rhoea. There appear to be no important differences in the efficacy of antimuscarinics for Parkinson's disease but some patients may tolerate one drug better than another. Those commonly used for Parkinson's disease include *benzatropine*, *orphenadrine*, *procyclidine*, and *trihexyphenidyl*.

- *Amantadine* is a weak dopamine agonist with some antimuscarinic activity although its activity as an antagonist of *N*-methyl-D-aspartate may also have a beneficial effect in Parkinson's disease. It has mild antiparkinsonian effects compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity but only a small proportion of patients derive much benefit. It is used similarly to antimuscarinics in early disease when symptoms are mild, but tolerance to its effects can occur rapidly.

Choice and implementation of drug treatment. If symptoms are mild, drug therapy may not be required in the early stages of the disease. When symptoms become troublesome but are still relatively mild *amantadine* or an *antimuscarinic* may be started; antimuscarinics are useful when tremor predominates but are generally more suitable for younger patients and in drug-induced rather than idiopathic parkinsonism. Some have begun treatment with *selegiline* immediately, but there have been doubts over whether it has a neuroprotective effect, as postulated, and also over long-term safety. There is no consensus on when to start dopaminergic treatment or whether to begin with *levodopa* or a *dopamine agonist*. For most patients treatment with levodopa eventually becomes necessary, but many neurologists delay initial treatment with levodopa because of the increased risk of motor complications. New patients, especially younger patients, therefore often begin treatment with a dopamine agonist, with levodopa reserved for the elderly, the frail, or those with intercurrent illness or more severe symptoms.

When levodopa does become necessary, the usual practice is to start with small doses, together with a peripheral dopa-decarboxylase inhibitor, and increase slowly to a dose which reduces disability to an acceptable level. Variations in response and diminishing effectiveness over the years necessitate careful adjustment of the size and form of the dose and the dosage schedule.

Complications of treatment. Fluctuations in mobility have been reported in more than half of patients on levodopa after 5 years of therapy. They generally proceed through predictable **'end-of-dose'** deterioration to the **'on-off'** phenomenon with marked very sudden swings from mobility to immobility. The cause of the fluctuations is not known, but multiple factors including desensitisation of dopamine receptors, interference with the response to dopamine by other levodopa metabolites such as 3-*O*-methyldopa, fluctuating plasma concentrations, and erratic transport of levodopa from blood to the brain have been suggested. It appears that as the disease progresses the capacity of the nigrostriatal dopaminergic system to synthesise and store dopamine, and to act as a buffer in maintaining dopamine brain concentrations, declines. Dopamine concentrations therefore become more dependent on levodopa dosage and the pattern of response will come to reflect more closely the rise and fall in levodopa concentrations. Eventually the effect of various factors that produce even small changes in plasma concentrations of levodopa will progressively become more pronounced.

Approaches to the management of 'end-of-dose' fluctuations include more frequent but smaller doses and the use of modified-release preparations. Addition of selegiline or partial replacement of levodopa by a dopamine agonist with a more prolonged action may also be tried.

Various attempts have been made to overcome the 'on-off' phenomenon. Those speculating that long-term treatment results in altered dopamine receptor sensitivity have used controlled withdrawal of levodopa for short periods ('drug holidays') but it is a dangerous procedure of doubtful value and no longer recommended.

Others have linked the 'on-off' phenomenon to variable plasma concentrations although, since transfer of levodopa into the brain involves active transport mechanisms, concentrations in plasma may not necessarily reflect those in the brain. Continuous intraduodenal or intravenous infusion of levodopa has been shown to reduce fluctuations in mobility, which suggests that dopamine receptors are still sensitive, although this is not practical for day-to-day management (but see below). However, there is evidence that some patients may benefit from modified-release formulations of levodopa with a peripheral dopa-decarboxylase or COMT inhibitor. As levodopa competes with amino acids for uptake into the brain, attempts to lessen fluctuations in dopamine brain concentrations have included taking levodopa on an empty stomach and also delaying most of a day's protein consumption until the evening. Addition of entacapone, rasagiline, selegiline, or a dopamine agonist may also help to reduce 'on-off' phenomena. If fluctuations remain a problem subcutaneous apomorphine is often effective. In some countries a gel formulation of levodopa with carbidopa is available for continuous infusion by an ambulatory pump into the duodenum when other available combination therapy has not been satisfactory.

Other complications of treatment with levodopa can include **dyskinesia**, which may respond to dosage adjustment or partial replacement of levodopa with a dopamine agonist. Amantadine may also be considered, although evidence is lacking. Some patients with Parkinson's disease may experience **severe pain** and **dystonia**; measures to increase 'on' periods can help reduce or eliminate pain in most patients.

Patients with Parkinson's disease can suffer from a range of **psychiatric effects**, such as depression, dementia, sleep disturbances, and psychosis, due to the adverse effects of drug therapy and to disease progression. It has been recommended that if patients develop psychotic reactions, an attempt to adjust their antiparkinsonian drugs should be tried before resorting to the use of antipsychotics. Although classical antipsychotics are usually contra-indicated because they can exacerbate parkinsonism, the atypical antipsychotics clozapine and quetiapine may be used in treatment-resistant psychosis—see Disturbed Behaviour, p.954. The cholinesterase inhibitor rivastigmine is licensed in some countries for the symptomatic treatment of mild to moderately severe dementia in Parkinson's disease. **Excessive daytime sleepiness** and **sudden onset of sleep** have been reported with dopamine agonists and patients should be warned of the possible risks (see Effects on Mental Function, under Adverse Effects of Levodopa, p.805). **Fibrotic reactions** resulting in cardiovascular and pulmonary adverse effects have been reported with ergot derivatives and patients should be monitored (see Fibrosis, under Adverse Effects of Bromocriptine, p.799). **Nausea and vomiting** induced by dopaminergics may be minimised by introducing the drug gradually and giving the dose with food, but if this is ineffective or apomorphine is being used these effects can be controlled by the antiemetic domperidone. Domperidone does not readily cross the blood-brain barrier and therefore acts mainly as a peripheral dopamine antagonist. Tolerance to the nausea usually develops after a few weeks and domperidone may then be withdrawn.

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Amantadine *(BAN, pINN)*

Amantadiini; Amantadin; Amantadina; Amantadinum. Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine.

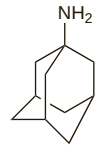
Амантадин

$C_{10}H_{17}N$ = 151.2.

CAS — 768-94-5.

ATC — N04BB01.

ATC Vet — QN04BB01.



Amantadine Hydrochloride *(BANM, USAN, pINNM)*

1-Adamantanamine Hydrochloride; Amantadiinihydrokloridi; Amantadine, chlorhydrate d'; Amantadin-hidroklorid; Amantadin-hydrochlorid; Amantadinhydroklorid; Amantadini hydrochloridum; Amantadino hidrochloridas; EXP-105-1; Hidrocloruro de amantadina; NSC-83653. Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine hydrochloride.

Амантадина Гидрохлорид

$C_{10}H_{17}N,HCl$ = 187.7.

CAS — 665-66-7.

ATC — N04BB01.

ATC Vet — QN04BB01.

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