rare in pregnancy (about 30 reported cases since 1962), and usually implicates an adenoma.

Spironolactone: Tumors have been reported in rats following high doses of spironolactone, probably by induction of species-specific liver enzymes (cytochrome P-450). Feminization of external genitalia was reported in male descendants of female rats exposed during gestation to daily doses of around 160 mg/kg body weight; endocrine disorders (changes in plasma hormone levels) were found in young male and female descendants as of about 80 mg/kg, and reduced prostate weight in male descendants following 40 mg/kg.

Eplerenone: Studies in rats and rabbits found no teratogenic effect; however, female rabbits showed weight loss and increased fetal resorption (after implantation) and increased miscarriage rates with the highest doses of eplerenone. In one case, an African woman aged 34 years was investigated at 21 weeks of pregnancy and showed stage 2–3 hypertension, 1.9 mmol/L hypokalemia and metabolic alkalosis (HCO_3^- 32 mEq/L), with a left adrenal mass which proved to be a Conn's adenoma; due to persistent hypokalemia and arrhythmia at 27 weeks, eplerenone 50 mg twice daily was initiated, resulting in normalized kalemia and blood pressure and the birth of a male child without signs of feminization [48]. Another case of pregnancy associated with Gitelman's syndrome was continued to full-term under 50 mg eplerenone twice daily; the child was in good health at 2 years of life [49]. Another case report concerned a woman with proven Conn's syndrome, operated on post-partum, and successfully treated in terms of kalemia and blood pressure by amiloride between weeks 19 and 38 of gestation.

In conclusion, in PA, spironolactone should be interrupted during pregnancy; the normal drop in blood pressure during the

first two trimesters authorizes this attitude. Nifedipine 20–60 mg/day should then be initiated. Kalemia should be monitored. If aldosterone needs to be blocked, eplerenone or amiloride should be prescribed [48].

Lactation

Canrenone, a spironolactone metabolite, passes into the breast milk; spironolactone is therefore not recommended in nursing mothers.

It is not known whether eplerenone passes into the breast milk after oral administration; preclinical studies found eplerenone and/or metabolites in milk in rats. Breast feeding should therefore be avoided in case of strict indications for eplerenone.

Rare adverse effects

Breast cancer

A carcinogenic effect of spironolactone on the mammary gland was disproven by a large retrospective cohort study of more than 1 million women aged over 55 years in the UK. Incidence of breast cancer at a mean 4.1 years' follow-up in 28,000 women exposed to spironolactone between 1987 and 2010 was comparable to that in controls matched for age and socioeconomic status [50].

Digestive hemorrhage

In 2 case-control studies [51,52] and 1 cohort study, increased incidence of upper digestive hemorrhage was associated with spironolactone administration.

Spironolactone reduces vascular reactivity to noradrenaline and adrenaline, and caution is mandatory in patients under local or general anesthesia.

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