Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Amantadine Hydrochloride). A white or almost white crystalline powder. It sublimes on heating. Freely soluble in water and in alcohol.
USP 31 (Amantadine Hydrochloride). A white or practically white crystalline powder. Soluble 1 in 2.5 of water, 1 in 5.1 of alcohol, 1 in 18 of chloroform, and 1 in 70 of macrogol 400. pH of a 20% solution in water is between 3.0 and 5.5.

Amantadine Sulfate *(pINNM)*

Amantadine, Sulfate d'; Amantadine Sulphate; Amantadini Sulfas; Sulfato de amantadina.

Амантадина Сульфат

$(C_{10}H_{17}N)_2.SO_4$ = 398.6.
CAS — 31377-23-8.
ATC — N04BB01.
ATC Vet — QN04BB01.

Adverse Effects

Most adverse effects associated with amantadine therapy appear to be dose-related and relatively mild; some resemble those of antimuscarinic drugs. They may be reversed by withdrawing therapy but many resolve despite continuation.

Livedo reticularis, sometimes associated with ankle oedema, is quite common in patients given very high doses of amantadine or with long-term therapy. CNS effects such as anxiety, inability to concentrate, dizziness, insomnia, nightmares, headache, and changes in mood may occur. Psychotic reactions, hallucinations, and confusion have been reported, especially in the elderly, patients with renal impairment or psychiatric disorders, and those also receiving antimuscarinics.

Other adverse effects reported have included orthostatic hypotension, palpitations, urinary retention, slurred speech, ataxia, lethargy, anorexia, nausea, vomiting, dry mouth, constipation, skin rash, diaphoresis, photosensitisation, and blurred vision. There have been isolated reports of congestive heart failure, leucopenia, neutropenia, dyskinesias, oculogyric episodes, and convulsions.

Effects on the cardiovascular system. Congestive heart failure has been reported with amantadine;[1] the patient had been receiving combined treatment with amantadine, levodopa, and orphenadrine for 4 years. Others have considered that while amantadine sometimes causes ankle oedema, an association between amantadine and heart failure is not proven.[2] Livedo reticularis, a mottled blue discoloration of the skin due to prominence of the normal pattern of venous drainage, has been reported[2] to occur in about 50% of all elderly patients given amantadine 100 to 300 mg daily for 2 to 6 weeks and was associated with oedema in 5 to 10%. Both livedo and oedema have usually been confined to the legs and may result from the catecholamine-releasing action of amantadine in certain vascular beds; the oedema was unlikely to be due to heart failure. Angina, dyspnoea, pulmonary congestion, or distension of neck veins has also been reported[2] in 4 of 89 parkinsonian patients treated with amantadine; only 2 of these 4 had had ankle oedema before heart failure developed. No patient had been seen in whom heart failure seemed due directly to amantadine.

See also Overdosage, below.

1. Vale JA, Maclean KS. Amantadine-induced heart-failure. *Lancet* 1977; **i:** 548.
2. Parkes JD, *et al.* Amantadine-induced heart-failure. *Lancet* 1977; **i:** 904.

Effects on electrolytes. For a report of a patient who developed hyponatraemia when given amantadine or levodopa, see Effects on Kidney Function under Levodopa, p.805.

Effects on the eyes. Superficial punctate keratitis and corneal abrasion with loss of visual acuity was seen in both eyes of a 64-year-old man about 3 weeks after starting treatment with amantadine 100 mg daily.[1] Symptoms resolved on stopping amantadine but recurred when re-treatment with amantadine was attempted. In another report,[2] a 14-year-old boy developed bilateral corneal oedema with visual loss associated with amantadine treatment. He had been taking amantadine 300 mg daily for several months with numerous other drugs; symptoms resolved when amantadine was stopped.

1. Nogaki H, Morimatsu M. Superficial punctate keratitis and corneal abrasion due to amantadine hydrochloride. *J Neurol* 1993; **240:** 388–9.
2. Hughes B, *et al.* Reversible amantadine-induced corneal edema in an adolescent. *Cornea* 2004; **23:** 823–4.

Effects on mental function. It has been suggested[1] that the ability of amantadine and memantine to cause psychotic disturbances in patients with Parkinson's disease might be related to their action as *N*-methyl-D-aspartate antagonists.

1. Riederer P, *et al.* Pharmacotoxic psychosis after memantine in Parkinson's disease. *Lancet* 1991; **338:** 1022–3.

Effects on the nervous system. Peripheral sensory motor neuropathy secondary to long-term (8 years) use of amantadine has been reported[1] in a 48-year-old woman with parkinsonism. Trophic skin ulcers, paraesthesias, and distal weakness resolved on stopping amantadine.

1. Shulman LM, *et al.* Amantadine-induced peripheral neuropathy. *Neurology* 1999; **53:** 1862–5.

Overdosage. A patient with postencephalitic parkinsonism who had taken an estimated 2.8 g of amantadine hydrochloride in a suicide attempt developed acute toxic psychosis with disorientation, visual hallucinations, and aggressive behaviour.[1] Convulsions did not occur, possibly because he had been receiving phenytoin, which was continued. The patient was treated with hydration and chlorpromazine and recovered in 4 days.

A 2-year-old child who had ingested 600 mg of amantadine hydrochloride developed symptoms of acute toxicity, including agitation and dystonic posturing, despite emesis with 'syrup of ipecac'.[2] She responded immediately to a trial of physostigmine 500 micrograms intravenously, repeated after 10 minutes. Her pupils remained moderately dilated until about 20 hours after the ingestion; thereafter she made a full recovery.

Cardiac arrest developed 4 hours after a 37-year-old woman ingested 2.5 g of amantadine hydrochloride and was treated successfully.[3] However, ventricular arrhythmias, including torsade de pointes, continued over the ensuing 48 hours and may have been exacerbated by use of isoprenaline and dopamine. The patient was subsequently stabilised with lidocaine by intravenous infusion, but died of respiratory failure 10 days after admission.

1. Fahn S, *et al*. Acute toxic psychosis from suicidal overdosage of amantadine. *Arch Neurol*, 1971; **25:** 45–8.
2. Berkowitz CD. Treatment of acute amantadine toxicity with physostigmine. *J Pediatr* 1979; **95:** 144–5.
3. Sartori M, *et al*. Torsade de pointe: malignant cardiac arrhythmia induced by amantadine poisoning. *Am J Med* 1984; **77:** 388–91.

Precautions

Amantadine is usually contra-indicated in severe renal disease and in patients with a history of epilepsy or other seizure disorders, or gastric ulceration. It should also not be given to patients with untreated angle-closure glaucoma. Amantadine should be used with caution in patients with cardiovascular or liver disease, renal impairment, recurrent eczema, or psychiatric disorders. Suicide attempts, in some cases fatal, and suicidal ideation have been reported in patients taking amantadine. Care should be taken in all elderly patients, who may be more sensitive to antimuscarinic effects, and in whom renal clearance is likely to be reduced.

In common with other drugs having antimuscarinic properties amantadine may cause blurred vision or impair alertness; patients so affected should not drive or operate machinery.

Treatment with amantadine should not be stopped abruptly in parkinsonian patients since they may experience a sudden marked clinical deterioration. There have been isolated reports of a neuroleptic malignant-like syndrome associated with abrupt withdrawal of amantadine, especially in patients also receiving antipsychotics.

Antiviral resistance. See Influenza under Uses and Administration, below.

Breast feeding. Amantadine is distributed into breast milk and licensed product information states that adverse effects have occurred in infants being breast fed by mothers taking amantadine.

Pregnancy. Amantadine should not be used during pregnancy; embryotoxicity and teratogenicity have been reported in *rats* given high doses.[1]

A complex cardiovascular lesion occurred in an infant whose mother had taken amantadine hydrochloride 100 mg daily during the first 3 months of pregnancy.[1] In another case, tetralogy of Fallot and limb deformities were seen in the neonate of a mother who was given amantadine hydrochloride 100 mg daily for 7 days during the 4th and 6th weeks of gestation.[2] However, a report of the use of amantadine during 2 separate pregnancies by a woman with multiple sclerosis noted no abnormalities in either infant.[3]

1. Nora JJ, *et al.* Cardiovascular maldevelopment associated with maternal exposure to amantadine. *Lancet* 1975; **ii:** 607.
2. Pandit PB, *et al.* Tibial hemimelia and tetralogy of Fallot associated with first trimester exposure to amantadine. *Reprod Toxicol* 1994; **8:** 89–92.
3. Levy M, *et al.* Fetal outcome following intrauterine amantadine exposure. *Reprod Toxicol* 1991; **5:** 79–81.

Renal impairment. Evidence of extremely limited excretion of amantadine was found in 12 patients who were either anephric or had negligible renal function after a single 100-mg dose of amantadine hydrochloride.[1] Only small amounts were removed by dialysis. It was suggested that amantadine should be given with caution to patients requiring maintenance haemodialysis; a single dose may provide adequate plasma concentrations for many days.[1]

Dosage regimens based on creatinine clearance[2] or fixed doses at extended intervals[3] have been published. However, both regimens have been criticised and a conservative approach to amantadine dosage in these patients recommended[4] (for the regimens in licensed product information, see Administration in Renal Impairment, below). The need for caution in using amantadine in patients with renal impairment is highlighted by a report of a patient with end-stage renal disease who progressed from delirium to coma after receiving amantadine 100 mg twice daily for 3 days.[5]

1. Soung L-S, *et al.* Amantadine hydrochloride pharmacokinetics in hemodialysis patients. *Ann Intern Med* 1980; **93:** 46–9.
2. Horadam VW, *et al.* Pharmacokinetics of amantadine hydrochloride in subjects with normal and impaired renal function. *Ann Intern Med* 1981; **94:** 454–8.
3. Wu MJ, *et al.* Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. *Clin Nephrol* 1982; **17:** 19–23.
4. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988; **14:** 35–51.
5. Macchio GJ, *et al.* Amantadine-induced coma. *Arch Phys Med Rehabil* 1993; **74:** 1119–20.

Withdrawal. Neuroleptic malignant syndrome occurred in a patient being treated for heat stroke when all his medication, including antipsychotics and amantadine, was withdrawn.[1] It is suggested that dopamine agonists should not be stopped in patients with hyperpyrexia at risk from this syndrome. In another report,[2] a 14-year-old boy being treated with amantadine for influenza A encephalopathy developed neuroleptic malignant syndrome when the drug was stopped after 5 days; the patient improved when amantadine treatment was resumed. The authors recommended a gradual reduction in dosage when stopping amantadine therapy.

Acute delirium developed in 3 elderly patients with Parkinson's disease after gradual withdrawal of long-term amantadine therapy;[3] symptoms resolved when amantadine was restarted.

1. Simpson DM, Davis GC. Case report of neuroleptic malignant syndrome associated with withdrawal from amantadine. *Am J Psychiatry* 1984; **141:** 796–7.
2. Ito T, *et al.* Neuroleptic malignant syndrome following withdrawal of amantadine in a patient with influenza A encephalopathy. *Eur J Pediatr* 2001; **160:** 401.
3. Factor SA, *et al.* Acute delirium after withdrawal of amantadine in Parkinson's disease. *Neurology* 1998; **50:** 1456–8.

Interactions

Amantadine may enhance the adverse effects of antimuscarinics and the dose of these drugs should be reduced when used with amantadine; adverse effects of levodopa may also be exacerbated.

Licensed product information states that amantadine should be used with caution in patients receiving drugs that affect the CNS. The rate of excretion of amantadine may be reduced by drugs that raise urinary pH.

Antiarrhythmics. *Quinine* and *quinidine* have been reported to reduce the renal clearance of amantadine in healthy male, but not female, subjects.[1] Patients taking these drugs together should be observed for signs of amantadine toxicity.

1. Gaudry SE, *et al.* Gender and age as factors in the inhibition of renal clearance of amantadine by quinine and quinidine. *Clin Pharmacol Ther* 1993; **54:** 23–7.

Antimalarials. For the possible effects of the use of *quinine* and *quinidine* with amantadine, see Antiarrhythmics, above.

Diuretics. A patient with Parkinson's disease, previously stabilised on amantadine hydrochloride 300 mg daily, developed symptoms of amantadine toxicity, including ataxia, myoclonus, and confusion, 7 days after starting treatment with a preparation containing *triamterene* and *hydrochlorothiazide* (*Dyazide*).[1] It was postulated that the effect was due to reduction of the tubular secretion of amantadine.

1. Wilson TW, Rajput AH. Amantadine-Dyazide interaction. *Can Med Assoc J* 1983; **129:** 974–5.

MAOIs. Hypertension occurred about 48 hours after starting treatment with *phenelzine sulfate* in a patient already receiving amantadine.[1]

1. Jack RA, Daniel DG. Possible interaction between phenelzine and amantadine. *Arch Gen Psychiatry* 1984; **41:** 726.

Pharmacokinetics

Amantadine hydrochloride is well absorbed from the gastrointestinal tract; peak concentrations in the plasma appear within about 4 hours after oral doses. Plasma protein binding is reported to be about 67%, with a substantial amount bound to erythrocytes; the concentration is about 2.7 times higher in erythrocytes than in plasma. It is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion although small amounts of an acetylated metabolite have also been detected in urine; the plasma elimination half-life

is reported to be about 15 hours in patients with normal renal function but is significantly prolonged in the elderly and in patients with renal impairment. The rate of elimination may be increased by acidification of the urine. Amantadine crosses the placenta and the blood-brain barrier. It is also distributed into breast milk.

◊ References.

1. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988; **14:** 35–51.

Uses and Administration

Amantadine is a weak dopamine agonist with some antimuscarinic activity; it is also an antagonist at *N*-methyl-D-aspartate receptors. Amantadine has mild antiparkinsonian activity and is used in the management of parkinsonism, mainly in early disease when symptoms are mild. It may improve bradykinesia, rigidity, and tremor but tolerance can develop.

Amantadine is also an antiviral that inhibits replication of influenza type A virus; it has very little or no activity against influenza type B virus. It is used prophylactically against infection with influenza type A virus and to ameliorate symptoms when given during the early stages of infection.

Amantadine has also been used in the management of herpes zoster.

Amantadine is usually given orally as the hydrochloride and the doses below are expressed in terms of this salt.

In **parkinsonism**, treatment is usually started with 100 mg daily, increasing to 100 mg twice daily after a week or more. Doses up to a maximum of 400 mg daily have occasionally been used. The lowest effective dose should be used in patients over 65 years of age because of the potential for reduced renal clearance in this age group. Withdrawal of amantadine treatment for parkinsonism should be gradual to avoid exacerbating the condition; UK licensed product information suggests decreasing the dose by half at weekly intervals.

The dose of amantadine in the UK for the treatment of **influenza A** is 100 mg daily, usually given for about 5 days. For the prophylaxis of influenza A the same dose is given for as long as protection from infection is required, which may be for about 6 weeks. If amantadine is being given with influenza vaccination then it is usually only given for up to 3 weeks after vaccination. Children aged 10 to 15 years may also be given 100 mg daily for the recommended period. A daily dose of less than 100 mg or 100 mg given at intervals greater than one day has been recommended for patients over 65 years of age.

Doses in the USA are higher than those in the UK: for the treatment of influenza A the daily dose is 200 mg daily as a single dose or in two divided doses, continued for 24 to 48 hours after the disappearance of symptoms. The same dose is given for the prophylaxis of influenza A for at least 10 days following exposure. If given with vaccination then amantadine should be taken for the next 2 to 4 weeks. The dose of amantadine should be reduced to 100 mg daily in patients aged 65 years and over, and in those who show intolerance to the higher dose. Children aged 1 to 9 years may be given 4.4 to 8.8 mg/kg daily to a maximum of 150 mg daily; older children may be given 100 mg twice daily.

In **herpes zoster**, treatment with 100 mg twice daily may be given for 14 days; if pain persists, treatment may be continued for a further 14 days.

The dosage of amantadine should be reduced in patients with renal impairment (see below).

Amantadine sulfate has been used similarly to the hydrochloride; it has been given by mouth or by intravenous infusion.

Administration. Amantadine sulfate has been used successfully in doses of up to 600 mg daily by intravenous infusion in the management of akinetic crisis in patients with Parkinson's disease.[1]

1. Gadoth N, *et al.* I.V. amantadine sulfate for extrapyramidal crisis. *Clin Pharm* 1985; **4:** 146.

Administration in renal impairment. The dose of amantadine should be reduced in patients with renal impairment by either reducing the total daily dose or by increasing the dosage interval in accordance with their creatinine clearance (CC).

In the UK the following doses are recommended:

- CC over 35 mL/min: 100 mg daily
- CC 15 to 35 mL/min: 100 mg every 2 to 3 days
- CC less than 15 mL/min: not recommended

In the USA the following doses are recommended:

- CC 30 to 50 mL/min: 200 mg on the first day followed by 100 mg daily thereafter
- CC 15 to 29 mL/min: 200 mg on the first day followed by 100 mg on alternate days
- CC less than 15 mL/min or those on haemodialysis: 200 mg every 7 days

See also under Precautions, above.

Extrapyramidal disorders. Amantadine has been used as an alternative to antimuscarinics[1] in the short-term management of *drug-induced extrapyramidal symptoms* (p.971). US licensed product information has recommended a usual dose of 200 mg daily in 2 divided doses increased up to 300 mg daily if necessary. However the development of tolerance has limited its usefulness. See also Parkinsonism, below.

Amantadine has been investigated in the management of *chorea* in patients with Huntington's disease.[2,3]

1. König P, *et al.* Amantadine versus biperiden: a double-blind study of treatment efficacy in neuroleptic extrapyramidal movement disorders. *Neuropsychobiology* 1996; **33:** 80–4.
2. Magnet MK, *et al.* Amantadine in the akinetic-rigid variant of Huntington's disease. *Ann Pharmacother* 2004; **38:** 1194–6.
3. Heckmann JM, *et al.* IV amantadine improves chorea in Huntington's disease: an acute randomized, controlled study. *Neurology* 2004; **63:** 597–8.

Hepatitis C. Amantadine has been investigated[1-4] as an addition to interferon-based antiviral regimens in the treatment of chronic hepatitis C infection (p.851). A meta-analysis[1] concluded that it was of no value in treatment-naive patients or relapsers, but that triple therapy with amantadine, ribavirin, and interferon improved sustained responses in patients previously unresponsive to therapy.

1. Deltenre P, *et al.* Evaluation of amantadine in chronic hepatitis C: a meta-analysis. *J Hepatol* 2004; **41:** 462–73.
2. Stauber RE, *et al.* Retreatment of patients with chronic hepatitis C not responding to interferon/ribavirin combination therapy with daily interferon plus ribavirin plus amantadine. *Wien Klin Wochenschr* 2004; **116:** 530–5.
3. Herrine SK, *et al.* Peginterferon alpha-2a combination therapies in chronic hepatitis C patients who relapsed after or had a viral breakthrough on therapy with standard interferon alpha-2b plus ribavirin: a pilot study of efficacy and safety. *Dig Dis Sci* 2005; **50:** 719–26.
4. Mangia A, *et al.* A randomized controlled trial of pegylated interferon alpha-2a (40 KD) or interferon alpha-2a plus ribavirin and amantadine vs interferon alpha-2a and ribavirin in treatment-naive patients with chronic hepatitis C. *J Viral Hepatitis* 2005; **12:** 292–9.

Hiccup. Amantadine[1] has been reported to have produced beneficial results in patients with intractable hiccups (p.976).

1. Askenasy JJM, *et al.* Persistent hiccup cured by amantadine. *N Engl J Med* 1988; **318:** 711.

Influenza. Amantadine has been used similarly to rimantadine (p.904) in the prophylaxis and treatment of influenza A (p.859). In adults, the two drugs are equally effective, but amantadine is associated with more adverse effects;[1] further study on their safety and efficacy in children and the elderly is considered warranted.[2] Amantadine reduced the duration of influenza A symptoms when given in a dose of 200 mg daily within 48 hours of the onset of symptoms.[3] Vaccination is usually the method of choice for prophylaxis of influenza but amantadine has been used in addition to vaccination in certain individuals or when vaccination is contra-indicated. Although amantadine is licensed in the UK and USA for the prophylaxis and treatment of influenza A, its use for such purposes is not recommended.[4-6] Resistance to amantadine may occur rapidly.[7] For further information see Resistance, under Rimantadine, p.904.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 21/06/06).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 29/05/08).
3. Nicholson KG, Wiselka MJ. Amantadine for influenza A. *BMJ* 1991; **302:** 425–6.
4. NICE. Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza: Technology Appraisal 58 (issued February 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/58_Flu_fullguidance.pdf (accessed 11/08/08)
5. NICE. Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza: Technology Appraisal 67 (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/67_Flu_prophylaxis_guidance.pdf (accessed 11/08/08)
6. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-6): 1–54. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5606.pdf (accessed 09/10/07)
7. Bright RA, *et al.* Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005; **366:** 1175–81.

Multiple sclerosis. Amantadine has been used to alleviate fatigue associated with multiple sclerosis (p.892). However, a systematic review[1] concluded that there was insufficient evidence to support its use in reducing fatigue in patients with multiple sclerosis; further large controlled studies are considered warranted.

1. Pucci E, *et al.* Amantadine for fatigue in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 29/05/08).

Neuroleptic malignant syndrome. Amantadine has been tried[1-3] in the treatment of the neuroleptic malignant syndrome (p.972).

1. McCarron MM, *et al.* A case of neuroleptic malignant syndrome successfully treated with amantadine. *J Clin Psychiatry* 1982; **43:** 381–2.
2. Amdurski S, *et al.* A therapeutic trial of amantadine in haloperidol-induced malignant neuroleptic syndrome. *Curr Ther Res* 1983; **33:** 225–9.
3. Woo J, *et al.* Neuroleptic malignant syndrome successfully treated with amantadine. *Postgrad Med J* 1986; **62:** 809–10.

Parkinsonism. Amantadine's mechanism of action in parkinsonism (p.791) is unclear but may be due to its antimuscarinic activity and alterations in dopamine release and reuptake. It has also been suggested that amantadine's action as a non-competitive antagonist of *N*-methyl-D-aspartate may have a beneficial effect.[1,2] It has mild antiparkinsonian activity compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity and is used in a similar manner to antimuscarinics mainly in the treatment of patients with early Parkinson's disease when symptoms are mild. It may also be useful for dyskinesias in more advanced disease.[3] However, few patients obtain much benefit and tolerance to its effects can occur. Moreover, two systematic reviews[4,5] concluded that there was insufficient evidence from randomised controlled trials on the safety and efficacy of amantadine in the treatment of both Parkinson's disease and levodopa-induced dyskinesias in late disease.

Licensed product information suggests that the effectiveness of amantadine may be prolonged by withdrawing it for 3 to 4 weeks, continuing with existing antiparkinsonian therapy or starting low-dose levodopa treatment if clinically necessary in the meantime.

1. Laing P. Stroke treatment. *Lancet* 1991; **337:** 1601.
2. Greenamyre JT, O'Brien CF. N-Methyl- -aspartate antagonists in the treatment of Parkinson's disease. *Arch Neurol* 1991; **48:** 977–81.
3. Thomas A, *et al.* Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004; **75:** 141–3.
4. Crosby N, *et al.* Amantadine in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/02/06).
5. Crosby NJ, *et al.* Amantadine for dyskinesia in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 16/02/06).

Withdrawal syndromes. *COCAINE.* Despite some early promising results a systematic review[1] considered that there was no evidence to support the use of dopamine agonists, including amantadine, in the treatment of cocaine dependence (p.1860).

1. Soares B, *et al.* Dopamine agonists for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 16/02/06).

Preparations

BP 2008: Amantadine Capsules; Amantadine Oral Solution;
USP 31: Amantadine Hydrochloride Capsules; Amantadine Hydrochloride Syrup.

Proprietary Preparations (details are given in Part 3)

Arg.: Actison; Ampakine; Virosol; ***Austral.:*** Symmetrel; ***Austria:*** Amant; Hofcomant; PK-Merz; Virucid†; ***Belg.:*** Amantan; ***Braz.:*** Mantidan; ***Canad.:*** Endantadine; Symmetrel; ***Chile:*** PK-Merz†; Prayanol; ***Cz.:*** Amantadol; PK-Merz; Viregyt-K; ***Fin.:*** Atarin; ***Fr.:*** Mantadix; ***Ger.:*** Adekin; Aman†; Amanta; Amantagamma; Amixx; AMT†; InfectoFlu; Infex; PK-Merz; tregor; ***Gr.:*** Hofcomant†; PK-Merz†; Symmetrel; ***Hong Kong:*** PK-Merz; Symmetrel†; ***Hung.:*** PK-Merz; Viregyt; ***India:*** Amantrel; ***Irl.:*** Symmetrel; ***Israel:*** A-Parkin; Influ-A†; Paritrel; PK-Merz; ***Ital.:*** Mantadan; ***Malaysia:*** PK-Merz; ***Mex.:*** Kinestrel; Padiken†; PK-Merz; ***Neth.:*** Symmetrel; ***NZ:*** Symmetrel; ***Philipp.:*** PK-Merz; ***Pol.:*** Amantix; Viregyt K; ***Port.:*** Parkadina; Profil†; ***S.Afr.:*** Antadine†; Symmetrel; ***Singapore:*** Symmetrel; ***Switz.:*** PK-Merz; Symmetrel; ***UK:*** Lysovir; Symmetrel; ***USA:*** Symmetrel; ***Venez.:*** Symmetrel†.

Multi-ingredient: ***Mex.:*** Antiflu-Des; Fluviatol; Rosel.

Apomorphine Hydrochloride *(BANM)*

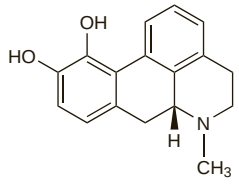
Apomorfiinihydrokloridi; Apomorfin Hidroklorür; Apomorfina, hidrocloruro de; Apomorfin-hidroklorid; Apomorfin-hydrochlorid hemihydrát; Apomorfinhydroklorid; Apomorfino hidrochloridas; Apomorfiny chlorowodorek; Apomorphine, chlorhydrate d'; Apomorphini hydrochloridum; Apomorphini Hydrochloridum Hemihydricum. 6aβ-Aporphine-10,11-diol hydrochloride hemihydrate; (*R*)-10,11-Dihydroxy-6a-aporphine hydrochloride hemihydrate; (6a*R*)-5,6,6a,7-Tetrahydro-6-methyl-4*H*-dibenzo[*de,g*]quinoline-10,11-diol hydrochloride hemihydrate.

$C_{17}H_{17}NO_2$,HCl,$\frac{1}{2}H_2O$ = 312.8.

CAS — 58-00-4 (apomorphine); 314-19-2 (anhydrous apomorphine hydrochloride); 41372-20-7 (apomorphine hydrochloride, hemihydrate).

ATC — G04BE07; N04BC07.

ATC Vet — QG04BE07; QN04BC07.



(apomorphine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.
Ph. Eur. 6.2 (Apomorphine Hydrochloride). White or faintly yellow to green-tinged greyish crystals or crystalline powder, the green tinge becoming more pronounced on exposure to air and light. Sparingly soluble in water and in alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.
USP 31 (Apomorphine Hydrochloride). Odourless, minute white or greyish-white, glistening crystals or white powder. It gradually acquires a green colour on exposure to light and air. Soluble 1 in 50 of water and 1 in 20 of water at 80°; soluble 1 in 50 of alcohol; very slightly soluble in ether and in chloroform. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Stability. Aqueous solutions of apomorphine hydrochloride decompose on storage and should not be used if they turn green or brown or contain a precipitate.

Adverse Effects

Treatment of parkinsonism. Apomorphine usually produces nausea and vomiting when given in therapeutic doses but these effects can be controlled by treatment with domperidone or trimethobenzamide. Transient sedation can be common during the first few weeks of treatment. Increased salivation and perspiration have also been reported. Apomorphine can produce neuropsychiatric disturbances including increasing cognitive impairment, personality changes, confusion, and hallucinations. Signs of CNS stimulation including euphoria, lightheadedness, restlessness, tremor, tachycardia, and tachypnoea occur less frequently. Apomorphine may induce dyskinesias during 'on' periods in patients with parkinsonism and these may be severe enough to require stopping therapy; postural instability and falls may also be a problem. Transient orthostatic hypotension may also occur infrequently. Eosinophilia has occurred rarely. The use of apomorphine with levodopa may cause haemolytic anaemia and treatment may need to be stopped if this cannot be satisfactorily controlled through dosage adjustment. Induration, nodule formation, and panniculitis, sometimes leading to ulceration, often develops at the site of subcutaneous injection.

Management of erectile dysfunction. The most common adverse effects have been nausea, headache, and dizziness. Other effects reported include yawning, rhinitis, pharyngitis, somnolence, infection, pain, increased cough, flushing, taste disturbances, and sweating. Fainting and syncope (vasovagal syndrome) have also occurred.

Overdosage with apomorphine can produce persistent vomiting, respiratory depression, bradycardia, hypotension, and coma; death may occur.

Akinesia. A 60-year-old man who was being investigated for parkinsonian symptoms became totally immobile and mute 15 minutes after receiving apomorphine 4 mg subcutaneously.[1] He remained conscious but was drowsy and sweating. Similar profound akinesia occurred on rechallenge with 2- and 6-mg doses. A diagnosis of probable nigrostriatal degeneration was made as the patient had previously shown no improvement with levodopa, but the mechanism of the idiosyncratic reaction to apomorphine was unclear.

1. Jenkins JR, Pearce JMS. Paradoxical akinetic response to apomorphine in parkinsonism. *J Neurol Neurosurg Psychiatry* 1992; **55:** 414–15.

Effects on the heart. A 67-year-old man developed palpitations with cold perspiration and chest pain, in addition to asthenia, salivation, nausea and vomiting, 5 minutes after receiving 3 mg apomorphine subcutaneously. An ECG showed atrial fibrillation with a ventricular frequency of 140 beats/minute.[1]

1. Stocchi F, *et al.* Transient atrial fibrillation after subcutaneous apomorphine bolus. *Mov Disord* 1996; **11:** 584–5.

Effects on mental function. Severe confusion, hallucinations, and acute psychosis were reported in 4 of 6 parkinsonian patients given subcutaneous apomorphine.[1] Three of the 4 had previously experienced mental disturbances while receiving lisuride. However, other studies failed to note effects on mental function in parkinsonian patients given apomorphine[2,3] and it has been suggested that the risk of psychosis in patients with no history of confusion or hallucinations is low.[3] UK licensed product information notes that apomorphine has been reported to exacerbate neuropsychiatric disturbances in patients with parkinsonism.

1. Ruggieri S, *et al.* Side-effects of subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **i:** 566.
2. Stibe CMH, *et al.* Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988; **i:** 403–6.
3. Poewe W, *et al.* Side-effects of subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **i:** 1084–5.

Hypersensitivity. Allergic reactions including contact dermatitis, severe rhinitis, and respiratory distress have been reported in 2 workers who came into contact with apomorphine powder.[1] Contact allergy has also been reported in a patient who developed a swollen nose and lips after intranasal use of apomorphine.[2] Skin testing in all these cases[1,2] gave a positive reaction to apomorphine. Biopsy of subcutaneous nodules, which develop at the site of injection in most patients using apomorphine subcutaneously, has not been able to clarify what type of reaction was responsible for the development of panniculitis.[3] Although the nodules may slowly resolve the sites are often unsuitable for reuse as absorption from them is unpredictable; concern has been expressed that this may limit long-term use of apomorphine.[3]

1. Dahlquist I. Allergic reactions to apomorphine. *Contact Dermatitis* 1977; **3:** 349–50.
2. van Laar T, *et al.* Nasolabiale allergische reactie op intranasale toediening van apomorfine bij de ziekte van Parkinson. *Ned Tijdschr Geneeskd* 1992; **136** (suppl 47): 26–7.
3. Acland KM, *et al.* Panniculitis in association with apomorphine infusion. *Br J Dermatol* 1998; **138:** 480–2.

Oedema. Severe reversible oedema of the lower limbs developed in a patient receiving subcutaneous apomorphine.[1] Oedema recurred when apomorphine was reintroduced, but to a lesser extent.

1. Vermersch P. Severe oedema after subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **ii:** 802.

Stomatitis. Stomatitis, severe enough to warrant stopping treatment, occurred in 4 of 8 patients after 2 to 6 months of therapy with sublingual apomorphine.[1]

1. Montastruc JL, *et al.* Sublingual apomorphine in Parkinson's disease: a clinical and pharmacokinetic study. *Clin Neuropharmacol* 1991; **14:** 432–7.

Treatment of Adverse Effects

In the UK, domperidone is usually given to control nausea and vomiting when apomorphine is used in the management of Parkinson's disease; pretreatment with domperidone for at least 2 days is advised before starting treatment with apomorphine. Usually domperidone can be withdrawn gradually over several weeks or longer although some patients may need to continue treatment indefinitely. In the USA, trimethobenzamide hydrochloride is used similarly, beginning 3 days before starting apomorphine treatment.

In overdosage an opioid antagonist such as naloxone has been given to treat excessive vomiting, and CNS and respiratory depression.

◊ References.

1. Bonuccelli U, *et al.* Naloxone partly counteracts apomorphine side effects. *Clin Neuropharmacol* 1991; **14:** 442–9.

Precautions

Apomorphine should not be given to patients with respiratory or CNS depression, hypersensitivity to opioids, neuropsychiatric problems, or dementia. It should be used with caution in patients prone to nausea and vomiting or when vomiting is likely to pose a risk. Apomorphine should also be used with care in patients with pulmonary, cardiovascular, or endocrine disease or with renal or hepatic impairment. Extra care is needed when starting treatment in elderly or debilitated patients and in those with a history of orthostatic hypotension. Patients who experience dizziness, lightheadedness, or syncope should not drive or operate machinery.

Treatment of parkinsonism. Apomorphine is not suitable for use in patients who have an 'on' response to levodopa marred by severe dyskinesia, hypotonia, or psychiatric effects; it should also not be used in those with hepatic impairment. Periodic monitoring of hepatic, renal, haematopoietic, and cardiovascular function has been advised and the *BNF* recommends that patients receiving apomorphine with levodopa should be screened for haemolytic anaemia on starting treatment and then every 6 months. Patients who develop anaemia, or those who have continuing confusion or hallucinations during treatment with apomorphine require observation and dosage adjustment under specialist supervision; treatment may need to be stopped. Excessive daytime sleepiness and sudden onset of sleep may also occur with apomorphine and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Local subcutaneous reactions can sometimes be reduced by using sodium chloride 0.9% to dilute injection solutions, by rotating injection sites, and possibly by use of ultrasound in areas of nodularity and induration.

Management of erectile dysfunction. UK licensed product information has warned that drugs for erectile dysfunction should be used with caution in patients with anatomical penile deformity.

Interactions

Apomorphine should be used with caution in patients receiving antihypertensives or organic nitrates as it may potentiate their hypotensive effects. Enhanced hypotensive effects may also occur when alcohol is given with apomorphine. The therapeutic effects of apomorphine may be antagonised by antipsychotics and other drugs that act as CNS dopamine inhibitors. The effect of apomorphine is possibly enhanced by entacapone and memantine.

Antiemetics. *Domperidone* (in the UK) and *trimethobenzamide* (in the USA) are used with apomorphine to control nausea and vomiting when it is prescribed for the management of parkinsonism. However, whether other antiemetics may safely be used is less clear. US licensed product information contra-indicates the use of *ondansetron* and related 5-HT_3 antagonists with apomorphine, on the grounds that profound hypotension and loss of consciousness has been reported in patients given this combination. However, UK licensed product information makes no mention of such a contra-indication, and licensed information for lower-dose products used in the management of erectile dysfunction notes that on the basis of interaction studies, ondansetron hydrochloride or *prochlorperazine maleate* may safely be given to patients receiving apomorphine for this indication.

Pharmacokinetics

Apomorphine is well absorbed after subcutaneous injection but undergoes extensive first-pass hepatic metabolism when given by mouth and oral bioavailability is low. However, it is readily absorbed after sublingual doses and peak plasma concentrations are achieved in about 40 to 60 minutes; bioavailability is reported to be about 17 to 18% compared with subcutaneous injection. Apomorphine is about 90% bound to plasma proteins, mainly to albumin.