Spironolactone
Newborn use only

2021

Alert	Spironolactone is a potassium-sparing diuretic and concomitant intake of potassium or ACE inhibitors may lead to hyperkalemia.
Indication	Diuretic primarily prescribed for its potassium-sparing effect. For heart failure, in conjunction with furosemide. For chronic lung disease, in conjunction with a thiazide diuretic. Bartter syndrome and Gitelman Syndrome.
Action	Spironolactone is a synthetic steroid that acts as a competitive aldosterone receptor antagonist, so inhibits sodium reabsorption and spares potassium. It is a weak diuretic. It also inhibits the interaction between dihydrotestosterone and the intracellular androgen receptor resulting in moderate antiandrogenic activity.
Drug type	Non-selective mineralocorticoid receptor antagonist.
Trade name	Aldactone; Spiractin
Presentation	Oral suspension prepared in pharmacy: 1 mg/mL; 2.5 mg/mL; 5 mg/mL.
Dose	1–3 mg/kg/dose 24 hourly. Dose can be divided into different intervals.
Dose adjustment	Therapeutic hypothermia – Not applicable. Renal impairment – Refer to precautions section. Hepatic impairment – Refer to precautions section.
Maximum dose	3 mg/kg/day
Total cumulative dose	
Route	Oral
Preparation	Oral suspension.
Administration	Administer undiluted with feeds.
Monitoring	Serum potassium at regular intervals.
Contraindications	Hyperkalaemia. Significant renal impairment. Anuria. Adrenal insufficiency.
Precautions	Use with caution in infants with renal or hepatic impairment. Monitor more frequently if infant is also given potassium.
Drug interactions	Spironolactone increases the effects of ACE inhibitors (leading to hyperkalemia), digoxin and sotalol.
Adverse reactions	Hyperkalaemia and metabolic acidosis. Antiandrogenic effects include reduced hirsutism and gynecomastia. There is one case report of an ovarian cyst in a neonate on spironolactone. Spironolactone interferes with 17-hydroxyprogesterone measurement, which is used to screen neonates for congenital adrenal hyperplasia. Reduces clearance of digoxin.
Compatibility	N/A
Incompatibility	N/A
Stability	Biochemical stability when stored in solution for 1 month.[1]
Storage	Check with local pharmacy.
Excipients	
Special comments	Pharmacokinetics not studied in infants. Absorption increased by food. Metabolised to active metabolites 7α-methylspironolactone and canrenone which are extensively bound to plasma protein at therapeutic concentrations and have extended half-lives.
Evidence	**Efficacy:** **In preterm infants > 3 weeks of age with CLD**: Acute and chronic administration of thiazide diuretic and spironolactone improved pulmonary mechanics.[2] A single study showed thiazide and spironolactone decreased the risk of death in infants who did not have access to corticosteroids, bronchodilators or aminophylline.[3] (LOE I, GOR C) Trials used spironolactone doses from 3 to 4 mg/kg/day. **Heart failure:** Spironolactone resulted in short-term improvement in heart failure secondary to congenital heart disease compared to potassium supplementation in infants treated with digoxin

	and a thiazide diuretic.[4] (LOE II GOR C) In adults with heart failure, the addition of aldosterone antagonists reduced mortality, hospitalisation rate, and hypokalaemia but increased creatinine and occurrence of hyperkalaemia.[5,6] (LOE 1/adults GOR C) **Bartter syndrome and Gitelman syndrome:** Spironolactone has been used to maintain serum potassium in patients with Bartter syndrome and Gitelman syndrome.[7] **Pharmacokinetics and pharmacodynamics:** Spironolactone is a non-selective mineralocorticoid receptor antagonist with moderate affinity for both progesterone and androgen receptors. Pharmacokinetics and pharmacodynamics have not been evaluated in newborn infants. In adults, absorption is estimated to be 80–90%. The onset of action for spironolactone is typically very slow, with a peak response sometimes occurring 48 hours or more after the first dose. Spironolactone is rapidly metabolised hepatically into a number of metabolites. The predominant metabolite, 7α-methylspironolactone, accounts for around 80% of the K^+-sparing effect of spironolactone. Spironolactone (88%) and its canrenone metabolite (99%) are extensively bound to plasma protein at therapeutic concentrations. In normal volunteers, the mean $t_{½}$ of spironolactone, canrenone, 7α-TMS and 6ß-hydroxy-7α-TMS were 1.4, 16.5, 13.8 and 15 hours, respectively. In cirrhotic patients, the $t_{½}$ of spironolactone and its metabolites are increased. The pharmacokinetics of spironolactone and its metabolites have not been specifically studied in the setting of renal insufficiency or end-stage renal disease.[8,9] **Safety:** Preterm infants receiving hydrochlorothiazide in combination with spironolactone may have an increased need for sodium and potassium supplementation.[3] (LOE II GOR B) The addition of spironolactone to a thiazide diuretic did not reduce the requirement for supplemental electrolytes over 2 weeks in a small trial.[10] (LOE II GOR C) Use of spironolactone in adults increases creatinine and the incidence of hyperkalaemia.[5] (LOE I GOR C) Spironolactone reduced digoxin clearance in infants.[11] (LOE IV GOR C)
Practice points	
References	1. Mathur LK, Wickman A. Stability of extemporaneously compounded spironolactone suspensions. Am J Hosp Pharm. 1989;46:2040-2. 2. Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. Cochrane Database Syst Rev. 2011:CD001817. 3. Albersheim SG, Solimano AJ, Sharma AK, Smyth JA, Rotschild A, Wood BJ, Sheps SB. Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. J Pediatr. 1989;115:615-20. 4. Hobbins SM, Fowler RS, Rowe RD, Korey AG. Spironolactone therapy in infants with congestive heart failure secondary to congenital heart disease. Arch Dis Child. 1981;56:934-8. 5. Hu LJ, Chen YQ, Deng SB, Du JL, She Q. Additional use of an aldosterone antagonist in patients with mild to moderate chronic heart failure: a systematic review and meta-analysis. Br J Clin Pharmacol. 2013;75:1202-12. 6. Anonymous. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). Am J Cardiol. 1996;78:902-7. 7. Fremont OT, Chan JC. Understanding Bartter syndrome and Gitelman syndrome. World J Pediatr. 2012;8:25-30. 8. Sica DA. Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. Heart Fail Rev. 2005;10:23-9. 9. Karim A. Spironolactone: disposition, metabolism, pharmacodynamics, and bioavailability. Drug Metab Rev. 1978;8:151-88. 10. Hoffman DJ, Gerdes JS, Abbasi S. Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled, randomized trial. J Perinatol. 2000;20:41-5. 11. Suematsu F, Minemoto M, Yukawa E, Higuchi S. Population analysis for the optimization of digoxin treatment in Japanese paediatric patients. J Clin Pharm Ther. 1999;24:203-8.

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