Therapeutic Reviews

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Spironolactone AHFS 24:32.20

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Class: Potassium-sparing diuretic; aldosterone antagonist.

Indications: Ascites and peripheral edema associated with portal hypertension and hyperaldosteronism (i.e. cirrhosis, hepatocellular cancer, extensive hepatic metastases), CHF, nephrotic syndrome, primary hyperaldosteronism, †hypertension.

Contraindications: Hyperkalemia, Addison's disease, anuria, severe renal impairment, concurrent use with potassium supplements or potassium-sparing diuretics.

Pharmacology

Spironolactone and two metabolites (7α-thiomethyl-spironolactone and canrenone) bind to cytoplasmic mineralocorticoid receptors and function as aldosterone antagonists. This results in a potassium-sparing diuretic effect in the distal tubules of the kidney.

A diuretic-induced reduction in plasma volume can activate several neurohumoral systems, e.g. the renin-aldosterone-angiotensin system, sympathetic nervous system, and ADH secretion, resulting in impaired renal perfusion and increased Na^+ and water resorption. These changes contribute towards a reduced effect of the diuretic ('diuretic resistance') and also renal impairment.

In patients with cirrhosis receiving spironolactone ± **furosemide**, improved renal function and diuresis is seen with co-administration of **octreotide** 300microgram SC b.i.d. or **clonidine** 75microgram PO b.i.d. due to inhibition of the renin-aldosterone-angiotensin (**octreotide** and **clonidine**) and sympathetic nervous (**clonidine**) systems.[1–3] Patients in the **clonidine** study were considered to have an overactive sympathetic nervous system based on a higher than normal serum norepinephrine (noradrenaline) level.[3]

Spironolactone also binds to the androgen receptor and to a lesser extent estrogen and progesterone receptors. The resultant anti-androgenic effect is used to treat acne and hirsutism in women, particularly when associated with polycystic ovary syndrome. It can also result in undesirable effects such as menstrual disorders and, in

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men, gynecomastia, breast pain or impotence. **Eplerenone**, an aldosterone antagonist with greater selectively for the mineralocorticoid receptor, has been used as an alternative in these circumstances;[4,5] it is substituted for spironolactone on a 1:1 basis.[6]

Caution is required when using spironolactone in patients with prostate cancer. Although there are reports of cancer regression in keeping with an androgen blocking effect, disease progression has also been reported.[7] It is suggested that spironolactone acts as an androgen receptor modulator and thus can exert both anti- and pro-androgenic effects.

Aldosterone binds to the mineralocorticoid receptor and activates pro-inflammatory and other cell pathways.[8–11] Thus, by preventing the binding of aldosterone, spironolactone has anti-inflammatory and other effects. Although the full therapeutic potential of this remains to be determined, benefit is seen with spironolactone in various experimental and clinical settings, with reductions in cancer growth, cancer cachexia and insulin resistance, for example.[12–14]

Ascites: Hyperaldosteronism is a concomitant of ascites associated with portal hypertension (a *transudate* with a relatively low albumin concentration, best indicated by a serum–ascites albumin difference of ≥11g/L) as seen in cirrhosis, hepatocellular cancer, extensive hepatic metastases.[15,16] Most evidence comes from cirrhosis, but spironolactone in a median daily dose of 200–300mg may benefit most patients with these conditions (90% in cirrhosis).[15–20]

In patients with cirrhosis, the combined use of spironolactone + **furosemide** provides a more rapid diuretic effect than spironolactone alone, but requires closer monitoring and more frequent dose adjustments.[18] Thus, particularly in outpatients, the initial use of spironolactone alone may be preferable.[20] In contrast, treatment with even large PO doses of a loop diuretic alone, e.g. **furosemide** 200mg, generally fails to reduce ascites.[21]

Note: Paracentesis is used for patients failing to respond to or tolerate diuretic therapy. Paracentesis is also preferable for patients with predominantly peritoneal ascites (an *exudate* with relatively high albumin concentration, best indicated by a serum–ascites albumin gradient of ≤11g/L) or chylous ascites as these are unlikely to respond to diuretics,[17,19] and also for patients with a tense distended abdomen in need of rapid relief. For patients requiring frequent paracentesis and a prognosis of >1 month, an indwelling tunnelled drain can be considered, e.g. Pleurx® catheter. Patients are taught to drain off fluid using special drainage sets with vacuum bottles, initially up to 2L every day for 1–2 weeks, and then as required, generally alternate days.

CHF: Spironolactone improves morbidity and mortality in patients with CHF and a reduced left ventricular ejection fraction. It is added in low dose (e.g. 12.5mg–25mg) to standard treatment.[6,22,23] Its aldosterone antagonist action helps reduce vascular and myocardial fibrosis, sympathetic nervous system activation, baroreceptor dysfunction and K^+ and Mg^{2+} depletion.[24]

Hypertension: Aldosterone antagonists are used as a fourth-line add-on therapy in patients with hypertension failing to respond to more usual antihypertensive drugs.[25,26]

Spironolactone is extensively metabolized. The 7α-thiomethyl-spironolactone and canrenone metabolites have long half-lives and are excreted in the urine. Consequently, because of their accumulation and increased risk of hyperkalemia, the use of spironolactone requires caution in mild–moderate renal impairment, and is generally contra-indicated in severe renal impairment.

Bioavailability 60–90%.
Onset of action 2–4h.
Maximum effect 7h (single dose), 2–3 days (multiple doses).
Time to peak plasma concentration 2–3h; active metabolites 3–4.5h PO.
Plasma half-life 1–1.5h; active metabolites 14–17h (multiple doses).
Duration of action >24h (single dose), 2–3 days (multiple doses).

Cautions

Prostate cancer (see Pharmacology).

Elderly; hepatic impairment, may induce reversible hyperchloremic metabolic acidosis in patients with decompensated hepatic cirrhosis; renal impairment (see Dose and use). Initial drowsiness and dizziness (may impair driving).

Drug interactions

Serious additive pharmacodynamic interactions with other drugs, notably *hyperkalemia* with potassium supplements (avoid concurrent use), table salt substitutes (contain both potassium and sodium chlorides), potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, certain antimicrobials (**trimethoprim**, **nitrofurantoin**), **ciclosporin**, LMWH and **tacrolimus**, particularly if other risk factors also present, e.g. elderly, renal impairment, diabetes.[27–29]

Spironolactone may induce *hyponatremia*, particularly if used with other diuretics. This natriuretic effect is reduced by **aspirin**, **indomethacin** and possibly other NSAIDs.

Spironolactone increases the plasma concentration of digoxin by up to 25% and can interfere with digoxin plasma concentration assays. The latter concern can be addressed by measuring free digoxin levels using a chemiluminescent assay.[28]

Undesirable effects

Very common (>10%): CNS disturbances (drowsiness, lethargy, confusion, headache, fever, ataxia, fatigue), GI disturbances (anorexia, dyspepsia, nausea, vomiting, peptic ulceration, colic).
Common (<10%, >1%): gastritis, hyperkalemia, gynecomastia, breast pain.[30]

Dose and use

To reduce the risk of gastric irritation, the patient should be advised to take the drug with food. If, despite this, once daily spironolactone causes nausea and vomiting, try giving in divided doses.

For patients with swallowing difficulties, although an unauthorized oral suspension can be compounded, it is expensive. A cheaper alternative is to disperse generic spironolactone tablets in water (takes about 10 minutes with stirring).

In patients with ascites and moderate renal impairment (e.g. eGFR 30−59mL/min/1.73m^2), halve the recommended dose.

Cirrhotic or malignant ascites associated with portal hypertension

Most experience comes from cirrhotic ascites.[15,16,18,20,21,31] Elimination of ascites may take 10−28 days:

- when close monitoring is possible (e.g. inpatients) spironolactone 100mg PO and **furosemide** 40mg PO each morning are started together. If necessary, both are increased every 3−5 days maintaining the 100mg:40mg ratio, up to a usual maximum of 400mg and 160mg respectively
- when close monitoring is *not* possible (e.g. outpatients) or when minimal fluid overload:
  - ➢ start with spironolactone alone 100−200mg PO each morning
  - ➢ if necessary, increase by 100mg every 3−5 days
  - ➢ typical maintenance dose 200−300mg/24h; maximum dose 400−600mg/24h
  - ➢ if not achieving the desired weight loss with spironolactone 300−400mg/24h, consider adding **furosemide** 40−80mg each morning.

Monitor body weight and renal function:

- adjust doses to achieve a weight loss of 0.5−1kg/24h (<0.5kg/24h when peripheral oedema absent)
- if Na^+ falls to <120mEq/L, temporarily stop diuretics
- if K^+ falls to <3.5mEq/L, temporarily stop or decrease the dose of **furosemide**
- if K^+ rises to >5.5mEq/L, halve the dose of spironolactone; if >6mmol/L, temporarily stop spironolactone
- if creatinine rises to >1.7mg/dL (>150micromol/L), temporarily stop diuretics.

Even if paracentesis becomes necessary, diuretics should be continued because they reduce the rate of recurrence. (Note. When >5L are to be removed, stop diuretics 2 days before paracentesis and start again 1−2 days afterwards.)[32]

Severe CHF (NYHA class III or IV disease)

Seek specialist advice. The following is based on several sets of published guidelines:

- do *not* prescribe spironolactone unless serum K^+ <5mEq/L and creatinine <2.3mg/dL (<200micromol/L) or eGFR >30mL/min/1.73m^2
- start with 12.5−25mg PO once daily; check serum K^+ and creatinine after 4−7 days
- if necessary, *after 1 month*, increase to 25−50mg once daily; check serum K^+ and creatinine after 1 week
- if K^+ rises to >5mmol/L, halve the dose; if >5.5mEq/L, stop spironolactone completely
- occasionally, higher doses are used
- it is particularly important to monitor potassium levels when spironolactone and an ACE inhibitor are prescribed concurrently.[22,24,29,33,34]

Resistant hypertension

Seek specialist advice. Used as a fourth-line add-on therapy for hypertension not responding to the combination of three more usual antihypertensive drugs:

- do not prescribe if serum K^+ is >4.5mEq/L
- start with 25mg PO once daily; check serum Na^+, K^+ and creatinine within 1 month and repeat at intervals thereafter
- typical dose 25−50mg once daily, maximum dose 100mg.[25,35]

Supply

Spironolactone (generic)

Tablets 25mg, 50mg, 100mg, 28 days @ 200mg each morning = $50.

Spironolactone oral suspension can also be prepared locally for individual patients.[36]

Abbreviations/Key

†	Off-label use
ACE	Angiotensin-converting enzyme
ADH	Antidiuretic hormone (vasopressin)
b.i.d.	bis in die, twice daily
CHF	Congestive heart failure
CNS	Central nervous system
GI	Gastrointestinal
LMWH	Low molecular weight heparin
NSAID	Nonsteroidal anti-inflammatory drug
PO	Per os, by mouth
SC	Subcutaneous

References

1. Kalambokis G, et al. Renal effects of treatment with diuretics, octreotide or both, in non-azotemic cirrhotic patients with ascites. Nephrol Dial Transplant 2005;20:1623−1629.

2. Kalambokis G, et al. The effects of treatment with octreotide, diuretics, or both on portal hemodynamics in non-azotemic cirrhotic patients with ascites. J Clin Gastroenterol 2006;40:342−346.

3. Lenaerts A, et al. Effects of clonidine on diuretic response in ascitic patients with cirrhosis and activation of sympathetic nervous system. Hepatology 2006;44:844−849.

4. Barnes BJ, Howard PA. Eplerenone: a selective aldosterone receptor antagonist for patients with heart failure. Ann Pharmacother 2005;39:68−76.

5. Dimitriadis G, et al. Eplerenone reverses spironolactone-induced painful gynaecomastia in cirrhotics. Hepatol Int 2011;5:738−739.

6. Ponikowski P, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129−2200.

7. Sundar S, Dickinson PD. Spironolactone, a possible selective androgen receptor modulator, should be used with caution in patients with metastatic carcinoma of the prostate. BMJ Case Rep 2012 Feb 25; pii: bcr1120115238.

8. Chantong B, et al. Mineralocorticoid and glucocorticoid receptors differentially regulate NF-kappaB activity and pro-inflammatory cytokine production in murine BV-2 microglial cells. J Neuroinflammation 2012;9:260.

9. Syngle A, et al. Effect of spironolactone on endothelial dysfunction in rheumatoid arthritis. Scand J Rheumatol 2009;38:15−22.

10. Syngle A, et al. Spironolactone improves endothelial dysfunction in ankylosing spondylitis. Clin Rheumatol 2013;32:1029−1036.

11. Sun YE, et al. Intrathecal injection of spironolactone attenuates radicular pain by inhibition of spinal microglia activation in a rat model. PLoS One 2012;7:e39897.

12. King S, et al. Evidence for aldosterone-dependent growth of renal cell carcinoma. Int J Exp Pathol 2014;95:244−250.

13. Springer J, et al. Prevention of liver cancer cachexia-induced cardiac wasting and heart failure. Eur Heart J 2014;35:932−941.

14. Ogino K, et al. Spironolactone, not furosemide, improved insulin resistance in patients with chronic heart failure. Int J Cardiol 2014;171:398−403.

15. Greenway B, et al. Control of malignant ascites with spironolactone. Br J Surg 1982;69:441−442.

16. Fernandez-Esparrach G, et al. Diuretic requirements after therapeutic paracentesis in non-azotemic patients with cirrhosis. A randomized double-blind trial of spironolactone versus placebo. J Hepatol 1997;26:614−620; erratum 1430.

17. Pockros P, et al. Mobilization of malignant ascites with diuretics is dependent on ascitic fluid characteristics. Gastroenterology 1992;103:1302−1306.

18. Moore KP, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003;38:258–266.

19. Becker G, et al. Malignant ascites: systematic review and guideline for treatment. Eur J Cancer 2006;42:589–597.

20. Runyon BA. Management of adult patients with ascites due to cirrhosis: Update 2012 American Association for the Study of Liver Diseases. Available from: https://www.aasld.org/sites/default/files/guideline_documents/adultascitesenhanced.pdf 2012.

21. Fogel M, et al. Diuresis in the ascitic patient: a randomized controlled trial of three regimens. J Clin Gastroenterol 1981;3(Suppl 1):73–80.

22. NICE. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care Clinical Guideline. CG108. Available from: www.nice.org.uk 2010.

23. Yancy CW, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:e240–e327.

24. Swedberg K, et al. Guidelines for the diagnosis and treatment of chronic heart failure. full text (update 2005). Eur Heart J 2005. Available from: 10.1093/eurheartj/ehi205.

25. NICE. Hypertension. Clinical Guideline. CG127. Available from: www.nice.org.uk 2011.

26. Wang C, et al. Efficacy and safety of spironolactone in patients with resistant hypertension: a meta-analysis of randomised controlled trials. Heart Lung Circ 2016;25:1021–1030.

27. Antoniou T, et al. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. CMAJ 2015;187:e138–e143.

28. Baxter K, Preston CL Stockley's Drug Interactions. London: Pharmaceutical Press Available from: www.medicinescomplete.com. Accessed July 2014.

29. MHRA. Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia. Drug Safety Update. Available from: www.gov.uk/drug-safety-update 2016.

30. Williams EM, et al. Use and side-effect profile of spironolactone in a private cardiologist's practice. Clin Cardiol 2006;29:149–153.

31. Sharma S, Walsh D. Management of symptomatic malignant ascites with diuretics: two case reports and a review of the literature. J Pain Symptom Manage 1995;10:237–242.

32. Twycross R, Wilcock A. Introducing palliative care, 5th ed. Nottingham. UK: Palliativedrugs.com Ltd., 2016:138–142.

33. Arnold JM, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. [erratum appears in Can J Cardiol 2006;22:271]. Can J Cardiol 2006;22:23–45.

34. Shchekochikhin D, et al. Increased spironolactone in advanced heart failure: effect of doses greater than 25 mg/day on plasma potassium concentration. Cardiorenal Med 2013;3:1–6.

35. Dahal K, et al. The effects of aldosterone antagonists in patients with resistant hypertension: a meta-analysis of randomized and nonrandomized studies. Am J Hypertens 2015;28:1376–1385.

36. Allen LV Jr, Erickson MA 3rd. Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. Am J Health Syst Pharm 1996;53:2073–2078.