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]

1. Currie TT, *et al.* Spironolactone and acute mountain sickness. *Med J Aust* 1976; **2:** 168–70.
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.

1. Cumming DC, *et al.* Treatment of hirsutism with spironolactone. *JAMA* 1982; **247:** 1295–8.
2. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol* 1985; **112:** 124–5.
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.
3. Kaplan NM. Cautions over the current epidemic of primary aldosteronism. *Lancet* 2001; **357:** 953–4.
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.

3. Porter NJ, Nikoletatos K. Low back pain associated with streptokinase. *BMJ* 1991; **302:** 112.
4. Pinheiro RF, *et al.* Low back pain during streptokinase infusion. *Arq Bras Cardiol* 2002; **78:** 233–5.
5. Lear J, *et al.* Low back pain associated with streptokinase. *Lancet* 1992; **340:** 851.
6. Fishwick D, *et al.* Thrombolysis and low back pain. *BMJ* 1995; **310:** 504.
7. Hannaford P, Kay CR. Back pain and thrombolysis. *BMJ* 1992; **304:** 915.
8. Lear J, Rajapakse R. Low back pain associated with anistreplase. *BMJ* 1993; **306:** 896.

Effects on the blood. Although falls in the haemoglobin value of patients receiving thrombolytics are most likely to be due to blood loss from haemorrhage, there has been a report of a patient who had signs of haemolytic anaemia after intravenous infusion of streptokinase.[1] In a subsequent test *in vitro* the patient's serum caused strong agglutination of streptokinase-treated red blood cells, supporting the view that streptokinase was responsible for the haemolysis.

1. Mathiesen O, Grunnet N. Haemolysis after intravenous streptokinase. *Lancet* 1989; **i:** 1016–17.

Effects on the eyes. Acute uveitis[1,2] and iritis,[3,4] associated with transient renal impairment in one patient,[3] have followed treatment of myocardial infarction with intravenous streptokinase. In one case uveitis was associated with serum sickness[2] and in all of them hypersensitivity to streptokinase was suspected.

1. Kinshuck D. Bilateral hypopyon and streptokinase. *BMJ* 1992; **305:** 1332.
2. Proctor BD, Joondeph BC. Bilateral anterior uveitis: a feature of streptokinase-induced serum sickness. *N Engl J Med* 1994; **330:** 576–7.
3. Birnbaum Y, *et al.* Acute iritis and transient renal impairment following thrombolytic therapy for acute myocardial infarction. *Ann Pharmacother* 1993; **27:** 1539–40.
4. Gray MY, Lazarus JH. Iritis after treatment with streptokinase. *BMJ* 1994; **309:** 97.

Effects on the kidneys. Transient proteinuria has been reported after use of streptokinase. In some patients proteinuria and renal impairment have developed about 7 days after thrombolytic therapy and have been associated with a syndrome resembling serum sickness,[1,2] suggesting a delayed hypersensitivity reaction; a similar case in a patient receiving anistreplase was associated with Henoch-Schönlein-like vasculitis.[3] These delayed reactions should be distinguished from the transient and apparently self-limiting proteinuria that has been reported in some patients in the first 24 to 72 hours after beginning streptokinase.[4,5] Proteinuria within the first 24 hours has been attributed to deposition of an immune complex in the glomeruli,[6] although haemodynamic and neurohormonal changes associated with acute myocardial infarction may be responsible since proteinuria has occurred in patients not receiving thrombolytic therapy.[7,8]

Streptokinase infusion has also been associated with acute oliguric renal failure due to acute tubular necrosis, apparently as a result of hypotension during the infusion, in a patient with existing renovascular narrowing.[9] Interestingly, it has been pointed out that a variant streptokinase may be the pathogenic agent in glomerulonephritis occurring after *Streptococcus pyogenes* infection.[10]

Renal failure has developed as a consequence of streptokinase-induced cholesterol embolism, see under Embolism, below.

1. Payne ST, *et al.* Transient impairment of renal function after streptokinase therapy. *Lancet* 1989; **ii:** 1398.
2. Callan MFC, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106.
3. Ali A, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106–7.
4. Argent N, Adams PC. Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106.
5. More RS, Peacock F. Haematuria and proteinuria after thrombolytic therapy. *Lancet* 1990; **336:** 1454.
6. Lynch M, *et al.* Proteinuria with streptokinase. *Lancet* 1993; **341:** 1024.
7. Pickett TM, Hilton PJ. Proteinuria and streptokinase. *Lancet* 1993; **341:** 1538.
8. von Eyben FE, *et al.* Albuminuria with or without streptokinase. *Lancet* 1993; **342:** 365–6.
9. Kalra PA, *et al.* Acute tubular necrosis induced by coronary thrombolytic therapy. *Postgrad Med J* 1991; **67:** 212.
10. Barnham M. Hypersensitivity and streptokinase. *Lancet* 1990; **335:** 535.

Effects on the liver. Raised serum-alanine aminotransferase values, and in some cases raised aspartate aminotransferase activity, were seen more frequently in 95 patients who received streptokinase than in 94 given placebo as part of a study in patients with myocardial infarction.[1] The mechanism for the raised aminotransferase activity was not clear; a concomitant rise in γ-glutamyltransferase activity and bilirubin concentration suggested an hepatic source.

For references to rupture of the liver occurring during treatment with streptokinase, see Haemorrhage, below.

1. Maclennan AC, *et al.* Activities of aminotransferases after treatment with streptokinase for acute myocardial infarction. *BMJ* 1990; **301:** 321–2.

Effects on the nervous system. There have been a few reports of Guillain-Barré syndrome after treatment with streptokinase.[1-4] Whether streptokinase was the cause is not certain although its antigenic properties do suggest that induction of an immunological reaction might be responsible.[3]

For discussion of cerebrovascular effects of streptokinase, see Haemorrhage, below.

1. Eden KV. Possible association of Guillain-Barré syndrome with thrombolytic therapy. *JAMA* 1983; **249:** 2020–1.
2. Leaf DA, *et al.* Streptokinase and the Guillain-Barré syndrome. *Ann Intern Med* 1984; **100:** 617.
3. Barnes D, Hughes RAC. Guillain-Barré syndrome after treatment with streptokinase. *BMJ* 1992; **304:** 1225.
4. Taylor BV, *et al.* Guillain-Barré syndrome complicating treatment with streptokinase. *Med J Aust* 1995; **162:** 214–15.

Effects on the respiratory system. Fatal acute respiratory distress syndrome occurred in a patient given streptokinase for pulmonary embolism.[1] It was suggested that streptokinase may have caused the pulmonary injury by altering vascular permeability due to generation of fibrinolytic products or via reperfusion oedema.

1. Martin TR, *et al.* Adult respiratory distress syndrome following thrombolytic therapy for pulmonary embolism. *Chest* 1983; **83:** 151–3.

Effects on the skin. Rashes may occur as an allergic reaction to streptokinase. For a report of skin necrosis possibly associated with cholesterol embolisation, see Embolism, below.

Embolism. Thrombolytic therapy has occasionally and paradoxically been associated with further embolism. This may be due to clots that break away from the treated thrombus, or to cholesterol crystals released after removal of fibrin from atheromatous plaques by thrombolysis.

Fatal pulmonary embolism has been reported,[1] apparently due to breakaway from a deep-vein thrombus under treatment. However, comparative studies have suggested that there is no evidence of a higher rate of such complications with streptokinase than with heparin.[2] When they do occur a good clinical response is usually seen to continued streptokinase.[2] Complications due to multiple microemboli were reported[3] in 7 of 475 consecutive patients treated with streptokinase or anistreplase for acute myocardial infarction. The sites of embolism were the legs (in 4) and brain (in 3); one patient apparently had systemic effects with skin infarction and renal impairment. Five of the 7 patients died. There has also been a report[4] of acute peripheral arterial thromboembolism in a patient given alteplase for ischaemic stroke.

Cholesterol embolisation can have many clinical manifestations depending on the location of the emboli. A classic presentation is livedo reticularis, gangrenous lower extremities, and acute renal failure.[5,6] Symptoms may appear within a few hours of starting thrombolytic treatment,[7] although in some cases they may not become evident for several days.[8-11]

1. Hill LN. Streptokinase therapy and breakaway pulmonary emboli. *Am J Med* 1991; **90:** 411–12.
2. Rogers LQ, Lutcher CL. Streptokinase therapy and breakaway pulmonary emboli. *Am J Med* 1991; **90:** 412–13.
3. Stafford PJ, *et al.* Multiple microemboli after disintegration of clot during thrombolysis for acute myocardial infarction. *BMJ* 1989; **299:** 1310–12.
4. Gomez-Beldarrain M, *et al.* Peripheral arterial embolism during thrombolysis for stroke. *Neurology* 2006; **67:** 1096–7.
5. Blankenship JC. Cholesterol embolisation after thrombolytic therapy. *Drug Safety* 1996; **14:** 78–84.
6. Wong FKM, *et al.* Acute renal failure after streptokinase therapy in a patient with acute myocardial infarction. *Am J Kidney Dis* 1995; **26:** 508–10.
7. Pochmalicki G, *et al.* Cholesterol embolisation syndrome after thrombolytic therapy for myocardial infarction. *Lancet* 1992; **339:** 58–9.
8. Ridker PM, Michel T. Streptokinase therapy and cholesterol embolization. *Am J Med* 1989; **87:** 357–8.
9. Pirson Y, *et al.* Cholesterol embolism in a renal graft after treatment with streptokinase. *BMJ* 1988; **296:** 394–5.
10. Dass H, Fescharek R. Skin necrosis induced by streptokinase. *BMJ* 1994; **309:** 1513–14.
11. Penswick J, Wright AL. Skin necrosis induced by streptokinase. *BMJ* 1994; **309:** 378.

Haemorrhage. Haemorrhage is a common adverse effect of thrombolytic therapy, and the problem and its management have been reviewed.[1] Thrombolytics are used to lyse pathological thrombi, but can also produce a 'lytic state' due to depletion of the natural plasmin inhibitor α_2-antiplasmin by excess plasmin production; they may also cause lysis of thrombi required for haemostasis.

Haemorrhage is a particular risk where there is existing or concomitant trauma. More than 70% of bleeding episodes occur at vascular puncture sites,[1] so invasive procedures should be avoided if possible; if catheterisation is considered essential meticulous care of the vascular puncture site is necessary. Bleeding or severe bruising in patients receiving thrombolytic therapy have also been associated with intramuscular injection of analgesics,[2] the use of an automatic blood-pressure measuring machine,[3] a pre-existing prosthetic abdominal aortic graft,[4] and recent dental extraction.[5] Other disease states may also contribute: haemospermia has been reported after thrombolysis in a patient with mild prostatic symptoms,[6] haemorrhagic bullae have been reported in a patient with lichen sclerosus et atrophicus,[7] and diabetic patients are at risk of retinal haemorrhage if they have diabetic retinopathy,[8] although any increase in risk seems to be small.[9] A review of the GUSTO-I Study[10] (40 903 patients) identified older age, low body-weight, female sex, and African ancestry as other factors that increased the risk of haemorrhage.

Intracranial haemorrhage leading to stroke is the most serious bleeding complication with thrombolytics, and has a high mortality. Assessment of data from national registries and large-scale trials has identified a number of risk factors for intracranial haemorrhage, including those mentioned above for overall haemorrhage, hypertension on admission, a history of stroke, and thrombolysis with current alteplase regimens.[11-14] The benefits and risks must be assessed for each patient and thrombolytic therapy should still be given to the elderly and to those with hypertension if the expected benefits are great. Intracranial haemorrhage is a particular concern with the use of thrombolytics for the treatment of ischaemic stroke. In the NINDS study, using alteplase, clinical outcome appeared to be improved despite an increased incidence of symptomatic intracerebral haemorrhage. Subgroup analysis[15] suggested that severe neurological deficit, brain oedema, and mass effect, before treatment, were risks associated with the increased incidence of haemorrhage.

Fibrin-specific thrombolytics such as alteplase were developed in the hope that they would have less systemic effect than fibrin-nonspecific thrombolytics such as streptokinase and therefore cause less bleeding. However, studies that have assessed comparative bleeding rates have failed to confirm this, although the use of adjunctive antithrombotics and different dose regimens makes comparison difficult. In GUSTO-I,[10] the bleeding rate with alteplase plus intravenous heparin was lower than with streptokinase plus intravenous heparin, but was similar to that with streptokinase plus subcutaneous heparin. However, the rate of intracranial haemorrhage was higher with alteplase.[16] In ASSENT-2,[17] which compared bolus doses of the highly fibrin-specific thrombolytic tenecteplase with front-loaded alteplase, tenecteplase produced fewer major non-cerebral bleeds than alteplase but the rates of intracranial haemorrhage were nearly identical. Although a meta-analysis[18] suggested that rates of intracranial haemorrhage may be higher with bolus thrombolytics, others have suggested that this may not be a problem with newer bolus regimens.[19]

Other bleeding complications reported with thrombolytics include rupture of the spleen[20,21] and liver,[22] and rupture of a follicle has been reported in a menstruating woman.[23] Rupture of the heart with fatal consequences has been reported, although thrombolytics do not appear to increase the overall risk of cardiac rupture following myocardial infarction,[24] except possibly for early rupture in women.[25]

Diffuse alveolar haemorrhage has been reported[26] in a patient treated with streptokinase after myocardial infarction. Intrapleural use was associated with life-threatening haemorrhage in empyema following cardiac surgery,[27] and with fatal haemorrhage in a case of aortic dissection misdiagnosed as empyema.[28]

1. Sane DC, *et al.* Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. *Ann Intern Med* 1989; **111:** 1010–22.
2. Morris GC, Sterry MJG. [case report]. *BMJ* 1991; **302:** 246.
3. Gibson P. [case report]. *BMJ* 1991; **302:** 1412.
4. London NJM, *et al.* Systemic thrombolysis causing haemorrhage around a prosthetic abdominal aortic graft. *BMJ* 1993; **306:** 1530–1.
5. Lustig JP, *et al.* Thrombolytic therapy for acute myocardial infarction after oral surgery. *Oral Surg Oral Med Oral Pathol* 1993; **75:** 547–8.
6. Keeling PJ, Lawson CS. Haemospermia: a complication of thrombolytic therapy. *Br J Hosp Med* 1990; **44:** 244.
7. Dunn HM, Fulton RA. Haemorrhagic bullae in a patient with lichen sclerosus et atrophicus treated with streptokinase. *Heart* 1996; **76:** 448.
8. Caramelli B, *et al.* Retinal haemorrhage after thrombolytic therapy. *Lancet* 1991; **337:** 1356–7.
9. Ward H, Yudkin JS. Thrombolysis in patients with diabetes. *BMJ* 1995; **310:** 3–4.
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11. Simoons ML, *et al.* Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993; **342:** 1523–8.
12. Aylward PE, *et al.* Relation of increased arterial blood pressure to mortality and stroke in the context of contemporary thrombolytic therapy for acute myocardial infarction: a randomized trial. *Ann Intern Med* 1996; **125:** 891–900.
13. Bovill EG, *et al.* Hemorrhagic events during therapy with recombinant tissue plasminogen activator, heparin, and aspirin for unstable angina (Thrombolysis in Myocardial Ischemia, Phase IIIB trial). *Am J Cardiol* 1997; **79:** 391–6.
14. Gurwitz JH, *et al.* Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. *Ann Intern Med* 1998; **129:** 597–604.
15. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke* 1997; **28:** 2109–18.
16. Gore JM, *et al.* Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial. *Circulation* 1995; **92:** 2811–18.
17. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354:** 716–22.
18. Mehta SR, *et al.* Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. *Lancet* 2000; **356:** 449–54.
19. Armstrong PW, *et al.* Bolus fibrinolysis: risk, benefit, and opportunities. *Circulation* 2001; **103:** 1171–3.
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21. Blankenship JC, Indeck M. Spontaneous splenic rupture complicating anticoagulant or thrombolytic therapy. *Am J Med* 1993; **94:** 433–7.
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26. Yigla M, *et al.* Diffuse alveolar hemorrhage following thrombolytic therapy for acute myocardial infarction. *Respiration* 2000; **67:** 445–8.
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28. Srivastava P, *et al.* Fatal haemorrhage from aortic dissection following instillation of intrapleural streptokinase. *Scott Med J* 2000; **45:** 86–7.

Hypersensitivity. Streptokinase is a bacterial protein and has antigenic activity. The formation of streptokinase-neutralising antibodies may reduce the efficacy of subsequent doses and increase the risk of hypersensitivity reactions.

In a series of 25 patients given intravenous streptokinase for myocardial infarction, titres of streptokinase-neutralising antibodies rose from a mean neutralisation capacity of 0.16 million units before treatment to a mean of 25.54 million units 2 weeks after treatment, the highest individual titre being 93 million units. After 12 weeks the neutralisation capacity was still sufficient in 24 patients to have neutralised a standard 1.5-million unit dose of streptokinase. After 17 to 34 weeks titres were still high enough in 18 of 20 patients examined to neutralise at least half a standard dose.[1] As these results indicate, giving standard doses of streptokinase within up to a year of a previous course may lead to reduced effect. Thus, the period in which it should not be repeated is usually between 5 days and 12 months post infarction (see Precautions, below). However, high titres of neutralising antibodies persisting for up to 7.5 years after use of streptokinase have been reported.[2-4] Since readministration also increases the risk of hypersensitivity reactions, it has been suggested[2,5] that repeat courses should not be given within 4 or more years, and that if a repeat course is needed a non-antigenic thrombolytic such as alteplase or urokinase should be used until it is known whether or not high *in-vitro* titres affect efficacy. Increased titres of streptokinase-neutralising antibodies have also been measured in patients given topical streptokinase for wounds.[6]

Anistreplase also appears susceptible to neutralisation by streptokinase antibodies.[7]

Plasmacytosis,[8,9] serum-sickness,[8,10,11] rhabdomyolysis,[12] renal impairment (see Effects on the Kidneys, above), uveitis and iritis (see Effects on the Eyes, above), arthritis,[13] and anaphylaxis[14-17] have been reported in patients receiving streptokinase and are thought to represent hypersensitivity reactions, in some cases perhaps due to previous exposure to streptococcal antigens during infection. Back pain (see above) may also represent a hypersensitivity reaction. In some patients there may be a delay of between 1 and 10 days before appearance of the reaction.[18] The incidence of severe hypersensitivity reactions is probably fairly low, however; in the GISSI study anaphylaxis was reported in only 7 of 5860 patients although other hypersensitivity reactions leading to withdrawal of streptokinase were reported in 99 patients, with a further 42 such reactions after completion of the infusion.[15] Some episodes of apparent anaphylaxis seen with streptokinase may be fibrinolysin-mediated rather than antibody-antigen reactions. Alteplase, which is considered non-antigenic, produced an anaphylactoid reaction in a patient who had a history of atopy.[19] Fibrinolysin, which activates complement cascade and the kinin system, is formed in quantity after the use of a thrombolytic. In most patients these effects are clinically insignificant, but in those who are strongly atopic there is the possibility of precipitating an anaphylactoid reaction.

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2. Elliott JM, *et al.* Neutralizing antibodies to streptokinase four years after intravenous thrombolytic therapy. *Am J Cardiol* 1993; **71:** 640–5.
3. Lee HS, *et al.* Raised levels of antistreptokinase antibody and neutralization titres from 4 days to 54 months after administration of streptokinase or anistreplase. *Eur Heart J* 1993; **14:** 84–9.
4. Squire IB, *et al.* Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. *Eur Heart J* 1999; **20:** 1245–52.
5. Jennings K. Antibodies to streptokinase. *BMJ* 1996; **312:** 393–4.
6. Green C. Antistreptokinase titres after topical streptokinase. *Lancet* 1993; **341:** 1602–3.
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9. Chan NS, *et al.* Plasmacytosis and renal failure after readministration of streptokinase for threatened myocardial reinfarction. *BMJ* 1988; **297:** 717–18.
10. Payne ST, *et al.* Transient impairment of renal function after streptokinase therapy. *Lancet* 1989; **ii:** 1398.
11. Callan MFC, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106.
12. Montgomery HE, *et al.* Rhabdomyolysis and multiple system organ failure with streptokinase. *BMJ* 1995; **311:** 1472.
13. Kelly MP, Bielawska C. Recurrence of a reactive arthritis following streptokinase therapy. *Postgrad Med J* 1991; **67:** 402.
14. McGrath KG, Patterson R. Anaphylactic reactivity to streptokinase. *JAMA* 1984; **252:** 1314–17.
15. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; **i:** 397–401.
16. Bednarczyk EM, *et al.* Anaphylactic reaction to streptokinase with first exposure: case report and review of the literature. *DICP Ann Pharmacother* 1989; **23:** 869–72.
17. Tisdale JE, *et al.* Streptokinase-induced anaphylaxis. *DICP Ann Pharmacother* 1989; **23:** 984–7.
18. Seibert WJ, *et al.* Streptokinase morbidity—more common than previously recognised. *Aust N Z J Med* 1992; **22:** 129–33.
19. Purvis JA, *et al.* Anaphylactoid reaction after injection of alteplase. *Lancet* 1993; **341:** 966–7.

Treatment of Adverse Effects

Allergic reactions may require treatment with antihistamines and corticosteroids, which have sometimes been given prophylactically. Anaphylaxis requires the use of adrenaline (for further details, see p.1205).

Severe haemorrhage not controlled by local pressure requires the streptokinase infusion to be stopped. Tranexamic acid, aminocaproic acid, or aprotinin may be of benefit. Packed red blood cells may be preferable to whole blood for replacement therapy; factor VIII preparations may also be given. Volume expansion may be necessary, but the use of dextrans should be avoided because of their platelet-inhibiting properties.

Precautions

Streptokinase should be used with great care, if at all, in patients at increased risk of bleeding, or those in whom haemorrhage is likely to prove particularly dangerous. It should thus be avoided in patients with active internal bleeding or a recent history of peptic ulcer disease, oesophageal varices, ulcerative colitis or other bleeding gastrointestinal lesions, in patients with pancreatitis, in patients with subacute bacterial endocarditis, in patients with coagulation defects including those due to liver or kidney disease, or after recent surgery, childbirth, or trauma. It should not be given to patients at increased risk of cerebral bleeding including those with severe hypertension, haemorrhage or recent stroke, or to patients with cerebral neoplasm. It should not be given in pregnancy, particularly in the first 18 weeks because of the risk of placental separation and it has been suggested that it should not be used during heavy vaginal bleeding.

Invasive procedures, including intramuscular injections, should be avoided during, and immediately before and after, streptokinase therapy as they may increase the risk of bleeding; care should be taken when physically handling patients. Streptokinase should also be used with care in elderly patients. Patients with mitral stenosis associated with atrial fibrillation are more likely to have left heart thrombus which may lead to cerebral embolism after thrombolytic therapy. Although there is a theoretical risk of retinal bleeding in patients with diabetic retinopathy the benefits of treatment generally outweigh the risk.

Anti-streptokinase antibodies are formed after streptokinase use, with antibody titres rising abruptly after about 5 days. These antibodies may cause resistance or hypersensitivity to subsequent doses of streptokinase. Therefore, further doses of streptokinase should not be given in the period between 5 days and 12 months after the initial dose (even longer periods have been suggested, see Hypersensitivity, under Adverse Effects, above); if thrombolytic therapy is required in this period an alternative non-antigenic drug should be used. High titres of anti-streptokinase antibodies may also occur in patients after some streptococcal infections such as streptococcal pharyngitis or acute rheumatic fever or in those with acute glomerulonephritis secondary to streptococcal infections; in such patients there may be resistance to streptokinase or a reduced effect.

Administration. Overinfusion of streptokinase may occur if a drop-counting infusion pump is employed.[1] This arises as a result of flocculation of the streptokinase solution producing translucent fibres that affect the drop-forming mechanism so increasing the drop size.

For a comment on the incidence of flocculation in streptokinase solutions, see Stability, above.

1. Schad RF, Jennings RH. Overinfusions of streptokinase. *Am J Hosp Pharm* 1982; **39:** 1850.

Aortic dissection. A report of 4 cases of the inappropriate use of streptokinase in patients with aortic dissection misdiagnosed as myocardial infarction.[1] Thrombolytics are likely to extend aortic dissection and adversely affect the outcome. Of the 2 patients who died, one, who would have been suitable for early operation, died through the delay caused by impaired clotting. Although early intervention with thrombolytics may be of major benefit in acute myocardial infarction it is important that accurate differential diagnosis takes place to exclude conditions such as aortic dissection and prevent avoidable deaths.

For a report of fatal haemorrhage with streptokinase used in aortic dissection misdiagnosed as empyema, see Haemorrhage under Adverse Effects, above.

1. Butler J, *et al.* Streptokinase in acute aortic dissection. *BMJ* 1990; **300:** 517–19.

Cardiopulmonary resuscitation. Thrombolytics are not recommended after prolonged or traumatic cardiopulmonary resuscitation because of the risk of haemorrhage. However, studies[1,2] in patients given cardiopulmonary resuscitation for cardiac arrest associated with acute myocardial infarction have suggested that thrombolytics are generally safe and that any increase in bleeding complications is outweighed by the benefits of thrombolysis.

1. Cross SJ, *et al.* Safety of thrombolysis in association with cardiopulmonary resuscitation. *BMJ* 1991; **303:** 1242.
2. Kurkciyan I, *et al.* Major bleeding complications after cardiopulmonary resuscitation: impact of thrombolytic treatment. *J Intern Med* 2003; **253:** 128–35.

Pregnancy. Thrombolytics are generally contra-indicated in pregnancy. However there are a few reports of their use and these have been briefly reviewed.[1] In most cases, thrombolytics were given at 28 weeks of pregnancy or later to patients with deep-vein thrombosis, pulmonary embolism, or prosthetic valve thrombosis. There were some reports of favourable maternal and fetal outcomes although therapy was associated with maternal haemorrhage, including spontaneous abortion and minor vaginal bleeding, especially when given near the time of delivery. There was one report of placental abruption with fetal death.

1. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *Ann Intern Med* 1996; **125:** 751–62.

Interactions

Oral anticoagulants, heparin, and antiplatelet drugs such as aspirin are often used with streptokinase, but may increase the risk of haemorrhage. The risk may also be increased with dextrans, and with other drugs that affect coagulation or platelet function.

◊ References.

1. Harder S, Klinkhardt U. Thrombolytics: drug interactions of clinical significance. *Drug Safety* 2000; **23:** 391–9.

Pharmacokinetics

Streptokinase is rapidly cleared from the circulation after intravenous use. Clearance is biphasic with the initial and more rapid phase being due to specific antibodies. A half-life of 23 minutes has been reported for the streptokinase-activator complex.

◊ References.

1. Grierson DS, Bjornsson TD. Pharmacokinetics of streptokinase in patients based on amidolytic activator complex activity. *Clin Pharmacol Ther* 1987; **41:** 304–13.
2. Gemmill JD, *et al.* A comparison of the pharmacokinetic properties of streptokinase and anistreplase in acute myocardial infarction. *Br J Clin Pharmacol* 1991; **31:** 143–7.

Uses and Administration

Streptokinase is a thrombolytic drug derived from various streptococci. It rapidly activates endogenous plasminogen, indirectly by means of a streptokinase-plasminogen complex, to plasmin (see Fibrinolysin, p.1287), which has fibrinolytic effects and can dissolve intravascular blood clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Streptokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p.1156).

Streptokinase is given by intravenous or sometimes intra-arterial infusion in the treatment of thromboembolic disorders such as myocardial infarction (p.1175), peripheral arterial thromboembolism (below), and venous thromboembolism (deep-vein thrombosis and pulmonary embolism) (p.1189). It has also been tried in ischaemic stroke (below), although alteplase is generally preferred. Streptokinase may be used to clear cannulas and shunts and is used topically with streptodornase to clear clots and purulent matter.

In acute **myocardial infarction** streptokinase is usually given intravenously as a single dose of 1.5 million units infused over 1 hour as soon as possible after the onset of symptoms. Streptokinase has also been given in a suitable dose by intracoronary infusion but coronary catheterisation with the aid of angiography is required, thus restricting use to suitably equipped centres.

In the treatment of **pulmonary embolism** and other **arteriovenous occlusions** an initial loading dose of streptokinase, normally 250 000 units infused intravenously over 30 minutes, is given to overcome any resistance due to circulating antibodies. This is followed by infusion of a maintenance dose of 100 000 units/hour for 24 to 72 hours, depending on the condition to be treated; for central retinal thrombosis, 12 hours may be adequate. Treatment should be controlled by monitoring the thrombin clotting time, which should be maintained at 2 to 4 times normal values. Since thrombolytic activity rapidly fades when the infusion stops, streptokinase treatment is generally followed after 3 to 4 hours by intravenous heparin infusion, and then oral anticoagulation, to prevent re-occlusion.

Streptokinase, as a solution containing 250 000 units in 2 mL is used to clear occluded cannulas; 1000 units/mL has been used to clear shunts of occluding thrombi.

◊ General references.

1. Fears R. Biochemical pharmacology and therapeutic aspects of thrombolytic agents. *Pharmacol Rev* 1990; **42:** 201–21.
2. Stringer KA. Beyond thrombolysis: other effects of thrombolytic drugs. *Ann Pharmacother* 1994; **28:** 752–6.
3. Ludlam CA, *et al.* Guidelines for the use of thrombolytic therapy. *Blood Coag Fibrinol* 1995; **6:** 273–85.

Administration in children. There are limited data on the use of systemic thrombolytic therapy for arterial or venous thromboembolism in children and various dosage regimens have been used, based on case studies. The most widely used drugs are streptokinase and alteplase. For streptokinase, the Eighth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy[1] suggests a loading dose of 2000 units/kg to be given intravenously, followed by continuous infusion of 2000 units/kg per hour for 6 to 12 hours. In the UK, the *BNFC* suggests a loading dose of 2500 to 4000 units/kg over 30 minutes, followed by infusion of 500 to 1000 units/kg per hour, continued until reperfusion occurs, up to a maximum of 3 days.

Alteplase may be preferred because of its fibrin specificity and low immunogenicity. The dose of alteplase suggested by the ACCP is 100 to 600 micrograms/kg per hour by continuous intravenous infusion over 6 hours, while the dose recommended by the *BNFC* is 100 to 500 micrograms/kg per hour for 3 to 6 hours. The use of alteplase to clear occluded catheters in children is discussed on p.1208.

1. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 454S–545S.

Empyema and pleural effusion. Thoracic empyema is treated with antibacterials and pleural drainage. Efficient removal of fluid may be impaired by fibrinous clots within the pleural cavity. Intrapleural instillation of streptokinase (100 000 to 750 000 units in up to 100 mL of sodium chloride 0.9%) has been reported to be effective in small series of patients[1-4] and there have been reports of the successful use of alteplase[5-7] and urokinase.[4,8] However, a double-blind trial[9] involving 454 patients found no benefit with streptokinase, and the role of thrombolytics remains unclear. A meta-analysis[10] found no evidence of benefit, although a systematic review[11] suggested that thrombolytics may reduce the need for surgical intervention. Intrapleural streptokinase has also been used successfully in a few patients with malignant multiloculated pleural effusion resistant to standard pleural drainage.[12]

Intrapericardial instillation of thrombolytics has been tried in a few patients with pericardial empyema to prevent the development of constrictive pericarditis.[13,14]

For reports of haemorrhage associated with intrapleural use of streptokinase, see Haemorrhage, under Adverse Effects, above.

1. Temes RT, *et al.* Intrapleural fibrinolytics in management of empyema thoracis. *Chest* 1996; **110:** 102–6.
2. Bouros D, *et al.* Role of streptokinase in the treatment of acute loculated parapneumonic pleural effusions and empyema. *Thorax* 1994; **49:** 852–5.
3. Davies RJO, *et al.* Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. *Thorax* 1997; **52:** 416–21.
4. Bouros D, *et al.* Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions: a prospective, double-blind study. *Am J Respir Crit Care Med* 1997; **155:** 291–5.
5. Bishop NB, *et al.* Alteplase in the treatment of complicated parapneumonic effusion: a case report. Abstract: *Pediatrics* 2003; **111:** 423. Full version: http://pediatrics.aappublications.org/cgi/reprint/111/2/e188 (accessed 16/06/04)
6. Walker CA, *et al.* Intrapleural alteplase in a patient with complicated pleural effusion. *Ann Pharmacother* 2003; **37:** 376–9.
7. Weinstein M, *et al.* Effectiveness and safety of tissue plasminogen activator in the management of complicated parapneumonic effusions. Abstract: *Pediatrics* 2004; **113:** 610. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/3/e182 (accessed 30/04/08)
8. Thomson AH, *et al.* Randomised trial of intrapleural urokinase in the treatment of childhood empyema. *Thorax* 2002; **57:** 343–7.
9. Maskell NA, *et al.* U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 2005; **352:** 865–74. Correction. *ibid.*; 2146.
10. Tokuda Y, *et al.* Intrapleural fibrinolytic agents for empyema and complicated parapneumonic effusions: a meta-analysis. *Chest* 2006; **129:** 783–90.
11. Cameron R, Davies HR. Intra-pleural fibrinolytic therapy versus conservative management in the treatment of adult parapneumonic effusions and empyema. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 30/04/08).
12. Davies CWH, *et al.* Intrapleural streptokinase in the management of malignant multiloculated pleural effusions. *Chest* 1999; **115:** 729–33.
13. Winkler W-B, *et al.* Treatment of exudative fibrinous pericarditis with intrapericardial urokinase. *Lancet* 1994; **344:** 1541–2.
14. Juneja R, *et al.* Intrapericardial streptokinase in purulent pericarditis. *Arch Dis Child* 1999; **80:** 275–7.

Intracardiac thrombosis. Thrombosis of prosthetic heart valves (see p.1187) is usually treated surgically, but thrombolytics have also been used. In a study[1] of patients with left-sided prosthetic valve thrombosis, thrombolytic therapy was found to be more successful than surgery, especially in those who were critically ill; most patients were given streptokinase. Another retrospective study[2] in which patients were given streptokinase, urokinase, or alteplase, concluded that thrombolytics were effective but embolic and haemorrhagic complications might limit their use.

1. Lengyel M, Vándor L. The role of thrombolysis in the management of left-sided prosthetic valve thrombosis: a study of 85 cases diagnosed by transesophageal echocardiography. *J Heart Valve Dis* 2001; **10:** 636–49.
2. Roudaut R, *et al.* Fibrinolysis of mechanical prosthetic valve thrombosis: a single-center study of 127 cases. *J Am Coll Cardiol* 2003; **41:** 653–8.

Ischaemic heart disease. Thrombolytics such as alteplase, streptokinase, and urokinase have an established role in the early management of acute myocardial infarction (p.1175). Myocardial infarction is caused by coronary artery occlusion, usually due to thrombosis, and thrombolytics are given intravenously to break up the thrombus or clot and restore the patency of the coronary artery, thereby limiting infarct size and irreversible damage to the myocardium. Reduction of ECG abnormalities and modification of ventricular remodelling may also contribute to their effect. Other antithrombotics, in particular aspirin and heparin, are given as adjunctive therapy.

Several large studies have established that thrombolytics can preserve left ventricular function and improve short-term and 1-year mortality figures;[1,2] benefit has been maintained in 5-year[3] and 10-year[4,5] follow-up studies. Benefit is greatest with early treatment. Trials such as the GISSI-1 study[6] and the ISIS-2 study[7] helped to establish that mortality is reduced if thrombolytics are given within 6 hours of the onset of symptoms[8] and further studies provided evidence[9,10] that patients presenting within 12 hours should receive a thrombolytic. Use after 12 hours has been associated with an increase in adverse effects,[8] and is usually reserved for patients with evidence of ongoing ischaemia. Prehospital thrombolysis is feasible and reduces the time to thrombolysis and short-term mortality.[11] Five-year follow-up of one study[12] has suggested that there is also a beneficial effect on long-term mortality.

Choice of thrombolytic depends on factors such as cost, method of administration, and contra-indications. Although streptokinase has been the most widely used, several large studies have compared clinical benefit in terms of improved left ventricular function and mortality and have shown no difference between streptokinase and other thrombolytics, including saruplase,[13] the tissue plasminogen activator alteplase,[14] anistreplase,[15] and reteplase[16] in overall efficacy. In the GUSTO-I study,[17] accelerated or 'front loaded' alteplase (that is, rapid intravenous dosage over 1⁄ hours rather than the conventional 3 hours) was more effective than streptokinase, although the study was criticised for not comparing like with like. On the other hand, alteplase might be associated with a greater risk of stroke than streptokinase.[18] Studies comparing bolus injections of reteplase with accelerated alteplase (GUSTO-III)[19] and tenecteplase with alteplase (ASSENT-2)[20] have also found no difference in mortality rate.

The overall effectiveness of thrombolytics is limited by persistent coronary occlusion, re-occlusion, and bleeding complications. Different thrombolytic regimens, such as bolus injections of reteplase, and combinations of thrombolytics, for example alteplase with streptokinase and alteplase with saruplase, have been investigated in attempts to improve patency rates. However, there has been concern that adverse effects may be higher with bolus injection. A study[21] comparing double-bolus alteplase with accelerated alteplase was terminated early when excess deaths were found in the group receiving bolus injections, and a subsequent meta-analysis[22] found a higher incidence of intracranial haemorrhage associated with bolus doses of various thrombolytics. Although use of thrombolytics before percutaneous coronary intervention (PCI) does not appear to be beneficial, a small study[23] has suggested that intracoronary streptokinase given immediately after PCI may improve microvascular reperfusion; however, there was no effect on clinical outcomes.

Thrombolytics have also been tried in other acute coronary syndromes, including unstable angina and non-ST elevation myocardial infarction (p.1157). Although small-scale studies reported some benefit the results were variable, and an overview[8] of trials in patients with suspected myocardial infarction, which included some patients with unstable angina, found that there was no mortality benefit in patients without ST elevation. In 2 studies that investigated alteplase (the TIMI-IIIB study[24] with 1473 patients) and anistreplase (the UNASEM study[25] involving 159 patients), thrombolysis failed to improve outcome and was associated with an excess of bleeding complications. Thrombolytic therapy is therefore not recommended for patients with unstable angina or non-ST elevation myocardial infarction.

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet* 1987; **ii:** 871–4.
2. Wilcox RG, *et al.* Effects of alteplase in acute myocardial infarction: 6-month results from the ASSET study. *Lancet* 1990; **335:** 1175–8.
3. Simoons ML, *et al.* Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. *J Am Coll Cardiol* 1989; **14:** 1609–15.
4. Baigent C, *et al.* ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *BMJ* 1998; **316:** 1337–43.
5. Franzosi MG, *et al.* Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 Study. *Circulation* 1998; **98:** 2659–65.
6. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; **i:** 397–402.
7. Second International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **ii:** 349–60.
8. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994; **343:** 311–22.
9. LATE Study Group. Late assessment of thrombolytic efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet* 1993; **342:** 759–66.
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Peripheral arterial thromboembolism. Thrombolytics including streptokinase may be used in the management of peripheral arterial thromboembolism (p.1178). Streptokinase has been injected intravenously or intra-arterially directly into the clot as an alternative to surgical treatment of the occlusion. It has also been infused intra-arterially to remove distal clots during surgery. The *intravenous* dose generally used is 250 000 units over 30 minutes followed by 100 000 units/hour. A lower dose of 5000 units/hour has been used *intra-arterially* directly into the clot[1] and for removal of distal clots during surgery streptokinase has been given intra-arterially in a dose of 100 000 units over 30 minutes or as five bolus doses of 20 000 units at 5-minute intervals.[2]

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Stroke. Stroke (p.1185) is normally considered a contra-indication to the use of thrombolytics, and clearly they would be inappropriate in acute haemorrhagic stroke. However, when stroke is associated with thrombotic occlusion there is evidence, as with myocardial infarction, that a degree of neuronal recovery is possible if the occlusion is reversed sufficiently quickly, and thrombolytics may therefore have a role in some patients with acute ischaemic stroke.

Early studies with intravenous thrombolytics in acute *ischaemic stroke* suggested a reduction in early death, although subsequent randomised trials produced disappointing results, with the exception of one with alteplase given within 3 hours of the onset of stroke (NINDS—National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial).[1] The studies using streptokinase—MAST-E (Multicentre Acute Stroke Trial-Europe),[2] ASK (Australian Streptokinase Trial),[3] and MAST-I (Multicentre Acute Stroke Trial-Italy)[4,5]—were terminated before completion because of adverse outcomes (intracranial bleeding and increased mortality) in the treatment groups, particularly in those receiving therapy more than 3 hours after stroke onset.[3] The study investigating alteplase given within 6 hours of the onset of symptoms (ECASS I—European Cooperative Acute Stroke Study)[6] reported that, although some patients might benefit, overall alteplase was associated with higher mortality rates and an increase in some intracranial bleeding (parenchymal haemorrhage). In the NINDS randomised study,[1] alteplase given within 3 hours of the onset of ischaemic stroke appeared to improve clinical outcome despite an increased incidence of symptomatic intracerebral haemorrhage. Patients treated with alteplase were more likely to have minimal or no disability 3 months after stroke,[1] and this benefit was maintained at 12 months.[7] However, there was no difference in mortality or rate of recurrence of stroke. A second ECASS study (ECASS II)[8] that hoped to confirm the early findings of the NINDS study failed to confirm a statistical benefit for alteplase over placebo and found no significant differences between patients who received alteplase within 3 hours or between 3 and 6 hours. A review[9] of several studies confirmed that alteplase needed to be given early, and preferably within 90 minutes, if it was to be effective.

On the basis of the NINDS study, alteplase given within 3 hours of the onset of ischaemic stroke is now recommended for selected patients in most guidelines on stroke management.[10-14] Despite their own disappointing results, the ECASS II investigators reached a similar conclusion. However, these recommendations have been criticised.[15,16] It has been pointed out[17,18] that very few patients will be eligible for treatment with alteplase, since the time of onset of symptoms is often uncertain and in many patients more than 3 hours elapses before a definite diagnosis of ischaemic stroke is made. In addition, the NINDS study[1] excluded patients with severe stroke and those taking anticoagulants. The rationale for exclusion of patients with severe stroke is that haemorrhagic transformation is more likely to occur with large areas of infarction.[17] However, size of infarct is difficult to identify by CT scanning.[17] Anticoagulants or antiplatelets are also contra-indicated in the first 24 hours after use of alteplase. The poor results obtained in studies using streptokinase have led to recommendations that streptokinase should be avoided in ischaemic stroke,[13] although an overview of thrombolytic studies[18] suggested that it may not be worse than alteplase and that the apparent hazards of streptokinase may be accounted for by differences in trial design (for example use with anticoagulants) and in patient population. Thus, while alteplase can be considered for those few patients meeting the entry criteria for the NINDS study, a systematic review[19] concluded that further large studies are required to establish more clearly the overall role of thrombolytics in acute ischaemic stroke. Studies of the use of alteplase outside the setting of a clinical trial have had mixed results.[20-22] However, an observational study[23] found that alteplase was safe and effective when used in accordance with guidelines, while another study[24] found that it could be used in elderly patients (80 years-of-age and older), a group normally excluded from clinical trials.

Intra-arterial thrombolytics may have advantages over intravenous use and may be used in selected patients.[12-14] Studies with nasaruplase[25] and urokinase[26] have suggested benefit up to 6 hours after stroke due to middle cerebral artery occlusion, and use of intra-arterial thrombolytics may therefore be considered in such patients.[12-14] Intra-arterial thrombolytics are also used in basilar artery occlusion, although evidence to support this is limited;[12,13,27] intravenous alteplase may be an alternative.[28] Combined use of intravenous and intra-arterial alteplase,[29] as well as use of adjunctive therapies such as therapeutic ultrasound[30] or antithrombotics, are under investigation but do not yet have an established role.[13]

Intravenous thrombolytics have no role in the management of acute *haemorrhagic stroke*, but they have been given locally to facilitate the aspiration of haematomas in both intracerebral[31] and subarachnoid haemorrhage. Small studies with urokinase have shown benefit in patients with intraventricular haemorrhage.

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Preparations

BP 2008: Streptokinase Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Streptase; ***Austral.:*** Streptase; ***Austria:*** Streptase; ***Belg.:*** Streptase; ***Braz.:*** Kabikinase†; Solustrep; Streptase; Streptokin; Streptonase; Unitinase†; ***Canad.:*** Streptase; ***Chile:*** Streptase†; ***Cz.:*** Kabikinase†; Streptase; ***Denm.:*** Streptase; ***Fin.:*** Streptase; ***Fr.:*** Streptase; ***Ger.:*** Streptase; ***Gr.:*** Streptase; ***Hong Kong:*** Streptase; ***Hung.:*** Streptase; ***India:*** Fibrokinase; STpase; Streptase; Zykinase; ***Indon.:*** Streptase; ***Irl.:*** Streptase†; ***Israel:*** Kabikinase; Streptase; ***Ital.:*** Streptase†; ***Malaysia:*** Streptase†; ***Mex.:*** Streptase; ***Neth.:*** Streptase; ***Norw.:*** Kabikinase†; Streptase; ***NZ:*** Streptase; ***Pol.:*** Streptase; ***Port.:*** Streptase; ***S.Afr.:*** Streptase; ***Spain:*** Kabikinase†; Streptase; ***Swed.:*** Streptase; ***Switz.:*** Streptase; ***Thai.:*** Streptase; ***UK:*** Streptase; ***USA:*** Streptase; ***Venez.:*** Streptase.

Multi-ingredient: ***Arg.:*** Varidasa†; ***Austral.:*** Varidase†; ***Austria:*** Varidase; ***Denm.:*** Varidase; ***Fin.:*** Varidase; ***Ger.:*** Varidase; ***Irl.:*** Varidase†; ***Ital.:*** Varidase†; ***Mex.:*** Varidasa; ***Norw.:*** Varidase; ***Pol.:*** Distreptaza; ***Port.:*** Varidasa†; ***Spain:*** Ernodasa; Varidasa; ***Swed.:*** Varidase; ***UK:*** Varidase†.

Strophanthin-K

Estrofantina; Kombé Strophanthin; Strophanthin; Strophanthoside-K.

CAS — 11005-63-3.

NOTE. Do not confuse with K-strophanthin-α which is Cymarin.

Pharmacopoeias. In *Chin.*

Profile

Strophanthin-K is a cardiac glycoside or a mixture of cardiac glycosides from strophanthus, the seeds of *Strophanthus kombe* (Apocynaceae) or other spp., adjusted by admixture with a suitable diluent such as lactose so as generally to possess 40% of the activity of anhydrous ouabain.

Strophanthin-K is a positive inotrope with general properties similar to those of digoxin (p.1259). It is poorly absorbed from the gastrointestinal tract but may be given intravenously in maintenance doses of 125 to 250 micrograms daily in the management of heart failure (p.1165).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Kombetin.

Suleparoid *(rINNM)*

Heparan Sulfate; Heparan Sulphate; Heparitin Sulfate; Suléparoïde; Suleparoide; Suleparoidum.

Сулепароид

CAS — 9050-30-0.

Suleparoid Sodium *(rINN)*

Heparan Sulfate Sodium; Sodium Heparitin Sulphate; Suleparoide sódico; Suléparoïde Sodique; Suleparoidum Natricum.

Сулепароид Натрий

CAS — 57459-72-0.

Profile

Suleparoid is a naturally occurring glycosaminoglycan given orally in the management of thromboembolic disorders; it is also used topically. Suleparoid sodium is a component of danaparoid sodium (p.1255).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Aremin; Arteven; Clarema; Hemovasal; Leparan†; Spatix†; Tavidan; Vas; Vasorema†.

Multi-ingredient: ***Ital.:*** Osmogel.

Sulodexide *(rINN)*

KRX-101; Sulodexida; Sulodexidum. Glucurono-2-amino-2-deoxyglucoglucan sulfate.

Сулодексид

CAS — 57821-29-1.
ATC — B01AB11.
ATC Vet — QB01AB11.