2 micrograms/mL 10 hours after injection. A plasma concentration of 38 micrograms/mL has been reported after the intravenous infusion of 500 mg over 30 minutes, reducing to 18 micrograms/mL 1 hour later. Amikacin has been detected in body tissues and fluids after injection; it crosses the placenta but does not readily penetrate into the CSF, although substantial penetration of the blood-brain barrier has been reported in children with meningitis.

A plasma half-life of about 2 to 3 hours has been reported in patients with normal renal function. Most of a dose is excreted by glomerular filtration in the urine within 24 hours.

◊ References.

1. Vanhaeverbeek M, *et al*. Pharmacokinetics of once-daily amikacin in elderly patients. *J Antimicrob Chemother* 1993; **31:** 185–7.
2. Gaillard J-L, *et al*. Cerebrospinal fluid penetration of amikacin in children with community-acquired bacterial meningitis. *Antimicrob Agents Chemother* 1995; **39:** 253–5.
3. Bressolle F, *et al*. Population pharmacokinetics of amikacin in critically ill patients. *Antimicrob Agents Chemother* 1996; **40:** 1682–9.
4. Canis F, *et al*. Pharmacokinetics and bronchial diffusion of single daily dose amikacin in cystic fibrosis patients. *J Antimicrob Chemother* 1997; **39:** 431–3.
5. Tod M, *et al*. Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. *Antimicrob Agents Chemother* 1998; **42:** 849–56.
6. Tréluyer JM, *et al*. Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants, and children. *Antimicrob Agents Chemother* 2002; **46:** 1381–7.

Uses and Administration

Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin and is used similarly to gentamicin (p.284) in the treatment of severe Gram-negative and other infections. It is given as the sulfate, and is generally reserved for the treatment of severe infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. Amikacin has also been given with antimycobacterials in the treatment of nontuberculous mycobacterial infections (p.181). As with gentamicin, amikacin may be used with penicillins and with cephalosporins; the injections should be given at separate sites.

Doses of amikacin sulfate are expressed in terms of amikacin base; 1.3 g of amikacin sulfate is equivalent to about 1 g of amikacin. Adults and children may be given 15 mg/kg daily in equally divided doses every 8 or 12 hours by intramuscular injection. In life-threatening infections, the dose may be increased in adults up to a maximum of 500 mg every 8 hours. A dose of 7.5 mg/kg daily in two divided doses (equivalent to 250 mg twice daily in adults) may be given for the treatment of uncomplicated urinary-tract infections. The same doses may be given by slow intravenous injection over 2 to 3 minutes, or by intravenous infusion. In adults, 500 mg in 100 to 200 mL of diluent has been infused over 30 to 60 minutes; proportionately less fluid should be given to children.

Neonates may be given 10 mg/kg as a loading dose, followed by 15 mg/kg daily in two divided doses. If given by intravenous infusion, an infusion period of 1 to 2 hours is recommended. It has been suggested that doses may need to be adjusted in preterm neonates.

Treatment should preferably not continue for longer than 7 to 10 days, and the total dose given to adults should not exceed 15 g. Peak plasma concentrations greater than 30 to 35 micrograms/mL or trough plasma concentrations greater than 5 to 10 micrograms/mL should be avoided. Dosage should be adjusted in all patients according to plasma-amikacin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p.284. As with some other aminoglycosides, once-daily dosage has been used successfully with amikacin without increasing toxicity, but local guidelines should be consulted (see also Once-daily Dosage, p.285).

A 0.25% solution has been instilled into body cavities in adults.

A liposomal formulation of amikacin is under investigation.

Preparations

BP 2008: Amikacin Injection;
USP 31: Amikacin Sulfate Injection.

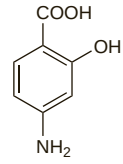
Proprietary Preparations (details are given in Part 3)
Arg.: Biklin; Greini; Riklinak; ***Austral.:*** Amikin; ***Austria:*** Biklin; ***Belg.:*** Amukin; ***Braz.:*** Amicacil†; Amicalin†; Amicilon; Aminocina†; Bactomicin†; Klebicil; Novamin; ***Canad.:*** Amikin†; ***Cz.:*** Amikin; Amikozit†; Miacin†; ***Fin.:*** Biklin; ***Fr.:*** Amiklin†; ***Ger.:*** Biklin; ***Gr.:*** Amicagel†; Amicasil; Amikan; Biorisan; Briklin; Cinegel; Durocin; Farcyclin; Flexelite; Fromentyl; Kancin-Gap; Lanomycin; Lifermycin; Likacin; Micalpha; Orlobin; Remikin; Roveniclin; Selaxa; Uzix; ***Hong Kong:*** Amikin; Apalin; Selemycin†; ***Hung.:*** Amikin; Likacin; ***India:*** Amcin; Amicin; Amicip; Mikacin; ***Indon.:*** Alostil; Amikin; Mikasin; ***Irl.:*** Amikin; ***Israel:*** Amikin†; ***Ital.:*** Amicasil; Amik; Amikan; BB-K8; Chemacin; Dramigel; Likacin; Lukadin; Mediamik; Migracin; Mikan; Mikavir; Nekacin; Pierami; ***Malaysia:*** Amikin†; Selemycin†; ***Mex.:*** Agnicin; Akacin; Amicina; Amikafur; Amikalem; Amikasons; Amikavi; Amikayect; Amikin; Amiyec; AMK; Baxi-K†; Beramikin; Biclin; Biokacin; Gamikal; Kafran; Kana; Karmikin; Libamic; Lisobac; Mikazul; Oprad; Plokim; Sermicina; Yectamid; ***Neth.:*** Amukin; ***NZ:*** Amikin; ***Philipp.:*** Amikacide; Amikin; Cidacid; Cinmik; Kamin; Kormakin; Nica; ***Pol.:*** Amikin; Biodacyna; ***Port.:*** Amic; Biclin; Kamina; ***Rus.:*** Amikozit (Амикозит); Selemycin (Селемицин); ***S.Afr.:*** Amikin; Kacinth-A; ***Singapore:*** Amikin; ***Spain:*** Biclin; Kanbine; ***Swed.:*** Biklin; ***Switz.:*** Amikin; ***Thai.:*** Akacin; Akicin; Amikasol†; Amikin; Anbikin; Siamik; Tipkin; Tybikin; ***Turk.:*** Amiketem; Amiklin; Amikozit; Mikasin; ***UAE:*** Mikacin; ***UK:*** Amikin; ***USA:*** Amikin; ***Venez.:*** Amikavax; Amikayect†; Behkacin; Biklin; Likacin.

Aminosalicylic Acid

Acidum Aminosalicylicum; Aminosalicílico, ácido; 4-Aminosalicylic Acid; Aminosalicylsyra; Aminosalisyylihappo; Aminosalylum; Para-aminosalicylic Acid; PAS; Pasalicylum. 4-Amino-2-hydroxybenzoic acid.

Аминосалициловая Кислота

$C_7H_7NO_3$ = 153.1.
CAS — 65-49-6.
ATC — J04AA01.
ATC Vet — QJ04AA01.



NOTE. Distinguish from 5-aminosalicylic acid (Mesalazine, p.1745).

Pharmacopoeias. In *US*.
USP 31 (Aminosalicylic Acid). A white or practically white, bulky powder that darkens on exposure to light and air; it is odourless or has a slight acetous odour. Slightly soluble in water and in ether; soluble in alcohol; practically insoluble in benzene. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a saturated solution in water is between 3.0 to 3.7. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Calcium Aminosalicylate

Aminosalicilato cálcico; Aminosalicylate calcium; Aminosalylcalcium; Aminosalylkalcium; Aminosalyylikalsium; Calcii Aminosalicylas; Calcii Para-aminosalicylas; Calcium PAS; Kalciumaminosalicylat; Kalsiumaminosalisylaatti. Calcium 4-amino-2-hydroxybenzoate trihydrate.

Аминосалицилат Кальция

$(C_7H_6NO_3)_2Ca,3H_2O$ = 398.4.
CAS — 133-15-3 (anhydrous calcium aminosalicylate).
ATC — J04AA03.
ATC Vet — QJ04AA03.

Pharmacopoeias. *Jpn* includes the heptahydrate.

Sodium Aminosalicylate

Aminosalicilato sódico; Aminosalicylan sodný dihydrát; Aminosalicylate Sodium; Aminosalylnatrium; Monosodium 4-Aminosalicylate Dihydrate; Natrii Aminosalicylas; Natrii aminosalicylas dihydricus; Natrii Paraaminosalicylas; Natrii Para-aminosalicylas; Natrio aminosalicilatas dihidratas; Natriumaminosalicylat; Natriumaminosalicylatdihydrat; Natriumaminosalisylaatti; Natriumaminosalisylaattidihydraatti; Pasalicylum Solubile; Sodium (aminosalicylate de) dihydraté; Sodium Para-aminosalicylate; Sodium PAS; Sodu aminosalicylan. Sodium 4-amino-2-hydroxybenzoate dihydrate.

Аминосалицилат Натрия

$C_7H_6NNaO_3,2H_2O$ = 211.1.
CAS — 133-10-8 (anhydrous sodium aminosalicylate); 6018-19-5 (sodium aminosalicylate dihydrate).
ATC — J04AA02.
ATC Vet — QJ04AA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US*.
Ph. Eur. 6.2 (Sodium Aminosalicylate Dihydrate). A slightly hygroscopic, white or almost white, crystalline powder, or white or almost white crystals. Freely soluble in water; sparingly soluble in alcohol, practically insoluble in dichloromethane. A 2% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.
USP 31 (Aminosalicylate Sodium). A white to cream-coloured, practically odourless crystalline powder. Soluble 1 in 2 of water; sparingly soluble in alcohol; very slightly soluble in chloroform and in ether. Its solutions decompose slowly and darken in colour. Prepare solutions within 24 hours of use. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a 2% solution in water is between 6.5 and 8.5. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Stability. Aqueous solutions of aminosalicylates are unstable and should be freshly prepared.

Solutions of sodium aminosalicylate in sorbitol or syrup degraded more quickly to *m*-aminophenol than those in glycerol or propylene glycol.[1] Colour developed in all solutions but was not found to be an accurate indicator of decomposition of sodium aminosalicylate as it reflected only oxidation of *m*-aminophenol.

1. Blake MI, *et al*. Effect of vehicle on the stability of sodium aminosalicylate in liquid dosage forms. *Am J Hosp Pharm* 1973; **30:** 441–3.

Adverse Effects and Treatment

Aminosalicylic acid and its salts may cause the adverse effects of salicylates (see Aspirin, p.20).

Gastrointestinal effects are common and include nausea, vomiting, and diarrhoea; they may be reduced by giving doses with food or with an antacid but occasionally may be severe enough that therapy has to be withdrawn. Alteration of gastrointestinal function may lead to malabsorption of vitamin B_{12}, folate, and lipids.

Hypersensitivity reactions have been reported in 5 to 10% of adults, usually during the first few weeks of treatment, and include fever, skin rashes; less commonly, arthralgia, lymphadenopathy, and hepatosplenomegaly may occur and, rarely, a syndrome resembling infectious mononucleosis. Other adverse effects which have been attributed to a hypersensitivity reaction to aminosalicylate include jaundice and encephalitis. Blood disorders reported include haemolytic anaemia in patients with G6PD deficiency, agranulocytosis, eosinophilia, leucopenia, and thrombocytopenia. Psychosis may occasionally occur. Prolonged treatment may induce goitre and hypothyroidism. Crystalluria may occur.

Effects on the liver. Drug-induced hepatitis occurred in 0.32% of 7492 patients receiving antituberculous drugs; aminosalicylic acid was the most common cause.[1]

1. Rossouw JE, Saunders SJ. Hepatic complications of antituberculous therapy. *Q J Med* 1975; **44:** 1–16.

Precautions

Aminosalicylic acid and its salts should be used with great care in patients with hepatic or renal impairment and in patients with gastric ulcer. They should be given with caution to patients with G6PD deficiency. The sodium salt should be used with caution in patients with heart failure.

Aminosalicylates interfere with tests for glycosuria using copper reagents and for urobilinogen using Ehrlich's reagent.

Breast feeding. Small amounts of aminosalicylic acid are present in breast milk. A maximum concentration of 1.1 microgram/mL has been reported in the breast milk of a lactating woman 3 hours after a 4-g dose of aminosalicylic acid.[1]

1. Holdiness MR. Antituberculosis drugs and breast feeding. *Arch Intern Med* 1984; **144:** 1888.

Pregnancy. The use of aminosalicylic acid or its salts is not recommended in pregnant patients due to gastrointestinal intolerance.[1] In addition it has been noted that, a study published in 1964 suggested that first-trimester exposure may be associated with congenital defects although other studies had not found similar effects.[2]

1. Snider D. Pregnancy and tuberculosis. *Chest* 1984; **86:** 10S–13S.
2. Briggs GG, *et al*. *Drugs in pregnancy and lactation.* 7th ed. Philadelphia: Lippincott Williams and Wilkins, 2005: 59.

Interactions

The adverse effects of aminosalicylates and salicylates may be additive. Probenecid may also increase toxicity by delaying renal excretion and enhancing plasma concentrations of aminosalicylate. The activity of aminosalicylic acid may be antagonised by ester-type local anaesthetics such as procaine.

Antimicrobial Action

Aminosalicylic acid is bacteriostatic and is active against *M. tuberculosis*. Other mycobacteria are usually resistant. It has a relatively weak action compared with other antituberculous drugs. Resistance develops quickly if aminosalicylic acid is used alone.

◊ References.

1. Rengarajan J, *et al*. The folate pathway is a target for resistance to the drug para-aminosalicylic acid (PAS) in mycobacteria. *Mol Microbiol* 2004; **53:** 275–82.