9. Macdonald JE, *et al.* Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. *Heart* 2004; **90:** 765–70.
10. Georges B, *et al.* Spironolactone and congestive heart-failure. *Lancet* 2000; **355:** 1369–70.
11. Juurlink DN, *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; **351:** 543–51.
12. Witham MD, *et al.* Tolerability of spironolactone in patients with chronic heart failure—a cautionary message. *Br J Clin Pharmacol* 2004; **58:** 554–7.

High-altitude disorders. Acetazolamide is generally the drug of choice for prophylaxis of high-altitude disorders (p.1168). Anecdotal reports[1-4] and a small-scale double-blind study[5] suggested that spironolactone could be useful in preventing acute mountain sickness, although a deterioration in pulmonary function despite spironolactone prophylaxis has been noted in a patient.[6]

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2. Snell JA, Cordner EP. Spironolactone and acute mountain sickness. *Med J Aust* 1977; **1:** 828.
3. Turnbull G. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; **280:** 1453.
4. Rutter LD. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; **281:** 618.
5. Brown GV, *et al.* Spironolactone in acute mountain sickness. *Lancet* 1977; **i:** 855.
6. Meyers DH. Spironolactone prophylaxis of mountain sickness. *BMJ* 1980; **281:** 1569.

Hirsutism. Hirsutism (p.2089) is frequently treated with antiandrogens, usually cyproterone or spironolactone. Spironolactone in doses of 50 to 200 mg daily has produced both subjective and objective improvement in hirsutism in patients with idiopathic hirsutism or polycystic ovary syndrome,[1-4] and its use has been reviewed.[5] It is preferably used with oral contraceptives,[6,7] to improve efficacy and menstrual irregularity and to avoid the risk of feminisation to a male fetus. Most studies have involved premenopausal women and it has been suggested[4,8] that spironolactone would be useful in women in whom cyproterone is contra-indicated or not tolerated. A randomised study (not placebo-controlled) found spironolactone 100 mg daily and cyproterone 100 mg daily to be equally effective,[9] while a systematic review[10] of the use of spironolactone in hirsutism concluded that it was significantly more effective than both cyproterone and finasteride for up to 12 months after treatment.

For reference to the use of spironolactone in alopecia, see above.

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3. Evans DJ, Burke CW. Spironolactone in the treatment of idiopathic hirsutism and the polycystic ovary syndrome. *J R Soc Med* 1986; **79:** 451–3.
4. Barth JH, *et al.* Spironolactone therapy for hirsute women. *Br J Dermatol* 1988; **119** (suppl 33): 17.
5. Christy NA, *et al.* Spironolactone for hirsutism in polycystic ovary syndrome. *Ann Pharmacother* 2005; **39:** 1517–21. Correction. *ibid.*; 1765.
6. Chapman MG, *et al.* Spironolactone in combination with an oral contraceptive: an alternative treatment for hirsutism. *Br J Obstet Gynaecol* 1985; **92:** 983–5.
7. Rittmaster RS. Hirsutism. *Lancet* 1997; **349:** 191–5.
8. West TET. Does spironolactone have a place in treating facial hirsutism in women? *BMJ* 1988; **296:** 1456.
9. O'Brien RC, *et al.* Comparison of sequential cyproterone acetate/estrogen versus spironolactone/oral contraceptive in the treatment of hirsutism. *J Clin Endocrinol Metab* 1991; **72:** 1008–13.
10. Farquhar C, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/06/05).

Hyperaldosteronism. Hyperaldosteronism (aldosteronism) is a disorder characterised by mineralocorticoid excess due to high circulating levels of aldosterone.[1-4] Mineralocorticoid excess due to other mineralocorticoids is rare. Primary hyperaldosteronism is usually caused by an aldosterone-producing adenoma (Conn's syndrome) or primary adrenal hyperplasia. Other causes include aldosterone-producing adrenal carcinoma, and glucocorticoid-suppressible hyperaldosteronism.

Secondary hyperaldosteronism is more common and results from conditions in which there is activation of the renin-angiotensin-aldosterone system, including diuretic therapy, and oedematous conditions such as heart failure, hepatic cirrhosis, and nephrotic syndrome. Bartter's syndrome (p.1670) also results in hyperaldosteronism.

Most patients with primary hyperaldosteronism are asymptomatic, although they may present with signs or symptoms of mineralocorticoid excess (p.1490). Diagnosis often follows the incidental discovery of hypokalaemia. Symptomatic hypokalaemia (p.1669) may develop in some patients, particularly those taking diuretics.

Diagnosis is confirmed by the presence of raised plasma and urinary aldosterone concentrations. However, the concentrations may be affected by serum-potassium concentration, posture, and time of day, and interpretation may be difficult. The plasma aldosterone:renin ratio may also be measured. In primary hyperaldosteronism the aldosterone concentration is raised but renin is suppressed, although this does not necessarily prove the diagnosis; in secondary hyperaldosteronism both are raised. Radiological and nuclear imaging are useful for further differentiating between adenoma and hyperplasia.

Hyperaldosteronism due to an aldosterone-producing adenoma is usually treated surgically. The aldosterone antagonist spironolactone may be given pre-operatively to lower the blood pressure and normalise the serum potassium. In patients who are not suitable for surgery, long-term medical management involves spironolactone, initially in high doses but reduced to the lowest dose for maintenance. If spironolactone is not tolerated, amiloride may be used as an alternative, but high doses are required. There has also been a report[5] of the successful use of eplerenone, another aldosterone antagonist; gynaecomastia had developed with spironolactone but resolved when treatment was changed to eplerenone. Trilostane, an adrenal suppressant, has been used to inhibit aldosterone synthesis.

In primary adrenal hyperplasia surgery is not usually effective and medical management with spironolactone or amiloride is required. Additional antihypertensive therapy may also be needed. Glucocorticoid-suppressible hyperaldosteronism, also known as familial hyperaldosteronism type I (FH-I), is a rare autosomal dominant form and may be treated with dexamethasone. However, this may not control the blood pressure and spironolactone or amiloride may be required in addition.

In secondary hyperaldosteronism the underlying condition should be treated, but spironolactone may be of benefit as part of the therapy.

1. Ganguly A. Primary aldosteronism. *N Engl J Med* 1998; **339:** 1828–34.
2. Stewart PM. Mineralocorticoid hypertension. *Lancet* 1999; **353:** 1341–7.
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4. Fraser R, *et al.* Cautions over idiopathic aldosteronism. *Lancet* 2001; **358:** 332.
5. Karagiannis A, *et al.* Eplerenone relieves spironolactone-induced painful gynaecomastia in a patient with primary aldosteronism. *Nephrol Dial Transplant* 2007; **22:** 293.

Precocious puberty. Spironolactone (as an anti-androgen) and testolactone were given to boys with familial precocious puberty (p.2081) for periods of up to 18 months. Rates of growth and bone maturation were restored to normal during combination therapy but not with either drug given alone.[1] However, after further treatment for 2 to 4.2 years there was a diminishing response manifested by the recurrence of clinical features of puberty and an increase in the bone maturation rate.[2] Addition of deslorelin appeared to restore the control of puberty,[2] and in a long-term study[3] growth rate remained normal for 6 years.

1. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
2. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
3. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.

Premenstrual syndrome. Spironolactone has been used for its diuretic and anti-androgenic properties in premenstrual syndrome (p.2099).

Preparations

BP 2008: Spironolactone Tablets;
USP 31: Spironolactone and Hydrochlorothiazide Tablets; Spironolactone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Aldactone; Drimux A; Espimax; Expal; Lanx; Modulactone; Normital; Osiren†; Rediun-E; ***Austral.:*** Aldactone; Spiractin; ***Austria:*** Aldactone; Spirobene; Spirohexal; Spirono; ***Belg.:*** Aldactone; Docspirono; Spirotop; ***Braz.:*** Aldactone; Aldosterin†; Espirolona; Spirоctan; ***Canad.:*** Aldactone; Novo-Spiroton; ***Chile:*** Alizar; Cardactona; ***Cz.:*** Spirolone†; Uractone†; Verospiron; Xenalon†; ***Denm.:*** Hexalacton; Spirix; Spiron; ***Fin.:*** Aldactone; Spiresis; Spirix; ***Fr.:*** Aldactone; Flumach; Practon; Spirоctan; Spironone; ***Ger.:*** Aldactone; Aquareduct†; duraspiron†; Jenaspiron; Osyrol; Spiro; Spirobeta; Spirogamma; Spirono; Verospiron; ***Gr.:*** Aldactone; Uridactone†; ***Hong Kong:*** Aldactone; ***Hung.:*** Huma-Spiroton; Spirolone†; Spiron; Verospiron; ***India:*** Aldactone; ***Indon.:*** Aldactone; Carpiaton; Letonal; Spirola; ***Irl.:*** Aldactone; ***Israel:*** Aldactone; Aldospirone; Spironol; ***Ital.:*** Aldactone; Spiroderm†; Spirolang; Uractone; ***Mex.:*** Aldactone; Biolactona; Quimolactona†; Vivitar; ***Neth.:*** Aldactone; ***Norw.:*** Aldactone; Spirix; ***NZ:*** Aldactone†; Spirotone; ***Philipp.:*** Aldactone; ***Pol.:*** Spironol; Verospiron; ***Port.:*** Aldactone; Aldonar; Nefrolactona†; ***Rus.:*** Aldactone (Альдактон)†; Verospiron (Верошпирон); ***S.Afr.:*** Aldactone; Spiractin; ***Singapore:*** Aldactone; Uractonum; ***Spain:*** Aldactone; ***Swed.:*** Aldactone; Spirix; Spiroscand†; ***Switz.:*** Aldactone; Primacton; Xenalon; ***Thai.:*** Aldactone; Altone; Berlactone†; Hyles; Pondactone; Spironex†; ***Turk.:*** Aldacton; ***UK:*** Aldactone; Spirospare†; ***USA:*** Aldactone; ***Venez.:*** Aldactone; Spirоctan†.

Multi-ingredient: ***Arg.:*** Aldactone-D; Aldazida; Lasilacton; ***Austria:*** Aldactone Saltucin; Buti-Spirobene; Deverol mit Thiazid; Digi-Aldopur; Furo-Aldopur; Furo-Spirobene; Furolacton; Lasilacton; Sali-Aldopur; Spirono comp; Supracid; ***Belg.:*** Aldactazine; Docspirochlor; ***Braz.:*** Aldazida; Lasilactona; ***Canad.:*** Aldactazide; Novo-Spirozine; ***Cz.:*** Spiro Compositum†; ***Fr.:*** Aldactazine; Aldalix; Practazin; Spirоctazine; ***Ger.:*** Aldactone Saltucin†; duraspiron-comp†; Furo-Aldopur; Furorese Comp; Osyrol Lasix; Risicordin†; Sali-Aldopur†; Spiro comp; Spiro-D; Spironolacton Plus†; Spironothiazid; Spirostada comp†; ***India:*** Lasilactone; Spiromide; ***Indon.:*** Aldazide; ***Irl.:*** Aldactide; ***Ital.:*** Aldactazide; Lasitone; Spiridazide; Spirofur; ***Mex.:*** Aldazida; Lasilacton; ***Philipp.:*** Aldazide; ***Port.:*** Aldactazine; Ondolen; ***S.Afr.:*** Aldazide; ***Spain:*** Aldactacine; Aldoleo; Miscidon†; Spirometon; ***Switz.:*** Aldozone; Furocombin; Furospir; Lasilactone; ***Turk.:*** Aldactazide; ***UK:*** Aldactide; Lasilactone; ***USA:*** Aldactazide; ***Venez.:*** Aldactazida; Teradal†.

Staphylokinase

Estafiloquinasa.

Profile

Staphylokinase is a thrombolytic derived from *Staphylococcus aureus*. Recombinant and modified forms are under investigation for the treatment of thromboembolic disorders, including acute myocardial infarction.

◊ References.

1. Vanderschueren S, *et al.* Thrombolytic therapy of peripheral arterial occlusion with recombinant staphylokinase. *Circulation* 1995; **92:** 2050–57.
2. Vanderschueren S, *et al.* Randomized coronary patency trial of double-bolus recombinant staphylokinase versus front-loaded alteplase in acute myocardial infarction. *Am Heart J* 1997; **134:** 213–19.
3. Armstrong PW, *et al.* Collaborative angiographic patency trial of recombinant staphylokinase (CAPTORS II). *Am Heart J* 2003; **146:** 484–8.

Streptokinase *(BAN, rINN)*

Estreptoquinasa; Plasminokinase; Sterptokinasum; Streptokinaasi; Streptokinas; Streptokinasum; Sztreptokináz.

Стрептокиназа

CAS — 9002-01-1.
ATC — B01AD01.
ATC Vet — QB01AD01.

Pharmacopoeias. *Eur.* (see p.vii) includes a concentrated solution.
Ph. Eur. 6.2 (Streptokinase Concentrated Solution; Streptokinasi Solutio Concentrata). A preparation of a protein obtained from culture filtrates of certain strains of haemolytic *Streptococcus* group C. It has the property of combining with human plasminogen to form plasminogen activator. The potency is not less than 510 international units per microgram of nitrogen. A clear, colourless liquid. pH 6.8 to 7.5. Store in airtight containers at a temperature of –20°. Protect from light.

Stability. The incorporation of albumin in commercial preparations of streptokinase has reduced the incidence of flocculation with streptokinase solutions. However, flocculation has occurred with small volumes prepared with sodium chloride 0.9% in sterilised glass containers apparently because of residual acid buffers that remain in empty evacuated containers after sterilisation.[1]

1. Thibault L. Streptokinase flocculation in evacuated glass bottles. *Am J Hosp Pharm* 1985; **42:** 278.

Units

The potency of streptokinase is expressed in international units and preparations are assayed using the second International Standard (1989).

The Christensen unit is the quantity of streptokinase that will lyse a standard blood clot completely in 10 minutes and is equivalent to the international unit.

Adverse Effects

In common with other thrombolytics streptokinase may cause haemorrhage, particularly from puncture sites; severe internal bleeding has occurred and may be difficult to control. Streptokinase is antigenic, and allergic reactions ranging from rashes to rarer anaphylactoid and serum-sickness-like symptoms have occurred. Fever, sometimes high, and associated symptoms such as chills and back or abdominal pain are quite frequent. Nausea and vomiting may occur. There have been a few reports of Guillain-Barré syndrome.

Streptokinase infusion may be associated with hypotension, both direct or as a result of reperfusion; bradycardia and arrhythmias may also occur due to reperfusion. The break-up of existing clots may occasionally produce emboli elsewhere; pulmonary embolism and acute renal failure due to cholesterol embolisation have been reported.

Back pain. Streptokinase infusion has been associated with the development of very severe low back pain, which resolves within a few minutes of stopping the infusion, and may be severe enough to warrant opioid analgesia.[1-4] The back pain may represent a hypersensitivity reaction. Providing that the pain is controlled and that dissecting aortic aneurysm is not suspected, it may still be possible to complete the streptokinase infusion.[4,5] Alternatively, immediate substitution with a different thrombolytic has been suggested.[6]

There have also been a few reports of low back pain associated with anistreplase infusion.[7,8]

1. Shah M, Taylor RT. Low back pain associated with streptokinase. *BMJ* 1990; **301:** 1219.
2. Dickinson RJ, Rosser A. Low back pain associated with streptokinase. *BMJ* 1991; **302:** 111–12.