4. Anonymous. Adenosine for acute cardiac arrhythmias. *Drug Ther Bull* 1993; **31:** 49–50.
5. Mason BA, *et al.* Adenosine in the treatment of maternal paroxysmal supraventricular tachycardia. *Obstet Gynecol* 1992; **80:** 478–80.
6. Afridi I, *et al.* Termination of supraventricular tachycardia with intravenous adenosine in a pregnant woman with Wolff-Parkinson-White syndrome. *Obstet Gynecol* 1992; **80:** 481–3.
7. Hagley MT, Cole PL. Adenosine use in pregnant women with supraventricular tachycardia. *Ann Pharmacother* 1994; **28:** 1241–2.
8. Hagley MT, *et al.* Adenosine use in a pregnant patient with supraventricular tachycardia. *Ann Pharmacother* 1995; **29:** 938.
9. Blanch G, *et al.* Cardioversion of fetal tachyarrhythmia with adenosine. *Lancet* 1994; **344:** 1646.
10. Kohl T, *et al.* Direct fetal administration of adenosine for the termination of incessant supraventricular tachycardia. *Obstet Gynecol* 1995; **85:** 873–4.

Ischaemic heart disease. Adenosine produces coronary vasodilatation and may be used to provide a pharmacological stress in patients undergoing assessment of their ischaemic heart disease when exercise stress is inappropriate.[1] It has been used with radionuclide imaging, echocardiography, and magnetic resonance imaging.

Adenosine has also been tried as an adjunct to prevent reperfusion injury in the management of acute myocardial infarction. Improved coronary blood flow has been reported[2] with intracoronary adenosine, and both intracoronary[3] and intravenous[4] adenosine have reduced infarct size, but no improvement in clinical outcomes has been shown.[5-7] A reduction in myonecrosis has also been reported[8] with intracoronary adenosine given at the start of non-urgent percutaneous coronary interventions.

1. Ali Raza J, *et al.* Pharmacological stress agents for evaluation of ischemic heart disease. *Int J Cardiol* 2001; **81:** 157–67.
2. Vijayalakshmi K, *et al.* Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006; **92:** 1278–84.
3. Claeys MJ, *et al.* Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004; **94:** 9–13.
4. Mahaffey KW, *et al.* Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. *J Am Coll Cardiol* 1999; **34:** 1711–20.
5. Ross AM, *et al.* A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol* 2005; **45:** 1775–80.
6. Quintana M, *et al.* Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis: results of the ATTenuation by Adenosine of Cardiac Complications (ATTACC) study. *Eur J Clin Pharmacol* 2003; **59:** 1–9.
7. Petronio AS, *et al.* Left ventricular remodeling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine. *Am Heart J* 2005; **150:** 1015. Full version: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870305007313.pdf (accessed 26/06/07)
8. Lee C-H, *et al.* Pretreatment with intracoronary adenosine reduces the incidence of myonecrosis after non-urgent percutaneous coronary intervention: a prospective randomized study. *Eur Heart J* 2007; **28:** 19–25.

Pain. Adenosine receptors are present in the CNS and there is some evidence[1,2] that adenosine, given intravenously or intrathecally, may have an analgesic effect.

1. Hayashida M, *et al.* Clinical application of adenosine and ATP for pain control. *J Anesth* 2005; **19:** 225–35.
2. Gan TJ, Habib AS. Adenosine as a non-opioid analgesic in the perioperative setting. *Anesth Analg* 2007; **105:** 487–94.

Pulmonary hypertension. Vasodilators have been tried in persistent pulmonary hypertension of the newborn (p.1179), but their use is generally restricted by lack of selectivity for the pulmonary circulation. A randomised placebo-controlled study[1] in 18 term infants with persistent pulmonary hypertension indicated that intravenous infusion of adenosine improved oxygenation without causing hypotension or tachycardia; however, the study was too small to assess any effect on mortality and/or the need for extracorporeal membrane oxygenation. Another observational study[2] in neonates with an inadequate response to inhaled nitric oxide suggested that addition of adenosine infusion also improved oxygenation.

1. Konduri GG, *et al.* Adenosine infusion improves oxygenation in term infants with respiratory failure. *Pediatrics* 1996; **97:** 295–300.
2. Ng C, *et al.* Adenosine infusion for the management of persistent pulmonary hypertension of the newborn. *Pediatr Crit Care Med* 2004; **5:** 10–13.

Preparations

USP 31: Adenosine Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Euritsin†; ***Austral.:*** Adenocor; Adenoscan; ***Austria:*** Adenoscan; Adrekar; ***Belg.:*** Adenocor; ***Braz.:*** Adenocard; ***Canad.:*** Adenocard; ***Chile:*** Tricor; ***Cz.:*** Adenocor; Adenoscan†; ***Denm.:*** Adenocor; ***Fin.:*** Adenocor; Adenoscan†; ***Fr.:*** Adenoscan; Krenosin; ***Ger.:*** Adenoscan; Adrekar; ***Gr.:*** Adenocor; ***Hong Kong:*** Adenoscan; ***Hung.:*** Adenocor; ***India:*** Adenoject; ***Irl.:*** Adenocor; ***Israel:*** Adenocor; ***Ital.:*** Adenoscan; Krenosin; ***Jpn:*** Adenoscan; ***Malaysia:*** Adenocor; ***Mex.:*** Krenosin; ***Neth.:*** Adenocor; Adenoscan; ***Norw.:*** Adenocor; ***NZ:*** Adenocor; ***Philipp.:*** Cardiovert; ***Pol.:*** Adenocor; ***Rus.:*** Vita-Iodurol (Вита-иодурол); ***S.Afr.:*** Adenocor; ***Singapore:*** Adenocor; ***Spain:*** Adenocor; Adenoscan; ***Switz.:*** Krenosine; ***Thai.:*** Adenocor; ***UK:*** Adenocor; Adenoscan; ***USA:*** Adenocard; Adenoscan; ***Venez.:*** Adenocor†.

Multi-ingredient: *Belg.:* Vitacic; ***Braz.:*** Aminotox†; Anekron; Betaliver†; Biohepax; Enterofigon; Epativan; Epocler; Hepacitron†; Hepatobe†; Hepatox; Hormo Hepatico†; Necro B-6; ***Cz.:*** Laevadosin†; ***Hung.:*** Vitacic†; ***Mon.:*** Vitacic; ***Philipp.:*** Godex; ***Rus.:*** Oftan Catachrom (Офтан Катахром); Vitacic (Витасик)†; ***Spain:*** Vitaphakol.

Adrenaline *(BAN)* ⊗

Epinephrine *(BAN, rINN)*; Adrenaliini; Adrenalin; Adrenalina; Adrénaline; Adrenalinum; Epinefriini; Epinefrin; Epinefrina; Epinefryna; Épinéphrine; Epinephrinum; Epirenamine; Levorenin; Suprarenin. (*R*)-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol.

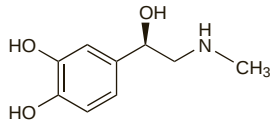
Эпинефрин

$C_9H_{13}NO_3$ = 183.2.

CAS — 51-43-4.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.



NOTE. Endogenous adrenaline and the monograph substance are the laevo-isomer.
ADN and EPN are codes approved by the BP 2008 for use on single unit doses of eye drops containing adrenaline where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet*.
US also includes the racemic substances Racepinephrine (Racepinefrine (*rINN*)) and Racepinephrine Hydrochloride (Racepinefrine Hydrochloride (*rINNM*)).
Ph. Eur. 6.2 (Adrenaline). A white or almost white crystalline powder, becoming coloured on exposure to air and light. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in hydrochloric acid. Store under nitrogen. Protect from light.
USP 31 (Epinephrine). A white to practically white, odourless, microcrystalline powder or granules, gradually darkening on exposure to light and air. With acids, it forms salts that are readily soluble in water, and the base may be recovered by the addition of ammonia water or alkali carbonates. Very slightly soluble in water and in alcohol; insoluble in chloroform, in ether, and in fixed and volatile oils. Solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Adrenaline Acid Tartrate *(BANM)* ⊗

Epinephrine Bitartrate *(rINNM)*; Adrenaliinitartraatti; Adrenaline Bitartrate; Adrenaline Tartrate; Adrénaline, Tartrate d'; Adrenalini Bitartras; Adrenalini tartras; Adrenalinii Tartras; Adrenalinium Hydrogentartaricum; Adrenalino tartratas; Adrenalin-tartarát; Adrenalintartrat; Bitartrato de epinefrina; Epinefrin-tartarát; Epinefryny wodorowinian; Epinephrine Acid Tartrate *(BANM)*; Épinéphrine, Bitartrate d'; Epinephrine Hydrogen Tartrate; Epinephrini Bitartras; Epinephrini Tartras; Epirenamine Bitartrate.

Эпинефрина Битартрат

$C_9H_{13}NO_3,C_4H_6O_6$ = 333.3.

CAS — 51-42-3.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *US*, and *Viet*.
Ph. Eur. 6.2 (Adrenaline Tartrate; Adrenaline Acid Tartrate BP 2008; Epinephrine Acid Tartrate BP 2008). A white to greyish-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably in a sealed tube under vacuum or under an inert gas. Protect from light.
USP 31 (Epinephrine Bitartrate). A white, or greyish-white or light brownish-grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 3 of water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its solutions in water are acid to litmus, having a pH of about 3.5. Store in airtight containers. Protect from light.

Stability. Studies on the stability of adrenaline injections.

1. Taylor JB, *et al.* Effect of sodium metabisulphite and anaerobic processing conditions on the oxidative degradation of adrenaline injection BP [1980]. *Pharm J* 1984; **232:** 646–8.
2. Stepensky D *et al.* Long-term stability study of -adrenaline injections: kinetics of sulfonation and racemization pathways of drug degradation. *J Pharm Sci* 2004; **93:** 969–80.

Adrenaline Hydrochloride *(BANM)* ⊗

Epinephrine Hydrochloride *(BANM, rINNM)*; Adrenalin Hidroklorür; Épinéphrine, Chlorhydrate d'; Epinephrini Hydrochloridum; Hidrocloruro de epinefrina.

Эпинефрина Гидрохлорид

$C_9H_{13}NO_3$,HCl = 219.7.

CAS — 55-31-2.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

Adverse Effects

Adrenaline is a potent sympathomimetic and may exhibit the adverse effects typical of both alpha- and beta-adrenoceptor stimulation (see p.1407). Adverse effects such as anxiety, dyspnoea, hyperglycaemia, restlessness, palpitations, tachycardia (sometimes with anginal pain), tremors, sweating, hypersalivation, weakness, dizziness, headache, and coldness of extremities may occur even with low doses. Since adrenaline does not readily cross the blood-brain barrier, its central effects may be largely a somatic response to its peripheral effects. Overdosage may cause cardiac arrhythmias and a sharp rise in blood pressure (sometimes leading to cerebral haemorrhage and pulmonary oedema); these effects may occur at normal dosage in susceptible subjects.

Adrenaline is a potent vasoconstrictor and gangrene may occur if adrenaline-containing local anaesthetic solutions are infiltrated into digits. Extravasation of parenteral adrenaline also results in intense vasoconstriction, leading to tissue necrosis and sloughing. Topical application of adrenaline to mucosal surfaces similarly causes vasoconstriction, which may induce hypoxia leading to compensatory rebound congestion of the mucosa. Inhalation of adrenaline has been associated with epigastric pain, which has been attributed to ingestion of some of the inhalation; it can be minimised by rinsing the mouth and throat with water after inhaling.

Adrenaline eye drops may produce severe smarting, blurred vision, and photophobia on instillation; they may also leave melanin-like deposits in the cornea and conjunctiva, and this has led to obstruction of the nasolachrymal ducts. Repeated use may cause oedema, hyperaemia, and inflammation of the eyes.

Effects on the eyes. In addition to the possibility of pigment deposition and local pain (see above) adrenaline eye drops have been associated with maculopathy, particularly in aphakic eyes (those devoid of a lens).[1] In one report,[2] maculopathy was noted in 15 patients over a period of 4 years; the patients were using adrenaline eye drops containing the hydrochloride, acid tartrate, or adrenaline borate complex (epinephryl borate). Blurring and distortion of vision were followed by decreased visual acuity, and by the appearance of oedema and sometimes haemorrhage in the macular region. A few patients developed cysts near the fovea. These effects appeared within a few weeks of, or several months after, starting therapy and were usually reversible. All except 1 of the patients were aphakic, and retrospective studies have suggested that the incidence of this complication may be up to 30% in aphakic patients.[1,2]

1. Classé JG. Epinephrine maculopathy. *J Am Optom Assoc* 1980; **51:** 1091–3.
2. Kolker AE, Becker B. Epinephrine maculopathy. *Arch Ophthalmol* 1968; **79:** 552–62.

Overdosage. Solutions of racepinefrine for nebulisation have inadvertently been given intravenously, resulting in severe overdosage of adrenaline. A 13-month-old infant[1] was given the equivalent of about 327 micrograms/kg of laevo-adrenaline. Marked pallor, pulselessness, and profound bradycardia developed, but the child responded to cardiopulmonary resuscitation and was subsequently discharged with no evidence of long-term sequelae. However, a 2-year-old child[2] given the equivalent of about 1800 micrograms/kg developed hypertension, tachycardia, and pulmonary oedema, followed by hypotension and subsequent renal failure, requiring transplantation. Subcutaneous overdosage with laevo-adrenaline in another child[3] led to arrhythmias and myocardial ischaemia, and there has also been a report[4] of myocardial infarction and acute renal failure in an adult after injection of the solution from an adrenaline inhaler.

1. Kurachek SC, Rockoff MA. Inadvertent intravenous administration of racemic epinephrine. *JAMA* 1985; **253:** 1441–2.

2. Dybvik T, *et al.* Accidental intravenous administration of 50 mg of racemic adrenaline in a 2-year-old boy. *Eur J Anaesthesiol* 1995; **12:** 181–3.
3. Davis CO, Wax PM. Prehospital epinephrine overdose in a child resulting in ventricular dysrhythmias and myocardial ischemia. *Pediatr Emerg Care* 1999; **15:** 116–18.
4. Woodard ML, Brent LD. Acute renal failure, anterior myocardial infarction, and atrial fibrillation complicating epinephrine abuse. *Pharmacotherapy* 1998; **18:** 656–8.

Treatment of Adverse Effects

As for Sympathomimetics, p.1407. Adrenaline has a short duration of activity due to inactivation in the body and treatment of severe toxic reactions in hypersensitive patients or after overdose is primarily supportive.

Digital injection. Inadvertent digital injection of adrenaline from autoinjector devices may cause acute ischaemia. Phentolamine injection has been successfully used to reverse the vasoconstriction,[1] and there has also been a report[2] of the use of iloprost infusion followed by a stellate ganglion block.

1. Velissariou I, *et al.* Management of adrenaline (epinephrine) induced digital ischaemia in children after accidental injection from an EpiPen. *Emerg Med J* 2004; **21:** 387–8.
2. Barkhordarian AR, *et al.* Accidental digital injection of adrenaline from an autoinjector device. *Br J Dermatol* 2000; **143:** 1359.

Precautions

As for Sympathomimetics, p.1407. Adrenaline is frequently used in emergency situations and any contra-indications are therefore relative.

Adrenaline may delay the second stage of labour and some licensed product information recommends that it should not be used during this time.

Adrenaline eye drops are contra-indicated in angle-closure glaucoma unless an iridectomy has been carried out.

Contact lenses. Adrenochrome staining of soft-contact lenses of patients using adrenaline eye drops has been reported.[1] Melanin deposits may also become locked into the lens; such deposits may be broken down by hydrogen peroxide. The prodrug, dipivefrine hydrochloride (p.2295) has been used without staining soft lenses.

1. Ingram DV. Spoiled soft contact lenses. *BMJ* 1986; **292:** 1619.

Infection. An open study[1] comparing adrenaline with dopamine for cardiovascular support in 23 patients critically ill with severe sepsis or malaria suggested that use of adrenaline was limited by the development of lactic acidosis. However, it has been pointed out[2] that 20 of the patients had responded to fluids, a situation in which the use of inotropic or vasopressor support was considered questionable, and that adrenaline has been widely used in the treatment of septic shock. A further controlled study[3] found that although adrenaline led to higher lactate concentrations than noradrenaline with dobutamine, the effect was transient. Nevertheless, it has been recommended[4] that adrenaline should only be used in septic shock if other treatments are ineffective.

1. Day NPJ, *et al.* The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet* 1996; **348:** 219–23. Correction. *ibid.*; 902.
2. Barry B, Bodenham A. Effects of dopamine and adrenaline infusions in severe infection. *Lancet* 1996; **348:** 1099–1100.
3. Levy B, *et al.* Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med* 1997; **23:** 282–7.
4. Hollenberg SM, *et al.* American College of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; **32:** 1928–48.

Interactions

As for Sympathomimetics, p.1407; adrenaline has direct alpha- and beta-agonist actions and its interactions are complex and may be hazardous. Particular caution is needed if adrenaline is given to patients taking beta blockers since severe hypertension may result; patients taking beta blockers may also have an impaired response to adrenaline if it is needed for anaphylaxis.

Local anaesthetics. It is common practice to give adrenaline with a local anaesthetic to produce vasoconstriction; the lowest effective concentration of adrenaline should be used. However, use with *cocaine* may increase the risk of cardiac arrhythmias and particular caution is required. See p.1860 for a report of severe complications with use of such a combination in otolaryngology.

Pharmacokinetics

As a result of enzymatic degradation in the gut and first-pass metabolism in the liver, adrenaline is almost totally inactive when given orally. Systemic absorption can occur after topical application for example of eye drops. Adrenaline acts rapidly after intramuscular and subcutaneous injection; the latter route is, however, sometimes considered to be slower and therefore less reliable for emergency use. Although absorption is slowed by local vasoconstriction it can be hastened by massaging the injection site.

Most adrenaline that is either injected into the body or released into the circulation from the adrenal medulla, is very rapidly inactivated by processes that include uptake into adrenergic neurones, diffusion, and enzymatic degradation in the liver and body tissues. The half-life of circulating adrenaline is only about 1 minute. One of the enzymes responsible for the chemical inactivation of adrenaline is catechol-*O*-methyltransferase (COMT), the other is monoamine oxidase (MAO). In general, adrenaline is methylated to metanephrine by COMT followed by oxidative deamination by MAO and eventual conversion to 4-hydroxy-3-methoxymandelic acid (formerly termed vanillylmandelic acid; VMA), or oxidatively deaminated by MAO and converted to 3,4-dihydroxymandelic acid which, in turn, is methylated by COMT, once again to 4-hydroxy-3-methoxymandelic acid; the metabolites are excreted in the urine mainly as their glucuronide and ethereal sulfate conjugates.

The ability of COMT to effect introduction of a methyl group is an important step in the chemical inactivation of adrenaline and similar catecholamines (in particular, noradrenaline). It means that the termination of the pharmacological response of catecholamines is not simply dependent upon MAO. In its role of neurotransmitter intraneuronal catecholamine (mainly noradrenaline) is, however, enzymatically regulated by MAO.

Adrenaline crosses the placenta to enter fetal circulation.

Uses and Administration

Adrenaline is an endogenous substance that is produced in the adrenal medulla and has important physiological effects. It is also used pharmacologically as a direct-acting sympathomimetic (see p.1408). It is a potent agonist at both alpha and beta adrenoceptors, although the effect on beta adrenoceptors is more marked, particularly at lower doses. These properties explain many aspects of its pharmacology, although the reflex compensating responses of the body also modulate its effects.

The major effects of adrenaline are dose-related and include:

- increased speed and force of cardiac contraction (with lower doses this causes increased systolic pressure yet reduced diastolic pressure since overall peripheral resistance is lowered, but with higher doses both systolic and diastolic pressure are increased as stimulation of peripheral alpha receptors increases peripheral resistance)
- increased blood flow to skeletal muscle (reduced with higher doses); reduced blood flow in the kidneys, mucosa, and skin; little direct effect on cerebral blood flow
- relaxation of bronchial smooth muscle
- hyperglycaemia and markedly increased oxygen consumption due to metabolic effects

Adrenaline has an important role in the management of acute allergic reactions and can be life-saving in patients with anaphylaxis and anaphylactic shock (below). It is also used in advanced cardiac life support (below). Adrenaline has been used in the treatment of acute asthma but more selective drugs are available, and it has no role in the chronic management of asthma (p.1108). It has been given by nebulisation in severe croup (p.1502). Other uses include the control of minor bleeding from the skin and mucous membranes, the management of open-angle (simple) glaucoma (p.1873), and use as an adjunct to local anaesthesia (p.1852). Adrenaline was formerly incorporated into creams used in the treatment of rheumatic and muscular disorders, and in rectal preparations used in the treatment of haemorrhoids. Racepinefrine (racemic adrenaline) and racepinefrine hydrochloride have been used for bronchodilatation.

Adrenaline is usually given by intramuscular injection, although it may also be given subcutaneously. In extreme emergencies, where a more rapid effect is required, adrenaline may be given as a dilute solution (1 in 10 000 or 1 in 100 000) by very slow intravenous injection or by slow intravenous infusion. Alternatively, if intravenous access cannot be obtained, it may also be given by the intraosseous (usually into the marrow of the tibia) or endotracheal routes. Adrenaline has sometimes been injected directly in the heart but current guidelines for the management of cardiac emergencies recommend intravenous injection; this may be into a central vein or peripherally, but in the latter case should be followed by 20 mL of intravenous fluid. Adrenaline may also be applied topically or given by inhalation. Aqueous solutions of adrenaline are usually prepared using the acid tartrate or the hydrochloride but the dosage is generally stated in terms of the equivalent content of adrenaline. Adrenaline acid tartrate 1.8 mg or adrenaline hydrochloride 1.2 mg is equivalent to about 1 mg of adrenaline.

The usual dose of adrenaline in **anaphylactic shock** is 500 micrograms (0.5 mL of a 1 in 1000 solution) by intramuscular injection repeated as necessary every 5 minutes. A dose of 300 micrograms (0.3 mL of a 1 in 1000 solution) may be appropriate for emergency self-administration, for example by autoinjector. The dose for children depends on age and weight, but is usually about 10 micrograms/kg by intramuscular injection. For further details on doses for children and for intravenous doses, see Anaphylaxis and Anaphylactic Shock, below.

In **advanced cardiac life support** the initial dose of adrenaline for adults is 1 mg intravenously (10 mL of a 1 in 10 000 solution) and this may be repeated as often as every 2 to 3 minutes throughout the resuscitation procedure. The dose for children is 10 micrograms/kg intravenously. Higher intravenous doses have been used in both adults and children for the second and subsequent doses but are no longer generally recommended. Intraosseous doses for adults and children are the same as those used intravenously. Endotracheal doses for adults are 2 to 3 times the intravenous dose; children may be given 100 micrograms/kg.

Adrenaline relaxes the bronchial musculature and has sometimes been injected subcutaneously or intramuscularly in the management of **acute asthmatic attacks**. However, in general, the use of adrenaline in asthma has been superseded by $beta_2$ agonists, such as salbutamol, which can alleviate bronchospasm with fewer effects on the heart. If adrenaline is to be used, the adult dose is 0.3 to 0.5 mL of a 1 in 1000 aqueous solution (300 to 500 micrograms); children have received 0.01 mL/kg (10 micrograms/kg) to a maximum of 0.5 mL (500 micrograms). Aqueous solutions with an adrenaline content equivalent to 1 in 100 have occasionally been used by inhalation as a spray to alleviate asthmatic attacks; these solutions must never be confused with the weaker strength used for injection. Pressurised aerosols delivering metered doses equivalent to about 160 micrograms to 275 micrograms of adrenaline have also been used; adults have been given 1 or 2 metered inhalations, repeated, if necessary, after 3 hours.

Adrenaline is often added to **local anaesthetics** to retard diffusion and limit absorption, to prolong the duration of effect, and to lessen the danger of toxicity. A concentration of 1 in 200 000 (5 micrograms/mL) is usually used; adrenaline should not be added when procedures involve digits, ears, nose, penis, or scrotum because of the risk of ischaemic tissue necrosis. A con-

centration of up to 1 in 80 000 (12.5 micrograms/mL) may be used in dental preparations where the total dose given is small.

Adrenaline constricts arterioles and capillaries and causes blanching when applied locally to mucous membranes and exposed tissues. It is used as an aqueous solution in strengths up to a 1 in 1000 dilution to check capillary **bleeding**, epistaxis, and bleeding from superficial wounds and abrasions, but it does not stop internal haemorrhage. It is usually applied as a spray or on pledgets of cotton wool or gauze.

In ophthalmology, adrenaline solutions of 0.5%, 1%, or 2% are used as eye drops instilled once or twice daily to reduce intra-ocular pressure in open-angle **glaucoma** and ocular hypertension. An adrenaline borate complex (epinephryl borate) is also used.

Advanced cardiac life support. Adrenaline has an important role in advanced cardiac life support (p.1156) since, through its alpha agonist effects, it causes peripheral vasoconstriction, thus increasing myocardial and cerebral blood flow. This should improve the efficacy of cardiopulmonary resuscitation or basic life support procedures, although there is no clinical study evidence for benefit.[1] Depending on the arrhythmia that has led to cardiac arrest, treatment starts with cardiopulmonary resuscitation and defibrillation. If these measures fail to restore a conventional rhythm, the next step involves the use of adrenaline.

For **adults**, adrenaline is given in a dose of 1 mg, ideally intravenously into a central vein. If such venous access is not practicable adrenaline may be given through a peripheral vein followed by a flush of 20 mL or more of sodium chloride injection; however, the response is slower than with central venous injection. This intravenous dose of 1 mg may be given about every 3 to 5 minutes[2-5] in further cycles of cardiopulmonary resuscitation and, if necessary, shocks. A higher dose of 5 mg or 100 micrograms/kg has been given but there is insufficient evidence of benefit and this is not recommended.[2-5] In ventricular fibrillation or pulseless ventricular tachycardia, a resuscitation attempt may reasonably last for anything from 10 minutes to 1 hour with adrenaline being given every 3 to 5 minutes during this period. Where the arrest is associated with asystole it is unlikely that a response will be achieved after 15 to 20 minutes.

The initial dose of 1 mg is reported to be based on the dose that was given by intracardiac injection, so it would be expected that a higher dose would be required for intravenous use. Although myocardial and cerebral perfusion are increased more with higher doses, a meta-analysis[6] of studies in adults found no evidence that this gave any survival benefit.

The intravenous dose for **children** is 10 micrograms/kg. Higher doses of 100 or 200 micrograms/kg have been used for the second and subsequent doses; however, as with adults, the use of the higher dose is not routinely recommended and both retrospective[7] and prospective[8] studies have found no improvement in outcome.

The intraosseous route is a practicable alternative to intravenous injection for adults as well as for children; doses are identical to those given intravenously. Alternatively, adrenaline can be given through the endotracheal tube that will have been inserted, but only if the intravenous or intraosseous route is unavailable. Endotracheal doses for adults should be 2 to 3 times those used intravenously; for children doses of 100 micrograms/kg have been suggested. The adrenaline solution should be diluted and administered deeply using a catheter; several rapid ventilations or inflations should follow. It is recognised that the endotracheal route is imperfect[2-4] and some workers consider it to be ineffective.[9]

Although covering a somewhat different clinical situation some guidelines also include resuscitation of newborn infants (during the first few hours after birth).[2-5] Adrenaline may be used when the heart rate remains below 60 beats/minute despite adequate ventilation and chest compression. The dose of adrenaline is 10 to 30 micrograms/kg given intravenously (generally into the umbilical vein) or by intraosseous injection. If neither of these routes are available, it may be given via the endotracheal tube; standard doses are probably ineffective[10] and doses of up to 100 micrograms/kg may be required, although there is little evidence to support this.[2,4,5]

1. Morley P. Vasopressin or epinephrine: which initial vasopressor for cardiac arrests? *Lancet* 2001; **358:** 85–6.
2. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2005. *Resuscitation* 2005; **67** (suppl 1): S1–S190. Also available at: http://www.erc.edu/index.php/guidelines_download_2005/en/? (accessed 09/02/06)
3. Resuscitation Council (UK). Resuscitation Guidelines 2005. Available at: http://www.resus.org.uk/pages/guide.htm (accessed 09/02/06)
4. The International Liaison Committee on Resuscitation (ILCOR). 2005 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2005; **112** (suppl I): III1–III136. Also available at: http://intl-circ.ahajournals.org/content/vol112/22_suppl/ (accessed 09/02/06) Also published in *Resuscitation* 2005; **67:** 157–341.
5. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; **112** (suppl 1): IV1–IV203. Available at: http://intl-circ.ahajournals.org/content/vol112/24_suppl/ (accessed 09/02/06)
6. Vandycke C, Martens P. High dose versus standard dose epinephrine in cardiac arrest — a meta-analysis. *Resuscitation* 2000; **45:** 161–6.
7. Carpenter TC, Stenmark KR. High-dose epinephrine is not superior to standard-dose epinephrine in pediatric in-hospital cardiopulmonary arrest. *Pediatrics* 1997; **99:** 403–8.
8. Perondi MBM, *et al.* A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest. *N Engl J Med* 2004; **350:** 1722–30.
9. McCrirrick A, Monk CR. Comparison of i.v. and intra-tracheal administration of adrenaline. *Br J Anaesth* 1994; **72:** 529–32.
10. Barber CA, Wyckoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *Pediatrics* 2006; **118:** 1028–34.

Anaphylaxis and anaphylactic shock. Anaphylaxis is usually a type 1 hypersensitivity reaction (p.561) in which there is IgE-mediated activation of mast cells and basophils, usually as a result of exposure to allergens such as drugs, foods, latex, and insect venoms. A clinically identical reaction can, however, be provoked by a type II mechanism, as in blood transfusion reactions, or a type III mechanism, as in drug-induced serum sickness reactions; anaphylactoid reactions are similar, but are caused by direct histamine release rather than hypersensitivity. Symptoms of anaphylaxis and anaphylactoid reactions include erythema, pruritus, urticaria, and angioedema; respiratory obstruction may result from oedema of the larynx or epiglottis. Gastrointestinal disturbances, bronchospasm, hypotension, and coma can occur in severe reactions.

Anaphylaxis is a medical emergency and prompt treatment of laryngeal oedema, bronchospasm, and hypotension is necessary. Adrenaline causes bronchodilatation and peripheral vasoconstriction, reducing oedema and increasing blood pressure, and is the cornerstone of management.[1-11] However, it may not always be effective,[5] and its use is not without hazard.[12] Antihistamines and corticosteroids may also have a role.

In early anaphylaxis, adrenaline is given by intramuscular injection. At this stage, vasodilatation is the main pathological change and cardiac output and blood flow to skin and muscle may be increased enabling intramuscular absorption of adrenaline to be sufficiently rapid and effective. The subcutaneous route has been used, especially by patients treating themselves, but intramuscular absorption is more rapid and is generally preferred.[3,5,6] Prefilled syringes for intramuscular or subcutaneous use may be given to those known to be at high risk of developing anaphylactic shock, allowing patients to self-administer their initial emergency treatment; however, they should still seek medical assistance as additional treatment may be required. Adrenaline has been given by inhalation in milder reactions, often with an antihistamine.[13] However, this should not be a substitute for adrenaline injection in patients with severe symptoms or a history of acute attacks, and the number of inhalations required may limit the use of this route in children.[14] As anaphylaxis progresses the intravascular volume becomes depleted, leading to the development of shock. At this stage it is probably necessary to give adrenaline intravenously, since absorption from other routes will be compromised; however, this route is hazardous and should only be used in life-threatening situations,[3,5,12] and by those experienced in its use.[5] The general principles used in the management of hypovolaemia and hypotension in shock are outlined on p.1183.

The dose of adrenaline for intramuscular injection is usually 500 micrograms (0.5 mL of a 1 in 1000 solution); this may be repeated at 5-minute intervals, according to blood pressure and pulse, until improvement occurs. A lower dose of 300 micrograms may be used,[3] and may be the highest dose available as an auto-injector.[5] Similar doses have been given subcutaneously. A more dilute solution of 1 in 10 000 is used intravenously; the dose is 500 micrograms (5 mL) given slowly at a rate of 100 micrograms/minute (1 mL/minute), stopping when a response has been obtained.[3] Alternatively, the UK Resuscitation Council recommends[5] that an intravenous bolus dose of 50 micrograms should be given, titrated according to response.

Various adrenaline dosage regimens have been suggested for children,[2,5,6] although there is little evidence to guide choice.[15] Most regimens are based on a dose of 10 micrograms/kg, and the following age-specific intramuscular doses, given as a 1 in 1000 solution, have been widely used:

- under 6 months: 50 micrograms (0.05 mL)
- 6 months to 6 years: 120 micrograms (0.12 mL)
- 6 to 12 years: 250 micrograms (0.25 mL)

However, to simplify dosing, particularly where auto-injectors are used, the UK Resuscitation Council now recommends[5] an intramuscular dose of 150 micrograms (0.15 mL) for children aged 6 years and younger (including those under 6 months) and 300 micrograms (0.3 mL) for those aged over 6 years; children aged over 12 years may be given 300 or 500 micrograms depending on body size and pubertal status. This may represent a relative overdose in children aged under 6 months but this may be considered acceptable if it allows an auto-injector to be used.[15] Intravenous therapy should only be used in specialist paediatric settings.[5] The *BNFC* recommends use of the 1 in 10 000 solution in a dose of 1 microgram/kg, given by slow intravenous injection over several minutes, repeated as required; a maximum single dose of 50 micrograms should not be exceeded.

A slow intravenous injection of an antihistamine, such as chlorphenamine, may be given immediately after the adrenaline and repeated over the next 24 to 48 hours to prevent relapse. Although antihistamines are particularly effective in the management of angioedema, pruritus, and urticaria, they remain second-line treatment. Intravenous corticosteroids have little place in the immediate management of anaphylaxis, since their beneficial effects are delayed for several hours, but in severely ill patients early use of hydrocortisone may help prevent deterioration after the primary treatment has been given. Patients should also be given oxygen as required.

Continuing deterioration with circulatory collapse, bronchospasm, or laryngeal oedema requires further treatment including intravenous fluids, a nebulised $beta_2$ agonist (such as salbutamol or terbutaline), intravenous aminophylline, assisted respiration (if necessary), and possibly, emergency tracheostomy.[3,4]

Patients taking non-cardioselective beta blockers may be relatively refractory to the effects of adrenaline used for anaphylactic shock (see Interactions for Sympathomimetics, p.1407); in such cases the use of a more selective $beta_2$ agonist such as salbutamol by intravenous injection should be considered. Glucagon is another alternative to adrenaline in such patients.[3,16] Vasopressin has also been used successfully,[17] including in a patient who failed to respond to adrenaline.

Prevention of anaphylaxis is important[7,8] and primarily involves avoidance of known allergens; other measures include desensitisation, particularly in patients who have reacted to bee or wasp venom.

1. Ewan PW. Treatment of anaphylactic reactions. *Prescribers' J* 1997; **37:** 125–32.
2. Ewan PW. Anaphylaxis. *BMJ* 1998; **316:** 1442–5. Correction. *ibid.*; 1587.
3. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 10.6: anaphylaxis. *Circulation* 2005; **112:** (suppl 1): IV143–IV145. Available at: http://circ.ahajournals.org/cgi/content/full/112/24_suppl/IV-143 (accessed 01/06/06)
4. Drain KL, Volcheck GW. Preventing and managing drug-induced anaphylaxis. *Drug Safety* 2001; **24:** 843–53.
5. Working Group of the Resuscitation Council (UK). Emergency treatment of anaphylactic reactions: guidelines for healthcare providers (revised January 2008). Available at: http://www.resus.org.uk/pages/reaction.pdf (accessed 05/06/08)
6. Anonymous. Injectable adrenaline for children. *Drug Ther Bull* 2003; **41:** 21–24.
7. Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 2003; **111:** 1601–8.
8. Ellis AK, Day JH. Diagnosis and management of anaphylaxis. *Can Med Assoc J* 2003; **169:** 307–11.
9. McLean-Tooke APC, *et al.* Adrenaline in the treatment of anaphylaxis: what is the evidence? *BMJ* 2003; **327:** 1332–5.
10. Brown SGA, *et al.* Anaphylaxis: diagnosis and management. *Med J Aust* 2006; **185:** 283–9. Correction. *ibid.*; 400. [dose]
11. Kemp SF. Office approach to anaphylaxis: sooner better than later. *Am J Med* 2007; **120:** 664–8.
12. Johnston SL, *et al.* Adrenaline given outside the context of life threatening allergic reactions. *BMJ* 2003; **326:** 589–90.
13. Hourihane JO'B, Warner JO. Management of anaphylactic reactions to food. *Arch Dis Child* 1995; **72:** 274.
14. Simons FER, *et al.* Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis? *Pediatrics* 2000; **106:** 1040–4.
15. Sicherer SH, Simons FER. Section on Allergy and Immunology, American Academy of Pediatrics. Self-injectable epinephrine for first-aid management of anaphylaxis. *Pediatrics* 2007; **119:** 638–46. Correction. *ibid.*; 1271. [dose] Also available at: http://pediatrics.aappublications.org/cgi/reprint/119/3/638 (accessed 19/08/08)
16. Lang DM. Anaphylactoid and anaphylactic reactions: hazards of β-blockers. *Drug Safety* 1995; **12:** 299–304.
17. Kill C, *et al.* Successful treatment of severe anaphylactic shock with vasopressin: two case reports. *Int Arch Allergy Immunol* 2004; **134:** 260–1.

Haemorrhage. Adrenaline has a long history of topical use to check minor bleeding. It constricts arterioles and capillaries and causes blanching. Local injection of adrenaline under endoscopic control is highly effective in controlling bleeding peptic ulcers (p.1702), and has also been combined with other therapies such as a contact thermal probe.[1] Nebulised adrenaline has been reported[2] to successfully control oropharyngeal haemorrhage.

1. Chung SSC, *et al.* Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for actively bleeding ulcers. *BMJ* 1997; **314:** 1307–11.
2. Rowlands RG, *et al.* Novel use of nebulised adrenaline in the treatment of secondary oropharyngeal haemorrhage. *J Laryngol Otol* 2002; **116:** 123–4.

Priapism. Alpha agonists such as adrenaline may be effective in the treatment of priapism (see under Metaraminol, p.1333). Low doses of dilute adrenaline solution have been given by intracavernosal injection in priapism caused by alprostadil (see p.2184). Aspiration of blood followed by intracavernosal irrigation with a dilute adrenaline solution was also reported to be effective treatment for priapism in a group of young patients (age range, 3.9 to 18.3 years) with sickle-cell disease.[1]

1. Mantadakis E, *et al.* Outpatient penile aspiration and epinephrine irrigation for young patients with sickle cell anemia and prolonged priapism. *Blood* 2000; **95:** 78–82.

Respiratory-tract disorders. Nebulised adrenaline may be used to reverse airway obstruction in inflammatory disorders such as croup since it relieves inflammation and also causes bronchodilatation. Although some studies in acute viral bronchiolitis (see Respiratory Syncytial Virus Infection, p.860) have shown improvement in clinical scores,[1,2] randomised studies have failed to find any difference in outcome between infants treated with adrenaline and either salbutamol[3] or placebo.[4] A systematic review[5] found insufficient evidence to support the use of adrenaline in inpatients, although there was a suggestion that it might be of short-term benefit in outpatients.

However, the *BNF* states that for severe croup not effectively controlled with corticosteroids, nebulised adrenaline solution 1 in 1000 may be given with close clinical monitoring in a dose of 400 micrograms/kg (up to a maximum of 5 mg) repeated after 30 minutes if necessary. The effects of nebulised adrenaline are expected to last 2 to 3 hours.

There has also been a report[6] of the successful use of nebulised adrenaline in a 15-month-old child with airway inflammation secondary to the ingestion of sodium hypochlorite.

1. Reijonen T, *et al.* The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; **149:** 686–92.
2. Menon K, *et al.* A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126:** 1004–7.
3. Patel H, *et al.* A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002; **141:** 818–24.
4. Wainwright C, *et al.* A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med* 2003; **349:** 27–35.
5. Hartling L, *et al.* Epinephrine for bronchiolitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 07/10/05).
6. Ziegler D, Bent G. Caustic-induced upper airway obstruction responsiveness to nebulized adrenaline. *Pediatrics* 2001; **107:** 807–8.

Preparations

BP 2008: Adrenaline Eye Drops; Adrenaline Injection; Adrenaline Solution; Bupivacaine and Adrenaline Injection; Dilute Adrenaline Injection I in 10,000; Lidocaine and Adrenaline Injection;
USP 31: Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Epinephrine Bitartrate for Ophthalmic Solution; Epinephrine Bitartrate Inhalation Aerosol; Epinephrine Bitartrate Ophthalmic Solution; Epinephrine Inhalation Aerosol; Epinephrine Inhalation Solution; Epinephrine Injection; Epinephrine Nasal Solution; Epinephrine Ophthalmic Solution; Epinephryl Borate Ophthalmic Solution; Lidocaine Hydrochloride and Epinephrine Injection; Prilocaine and Epinephrine Injection; Procaine Hydrochloride and Epinephrine Injection; Racepinephrine Inhalation Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: EpiPen; ***Austral.:*** EpiPen; ***Austria:*** EpiPen; Suprarenin; ***Belg.:*** EpiPen; ***Braz.:*** Drenalin; Nefrin†; ***Canad.:*** EpiPen; Twinject; Vaponefrin; ***Cz.:*** Anapen; EpiPen; Glaucon†; ***Denm.:*** EpiPen; ***Fin.:*** EpiPen; ***Fr.:*** Anahelp; Anapen; ***Ger.:*** Anapen; Fastjekt; InfectoKrupp; Suprarenin; ***Gr.:*** Anapen; EpiPen; ***Hung.:*** Anapen; EpiPen; Tonogen; ***Irl.:*** Anapen; Eppy†; ***Israel:*** EpiPen; ***Ital.:*** Fastjekt; ***Malaysia:*** EpiPen; ***Mex.:*** Pinadrina; ***Neth.:*** EpiPen; ***Norw.:*** EpiPen; ***NZ:*** EpiPen; ***Philipp.:*** Adrenin; ***Pol.:*** Anapen; EpiPen; Fastjekt; ***Port.:*** Anapen; EpiPen; ***S.Afr.:*** Adrenotone; Ana-Guard; EpiPen; Eppy; Simplene; ***Spain:*** Adreject; ***Swed.:*** Anapen; EpiPen; Eppy†; ***Switz.:*** EpiPen; ***UK:*** Anapen; EpiPen; ***USA:*** AsthmaHaler Mist; AsthmaNefrin; Epifrin†; Epinal; EpiPen; Glaucon†; microNefrin; Nephron; Primatene Mist; Primatene Mist Suspension; S-2.

Multi-ingredient: ***Arg.:*** Asmopul†; Yanal; ***Austral.:*** Rectinol; ***Ger.:*** Links-Glaukosan†; Mydrial-Atropin†; ***Hung.:*** Hemorid; Noditran†; ***India:*** Brovon; ***Irl.:*** Ganda; ***Ital.:*** Pilodren†; Rinantipiol†; ***Port.:*** Adrinex†; ***Spain:*** Coliniocilina Adren Astr; Epistaxol; ***Switz.:*** Haemocortin; ***UK:*** Brovon; ***USA:*** Ana-Kit; E-Pilo†; Emergent-Ez; PE†.

Used as an adjunct in: ***Arg.:*** Caina G; Duracaine; Gobbicaina; Larjancaina; Xylocaina; ***Austral.:*** Citanest Dental; Lignospan†; Marcain; Nurocain; Scandonest†; Xylocaine; ***Austria:*** Neo-Xylestesin; Neo-Xylestesin forte; Scandonest; Septanest; Ubistesin; Ultracain Dental; Xylanaest; Xylocain; ***Belg.:*** Citanest; Marcaine; Ubistesin†; Xylocaine; ***Braz.:*** Bupiabbott Plus; Lidocabbott; Lidogeyer†; Marcaina; Neocaina; Novabupi; Xylestesin; Xylocaina; ***Canad.:*** Astracaine†; Citanest†; Marcaine; Sensorcaine; Xylocaine; ***Cz.:*** Marcaine; Scandonest; Septanest S; Supracain; Ubistesin; Ultracain D-S†; Xylestesin-A†; ***Denm.:*** Carbocain; Marcain; Scandonest; Septanest; Septocaine; Ubistesin; Xylocain; Xyloplyin; ***Fin.:*** Marcain; Septocaine; Ubistesin; Ultracain D-Suprarenin; Xylocain; ***Fr.:*** Alphacaine; Marcaine†; Predesic†; Ubistesin Adrenalinee; Xylocaine; ***Ger.:*** Ubistesin; Ultracain D-S; Ultracain Suprarenin; Xylestesin-A, Xylestesin centro†; Xylestesin-S†; Xylocain; Xylocitin; Xylonest; ***Gr.:*** Marcaine; Xylocaine; ***Hong Kong:*** Marcain; Ubistesin; Xylestesin-A; Xylocaine; ***Hung.:*** Ubistesin; Ultracain D-S; ***India:*** Gesicain; Xylocaine; ***Indon.:*** Extracaine; Pehacain; ***Irl.:*** Marcain; Xylocaine; ***Israel:*** Kamacaine; Lidocadren†; Marcaine; ***Ital.:*** Alfacaina; Bupicain; Bupiforan; Bupisen; Bupisolver; Bupixamol; Carbocaina; Carbosen; Cartidont; Citocartin; Ecocain; Lident Adrenalina†; Lident Andrenor†; Marcaina; Mepi-Mynol; Mepicain; Mepident; Mepiforan; Mepisolver; Mepivamol; Molcain†; Optocain; Primacaine†; Sarticain; Scandonest; Septanest; Ubistesin; Xilo-Mynol; Xylonor; Xyloplyina; ***Malaysia:*** Denkan; Marcain; ***Mex.:*** Buvacaina; Pisacaina; Unicaine; Xylocaina; ***Neth.:*** Bupiforan; Citanest; Lignospan; Marcaine; Scandicaine; Septanest; Ubistesin; Ultracain D-S; Xylocaine; ***Norw.:*** Marcain; Septocaine; Xylocain; ***NZ:*** Marcain; Septanest; Topicaine; Xylestesin-A; Xylocaine; ***Philipp.:*** Dentocaine; ***Pol.:*** Marcaine; ***Port.:*** Alphacaine; Artinibsa; Artinostrum; Bupinostrum; Lidonostrum; Lincaina; Meganest; Octocaine; Scandinibsa; Septanest; Ubistesin; Xilonibsa; ***Rus.:*** Ultracain (Ультракаин); ***S.Afr.:*** Lignospan Special†; Macaine; Scandonest†; Xylotox; ***Singapore:*** Xylocaine; ***Spain:*** Anestesia Topi Braun C/A; Articaina C/E; Meganest; Octocaine; Scandinibsa; Ultracain; Xilonibsa; Xylonor Especial; ***Swed.:*** Carbocain; Marcain; Xylocain; ***Switz.:*** Alphacaine; Carbostesin; Lignospan†; Rapidocaine; Rudocaine; Scandonest; Septanest; Ubistesin; Ultracaine D-S; Xylestesin-S "special"†; Xylocain; Xylonest; Xyloplyin†; ***Thai.:*** Lidocation; Lidocaton†; Xylocaine; ***Turk.:*** Jetokain; Jetosel; Ultracain; ***UAE:*** Ecocain; ***UK:*** Lignostab-A†; Septanest; Xylocaine; Xylotox†; ***USA:*** Citanest; Duranest†; Marcaine; Octocaine; Sensorcaine; Septocaine; Xylocaine.

Ajmaline

Aimaliini; Ajmalin; Ajmalina; Ajmalinum; Rauwolfine. (17*R*,21*R*)-Ajmalan-17,21-diol.

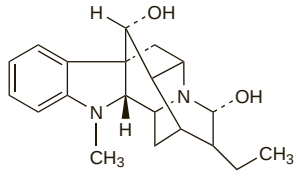
Аймалин

$C_{20}H_{26}N_2O_2$ = 326.4.

CAS — 4360-12-7.

ATC — C01BA05.

ATC Vet — QC01BA05.



Pharmacopoeias. In *Jpn.*

Adverse Effects

Ajmaline depresses the conductivity of the heart, and at high doses can cause heart block. At very high doses it may produce a negative inotropic effect. High doses may cause cardiac arrhythmias, coma, and death. Arrhythmias have also been reported after usual intravenous doses (see below). Adverse neurological effects have been reported including eye twitching, convulsions, and respiratory depression. Hepatotoxicity and agranulocytosis may occasionally occur.

Effects on the heart. Electrophysiologic study[1] in 1955 patients revealed that ajmaline 1 mg/kg given intravenously could induce arrhythmias; 63 developed a supraventricular arrhythmia and 7 an atrioventricular re-entrant tachycardia. Ventricular tachycardia[2,3] and torsade de pointes[4] have been reported during diagnostic use.

1. Brembilla-Perrot B, Terrier de la Chaise A. Provocation of supraventricular tachycardias by an intravenous class I antiarrhythmic drug. *Int J Cardiol* 1992; **34:** 189–98.
2. Rolf S, *et al.* The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003; **24:** 1104–12.
3. Pinar Bermúdez E, *et al.* Spontaneous sustained monomorphic ventricular tachycardia after administration of ajmaline in a patient with Brugada syndrome. *Pacing Clin Electrophysiol* 2000; **23:** 407–9.
4. Haverkamp W, *et al.* Torsade de pointes induced by ajmaline. *Z Kardiol* 2001; **90:** 586–90.

Precautions

As for Quinidine, p.1384.

Interactions

Antiarrhythmics. Oral use of *quinidine* with ajmaline increased plasma concentrations of ajmaline considerably in 4 healthy subjects; the elimination half-life of ajmaline was increased about twofold.[1] The pharmacokinetics of quinidine did not seem to be affected by ajmaline.

1. Hori R, *et al.* Quinidine-induced rise in ajmaline plasma concentration. *J Pharm Pharmacol* 1984; **36:** 202–4.

Uses and Administration

Ajmaline is an alkaloid obtained from the root of *Rauwolfia serpentina* (Apocynaceae). It is a class Ia antiarrhythmic (p.1153) used in the treatment of supraventricular and ventricular arrhythmias (p.1160) and for differential diagnosis of Wolff-Parkinson-White syndrome. Ajmaline is given by intravenous injection in a usual dose of 50 mg over at least 5 minutes. It may also be given by intravenous infusion, and has been given orally and by intramuscular injection.

Ajmaline has also been used as the hydrochloride, monoethanolate, and phenobarbital salts.

Brugada syndrome. Brugada syndrome is a congenital disorder affecting myocardial sodium channels and may be associated with sudden cardiac death. Class 1a antiarrhythmics such as ajmaline block the sodium channel and may have a role in the diagnosis of Brugada syndrome, although they are not suitable for treatment.

References.

1. Rolf S, *et al.*The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003; **24:** 1104–12.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Gilurytmal; ***Cz.:*** Gilurytmal†; ***Ger.:*** Gilurytmal.

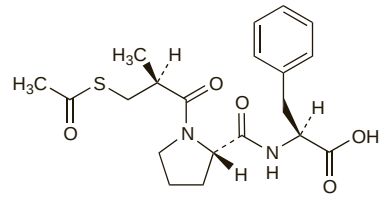
Alacepril *(rINN)*

Alacépril; Alaceprilum; DU-1219. *N*-{1-[(*S*)-3-Mercapto-2-methylpropionyl]-L-prolyl}-3-phenyl-L-alanine acetate.

Алацеприл

$C_{20}H_{26}N_2O_5S$ = 406.5.

CAS — 74258-86-9.



Pharmacopoeias. In *Jpn.*

Profile

Alacepril is an ACE inhibitor (p.1193) used in the treatment of hypertension (p.1171). It is converted to captopril and desacetylalacepril (DU-1227) in the body after oral doses. It is given orally in a usual dose of 25 to 75 mg daily, as a single dose or in two divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Cetapril.

Aliskiren Fumarate *(USAN, rINNM)*

Aliskiren Hemifumarate; Aliskirène, Fumarate de; Aliskireni Fumaras; CGP-60536B; Fumarato de aliskireno; SPP-100 (aliskiren or aliskiren fumarate). Bis(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide fumarate (2:1).

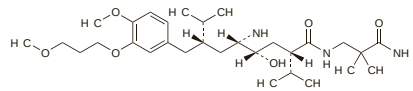
Алискирена Фумарат

$(C_{30}H_{53}N_3O_6)_2,C_4H_4O_4$ = 1219.6.

CAS — 173334-57-1 (aliskiren); 173334-58-2 (aliskiren fumarate).

ATC — C09XA02.

ATC Vet — QC09XA02.



(aliskiren)

Adverse Effects and Precautions

Aliskiren is generally well-tolerated but may produce dose-related gastrointestinal adverse effects including diarrhoea, abdominal pain, dyspepsia, and gastro-oesophageal reflux. Other adverse effects include hypotension, headache, dizziness, fatigue, back pain, and cough; rashes, hyperuricaemia, gout, and renal calculi may also occur. Angioedema has been reported rarely, and there have also been reports of seizures. As with other inhibitors of the renin-angiotensin system, dose-related decreases in haemoglobin have been reported.

Aliskiren should be avoided in pregnancy since drugs acting on the renin-angiotensin system have been associated with fetal and neonatal morbidity and mortality. It should be used with caution in patients with renal impairment or renovascular hypertension. Patients with sodium or volume depletion (for example those receiving high-dose diuretics) may experience symptomatic hypotension on starting aliskiren and treatment should begin under close medical supervision.

Interactions

Use of aliskiren with other antihypertensives or drugs that cause hypotension may have an additive effect. Renal function and electrolytes should be monitored in diabetic patients taking aliskiren and ACE inhibitors since there is an increased risk of hyperkalaemia and renal impairment.