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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.

Profile

Sulodexide is a heparinoid consisting of a mixture of low-molecular-weight heparin and dermatan sulfate. It is used as a hypolipidaemic and antithrombotic and has been given orally and parenterally for peripheral vascular disease and cerebrovascular disease. It is also included in preparations used topically for local vascular inflammation and soft-tissue disorders. Sulodexide has also been investigated for the treatment of diabetic nephropathy.

◊ References.

1. Ofosu FA. Pharmacological actions of sulodexide. *Semin Thromb Hemost* 1998; **24:** 127–38.
2. Weiss R, *et al*. The role of sulodexide in the treatment of diabetic nephropathy. *Drugs* 2007; **67:** 2681–96.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Vessel Due F; ***Hung.:*** Vessel Due F; ***Ital.:*** Clarens; Provenal; Ravenol; Treparin; Vessel; ***Malaysia:*** Vessel Due F; ***Philipp.:*** Vessel Due F; ***Pol.:*** Vessel Due F; ***Port.:*** Vessel; ***Rus.:*** Vessel Due F (Вессел Дуэ Ф); ***Spain:*** Aterina; Luzone; ***Venez.:*** Vessel Due.

Multi-ingredient: ***Ital.:*** Dermoangiopan†; Vessiflex†.

Sympathomimetics ⊗

Adverse Effects

Sympathomimetics may produce a wide range of adverse effects, generally resembling the effect of excessive stimulation of the sympathetic nervous system. These effects are mediated by the different types of adrenergic receptor, and the effects of individual drugs depend to a large extent on their relative activity at the different receptors, as well as the body's homoeostatic response. While many sympathomimetics are relatively selective for specific receptors, this depends on the dose, and at higher doses most have effects on all receptors.

Central effects may occur with all sympathomimetics and include anxiety, fear, restlessness, insomnia, confusion, irritability, headache, and psychotic states; dyspnoea, weakness, anorexia, nausea, and vomiting are also common. Although some sympathomimetics have direct effects, others do not cross the blood-brain barrier and their central effects appear to be a somatic response.

The most important adverse effects of the sympathomimetics are those that affect the cardiovascular system. Palpitations, tachycardia, and arrhythmias mainly result from stimulation of cardiac beta receptors, and there is also an increase in cardiac contractility; this may result in angina or cardiac arrest.

The effects on blood vessels depend on the relative effects at alpha and beta receptors, since most blood vessels have both. Stimulation of alpha receptors produces vasoconstriction, with resultant hypertension, and this may be severe enough to lead to cerebral haemorrhage or pulmonary oedema, particularly in overdosage. There may also be reflex bradycardia. Conversely, hypotension, with dizziness and fainting, and flushing, may occur due to $beta_2$-induced vasodilatation, and may contribute to tachycardia.

Alpha-mediated vasoconstriction causes cold extremities, since blood vessels supplying the skin and mucosa have only alpha receptors; this may lead to gangrene, particularly when sympathomimetics are infiltrated into digits. Extravasation similarly may cause tissue necrosis and sloughing. Topical application to mucosal surfaces also causes vasoconstriction, pain, and irritation; hypoxia may lead to rebound mucosal congestion.

Other effects include mydriasis, difficulty in micturition and urinary retention, piloerection, sweating, and increased salivation, all of which result from $alpha_1$ stimulation. Hypokalaemia and muscle tremor may occur as a result of $beta_2$ stimulation, although tremor may also occur as a somatic response. Effects on the uterus are complex and depend on the stage of the menstrual cycle; labour may be inhibited by $beta_2$ stimulation. Hyperglycaemia may occur due to complex metabolic effects, and lactic acidosis has also been reported.

Effects on the heart. The heart has mainly $beta_1$ adrenoceptors and cardiac arrhythmias are most likely with $beta_1$ agonists; increased mortality has been reported with the use of beta agonists in heart failure (see Ibopamine, p.1312). A review[1] of vasopressor sympathomimetics, which are mainly used for their alpha-agonist properties, concluded that dopamine and adrenaline were associated with the highest risk, mainly of dose-related sinus tachycardia and ventricular arrhythmias. However, the clinical significance of most arrhythmias occurring with dopamine was considered questionable; supraventricular or ventricular arrhythmias with adrenaline were most likely in patients receiving general anaesthesia or with underlying disorders of cardiac conduction. The risk with noradrenaline was uncertain, though there are few clinical reports, while phenylephrine and methoxamine were thought unlikely to cause problems. Overall the frequency of serious problems with this class of drugs did not seem to be high, and benefits outweighed the risks in most patients.

Sympathomimetics may cause myocardial ischaemia, particularly in patients with ischaemic heart disease, and severe cardiovascular effects have occurred with the use of dobutamine for cardiac stress testing (see Diagnosis and Testing, p.1272). In addition, myocardial infarction has been reported in an 11-year-old boy treated with nebulised racepinefrine for symptoms of croup,[2] and there have also been reports of myocardial ischaemia associated with adrenaline overdosage (see p.1203).

1. Tisdale JE, *et al*. Proarrhythmic effects of intravenous vasopressors. *Ann Pharmacother* 1995; **29:** 269–81.
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Topical use. Systemic effects may occasionally follow the local or topical use of sympathomimetics, for example as eye drops for the treatment of glaucoma.[1] Psychiatric effects including hallucinations and paranoia have also occurred after both proper and improper use of sympathomimetics in decongestant preparations.[2]

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
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Treatment of Adverse Effects

Most sympathomimetics have a short duration of action and treatment of adverse effects is mainly supportive; if given by infusion, stopping it or reducing the rate will be sufficient in many cases. A rapidly-acting alpha blocker, such as phentolamine, may be given to reverse $alpha_1$-mediated effects such as hypertension, while a beta blocker may be given for $beta_1$-mediated effects such as cardiac arrhythmias. In severe hypertension, rapidly-acting vasodilators such as glyceryl trinitrate have also been used.

In the case of extravasation of an alpha agonist, or injection into a digit, an alpha blocker such as phentolamine should be given as soon as possible to prevent tissue necrosis and ischaemic damage.

Non-catecholamine sympathomimetics may have a longer duration of action and adverse effects, particularly hypertension, may be prolonged.

Precautions

Sympathomimetics should be used with caution in patients with cardiovascular disorders, who may have an increased susceptibility to their effects. Particular care is needed in patients with cardiac arrhythmias, ischaemic heart disease, or hypertension. All sympathomimetics should generally be avoided in severe hypertension, although alpha agonists are particularly hazardous; they should also be used with caution in patients with occlusive vascular disease, who are at increased risk of peripheral ischaemia. $Beta_1$ agonists are a particular hazard in tachycardia. Sympathomimetics with $beta_2$ effects should be used with caution in obstructive cardiomyopathy and other disorders where a reduction in total peripheral resistance could be harmful.

Sympathomimetics should be avoided in phaeochromocytoma. Caution is also needed in patients with hyperthyroidism, who may be at increased risk of effects on the heart; elevated thyroid hormone concentrations may also enhance adrenoceptor sensitivity. Diabetics and elderly patients have a high incidence of atherosclerotic disease and may also be at higher risk; the effects of sympathomimetics on blood glucose should also be considered.

Alpha agonists in particular should be used with caution in angle-closure glaucoma, as well as in patients with prostate disorders, who may be at increased risk of urinary retention. Sympathomimetics with vasoconstrictor effects may reduce placental perfusion and should possibly be avoided in pregnancy; adrenaline and others with $beta_2$-mediated effects may also inhibit labour.

If sympathomimetics are used for circulatory support, hypovolaemia, metabolic acidosis, and hypoxia or hypercapnia should be corrected either before starting the sympathomimetic or while it is being given. Blood pressure should be monitored regularly during treatment.

Interactions

Interactions with sympathomimetics are complex and may be hazardous; they result mainly from their pharmacological actions at alpha and beta receptors.

Increased cardiac effects may occur with drugs that increase the sensitivity of the myocardium to $beta_1$ agonists; hazardous arrhythmias may occur with volatile anaesthetics, particularly cyclopropane or halothane. Caution is also required with thyroid hormones, and with drugs that affect cardiac conduction, such as cardiac glycosides and antiarrhythmics.

All sympathomimetics affect blood pressure and should be used with caution with antihypertensive drugs or drugs that cause hypotension, particularly those whose action involves the sympathetic nervous system. Direct-acting sympathomimetics with alpha-agonist actions specifically reverse the hypotensive effect of adrenergic neurone blockers such as guanethidine, and severe hypertension may result. There are also complex interactions between both alpha and beta blockers and sympathomimetics, particularly those that have actions at both types of receptor. Alpha blockers antagonise the effects at alpha receptors but leave the beta-mediated effects unopposed, leading to an increased risk of hypotension and tachycardia. Beta blockers, especially those that are non-selective, antagonise the effects at beta receptors but leave the alpha-mediated effects unopposed, increasing the risk of hypertension and reflex bradycardia. They also antagonise the bronchodilating effects of $beta_2$ agonists. Severe anaphylaxis in patients taking non-cardioselective beta blockers may not respond to adrenaline (see below).

Hazardous interactions resulting in severe hypertension may occur with MAOIs (including RIMAs) and sympathomimetics, especially those that have indirect actions, since MAOIs increase the amount of noradrenaline stored in adrenergic nerve endings. Sympathomimetics for which the risk is particularly high include dexamfetamine, dopamine, dopexamine, ephedrine, isometheptene, mephentermine, metaraminol, methylphenidate, phentermine, phenylephrine, phenylpropanolamine, and pseudoephedrine. The effects of direct-acting sympathomimetics such as adrenaline and noradrenaline may also be slightly enhanced. For additional warnings see under Phenelzine (p.418) and Moclobemide (p.411).

Tricyclic antidepressants block the inactivation of adrenaline and noradrenaline by uptake into the nerve endings and may increase their effect; hypertension and arrhythmias may occur. Conversely, the effect of indirectly-acting sympathomimetics could theoretically be reduced by tricyclics, although there is little clinical evidence that this occurs. There is also no evidence that an interaction occurs when local anaesthetic solutions containing adrenaline or noradrenaline are used in patients taking MAOIs or tricyclics, although great care needs to be taken to avoid inadvertent intravenous injection of these local anaesthetic preparations.