Entacapone *(BAN, USAN, rINN)*

Entacapona; Entacaponum; Entakapon; Entakaponi; OR-611. (*E*)-α-Cyano-*N*,*N*-diethyl-3,4-dihydroxy-5-nitrocinnamamide; (*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylacrylamide.

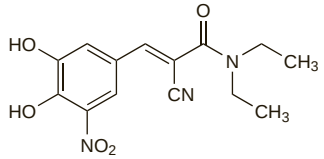
Энтакапон

$C_{14}H_{15}N_3O_5$ = 305.3.

CAS — 130929-57-6.

ATC — N04BX02.

ATC Vet — QN04BX02.



Adverse Effects

The most frequent adverse effects produced by entacapone relate to increased dopaminergic activity and occur most commonly at the start of treatment; reduction of the levodopa dosage may reduce the severity and frequency of such effects. Adverse effects may include nausea, vomiting, abdominal pain, constipation, diarrhoea, colitis, dry mouth, and dyskinesias. Other commonly reported adverse effects include dizziness, insomnia, nightmares, hallucinations, confusion, fatigue, and increased sweating. There have been rare reports of agitation, urticaria, erythematous or maculopapular rash, anorexia, and weight decrease. Increases in liver enzyme values have been reported rarely; there have also been isolated cases of cholestatic hepatitis. Isolated cases of neuroleptic malignant syndrome have been reported after abrupt reduction or withdrawal of entacapone; there have also been isolated cases of rhabdomyolysis. It may produce a harmless reddish-brown discoloration of the urine. Skin, hair, beard, and nail discolorations have been reported.

◊ References.

1. Brooks DJ. Safety and tolerability of COMT inhibitors. *Neurology* 2004; **62** (Suppl 1): S39–S46.

Precautions

Entacapone is contra-indicated in patients with phaeochromocytoma and in patients with a history of neuroleptic malignant syndrome or nontraumatic rhabdomyolysis. It should be avoided in patients with hepatic impairment, and given with caution to patients with biliary obstruction. A general medical evaluation, including liver function, should be considered in those who experience progressive anorexia, asthenia, and weight decrease within a relatively short period of time.Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, in Levodopa, p.805) and again, 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.

Treatment with entacapone should not be stopped abruptly; when necessary withdrawal should be made gradually, increasing the dose of levodopa as required.

Genetic polymorphism. For reference to slow metabolisers being more susceptible to COMT-inhibitor induced hepatotoxicity, see under Tolcapone, p.820.

Interactions

Use of entacapone with a non-selective MAOI is contra-indicated. Entacapone should be used with caution in patients receiving drugs metabolised by catechol-*O*-methyltransferase (COMT) including adrenaline, apomorphine, dobutamine, dopamine, isoprenaline, methyldopa, noradrenaline, paroxetine, and rimiterol. Caution is also advised when used with certain antidepressants including the tricyclics, reversible inhibitors of monoamine oxidase type A, and noradrenaline reuptake inhibitors such as venlafaxine.

Entacapone may aggravate levodopa-induced orthostatic hypotension and should be used cautiously in patients who are taking other drugs which may cause orthostatic hypotension.

Entacapone may form chelates with iron preparations in the gastrointestinal tract; the two drugs should be taken at least 2 to 3 hours apart.

Pharmacokinetics

There are large intra- and interindividual variations in the absorption of entacapone. Peak plasma concentrations are achieved about one hour after oral doses. Entacapone undergoes extensive first-pass metabolism and oral bioavailability is about 35%. Absorption is not affected significantly by food. Entacapone is about 98% bound to plasma proteins. It is eliminated mainly in the faeces with about 10 to 20% being excreted in the urine, mainly as glucuronide conjugates. Entacapone is thought to be distributed into breast milk on the basis of studies in *rats*.

◊ Entacapone is rapidly absorbed from the gastrointestinal tract and bioavailability after oral doses has been reported to range from 29 to 46%. It does not cross the blood-brain barrier. Over half of a dose appears in the faeces with smaller amounts being excreted in the urine as glucuronides of entacapone and its (*Z*)-isomer. Elimination half-lives of about 1.6 to 3.4 hours have been reported for entacapone.

References.

1. Wikberg T, *et al.* Identification of major metabolites of the catechol-O-methyltransferase inhibitor entacapone in rats and humans. *Drug Metab Dispos* 1993; **21:** 81–92.
2. Keränen T, *et al.* Inhibition of soluble catechol-O-methyltransferase and single-dose pharmacokinetics after oral and intravenous administration of entacapone. *Eur J Clin Pharmacol* 1994; **46:** 151–7.

Uses and Administration

Entacapone is a selective, reversible, peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of dopamine and levodopa. It is used as an adjunct to combination preparations of levodopa and dopa-decarboxylase inhibitors, in patients with Parkinson's disease and 'end-of-dose' motor fluctuations who cannot be stabilised on levodopa combinations alone. Entacapone is given orally in a dosage of 200 mg at the same time as each dose of levodopa with dopa-decarboxylase inhibitor, up to a maximum of 200 mg ten times daily. It is often necessary to gradually reduce the dosage of levodopa by about 10 to 30% within the first few weeks after starting treatment with entacapone; this effect may be more marked in the presence of benserazide than of carbidopa.

Entacapone may also be given as a combination preparation with carbidopa and levodopa; for dosage details, see Levodopa, p.808.

Parkinsonism. Entacapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT), with mainly peripheral actions. It is given as adjunctive therapy to patients with Parkinson's disease (p.791) experiencing fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations. When levodopa is given with a peripheral dopa-decarboxylase inhibitor, *O*-methylation then becomes the predominant form of metabolism of levodopa; therefore adding a peripheral COMT inhibitor such as entacapone potentially extends the duration and effect of levodopa in the brain, and thus allows levodopa to be given less often and in lower doses.

References.

1. Holm KJ, Spencer CM. Entacapone: a review of its use in Parkinson's disease. *Drugs* 1999; **58:** 159–177.
2. Anonymous. Entacapone for Parkinson's disease. *Med Lett Drugs Ther* 2000; **42:** 7–8.
3. Chong BS, Mersfelder TL. Entacapone. *Ann Pharmacother* 2000; **34:** 1056–65.
4. Myllyla VV, *et al.* Twelve-month safety of entacapone in patients with Parkinson's disease. *Eur J Neurol* 2001; **8:** 53–60.
5. Poewe WH, *et al.* Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). *Acta Neurol Scand* 2002; **105:** 245–55.
6. Brooks DJ, *et al.* Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. *J Neurol Neurosurg Psychiatry* 2003; **74:** 1071–9.
7. Fenelon G, *et al.* Efficacy and tolerability of entacapone in patients with Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearing-off motor fluctuations: a randomized, double-blind, multicentre study. *J Neural Transm* 2003; **110:** 239–51.
8. Olanow CW, Stocchi F. COMT inhibitors in Parkinson's disease: can they prevent and/or reverse levodopa-induced motor complications? *Neurology* 2004; **62** (suppl 1): S72–S81.
9. Deane KHO, *et al.* Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).
10. Poewe W. The role of COMT inhibition in the treatment of Parkinson's disease. *Neurology* 2004; **62** (suppl 1): S31–S38.
11. Schrag A. Entacapone in the treatment of Parkinson's disease. *Lancet Neurol* 2005; **4:** 366–70.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Comtan; ***Austral.:*** Comtan; ***Austria:*** Comtan; ***Belg.:*** Comtan; ***Braz.:*** Comtan; ***Canad.:*** Comtan; ***Cz.:*** Comtan; Comtess; ***Denm.:*** Comtess; ***Fin.:*** Comtess; ***Fr.:*** Comtan; ***Ger.:*** Comtess; ***Gr.:*** Comtan; ***Hong Kong:*** Comtan; ***Hung.:*** Comtan; ***Indon.:*** Comtan; ***Irl.:*** Comtess; ***Israel:*** Comtan; ***Ital.:*** Comtan; ***Malaysia:*** Comtan; ***Mex.:*** Comtan; ***Neth.:*** Comtan; Comtess; ***Norw.:*** Comtess; ***NZ:*** Comtan; ***Philipp.:*** Comtan; ***Pol.:*** Comtan; ***Port.:*** Comtan; Comtess; ***S.Afr.:*** Comtan; ***Singapore:*** Comtan; ***Spain:*** Comtan; ***Swed.:*** Comtess; ***Switz.:*** Comtan; ***Thai.:*** Comtan; ***Turk.:*** Comtan; ***UK:*** Comtess; ***USA:*** Comtan; ***Venez.:*** Comtan.

Multi-ingredient: ***Arg.:*** Stalevo; ***Austral.:*** Stalevo; ***Belg.:*** Stalevo; ***Braz.:*** Stalevo; ***Chile:*** Stalevo; ***Cz.:*** Stalevo; ***Denm.:*** Stalevo; ***Fin.:*** Stalevo; ***Fr.:*** Stalevo; ***Ger.:*** Stalevo; ***Gr.:*** Stalevo; ***Hong Kong:*** Stalevo; ***Hung.:*** Stalevo; ***Indon.:*** Stalevo; ***Irl.:*** Stalevo; ***Israel:*** Stalevo; ***Ital.:*** Stalevo; ***Malaysia:*** Stalevo; ***Mex.:*** Stalevo; ***Neth.:*** Stalevo; ***Norw.:*** Stalevo; ***Philipp.:*** Stalev; ***Pol.:*** Stalevo; ***Port.:*** Stalevo; ***Rus.:*** Stalevo (Сталево); ***Singapore:*** Stalevo; ***Spain:*** Stalevo; ***Swed.:*** Stalevo; ***Switz.:*** Stalevo; ***Thai.:*** Stalevo; ***Turk.:*** Stalevo; ***UK:*** Stalevo; ***USA:*** Stalevo; ***Venez.:*** Stalevo.

Levodopa *(BAN, USAN, rINN)*

Dihydroxyphenylalanine; L-Dopa; 3-Hydroxy-L-tyrosine; Laevodopa; Lévodopa; Levodopum. (–)-3-(3,4-Dihydroxyphenyl)-L-alanine.

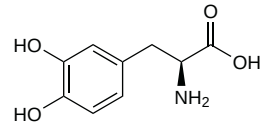
Леводопа

$C_9H_{11}NO_4$ = 197.2.

CAS — 59-92-7.

ATC — N04BA01.

ATC Vet — QN04BA01.



NOTE. Compounded preparations of levodopa may be represented by the following names:

- Co-beneldopa (*BAN*)—benserazide 1 part and levodopa 4 parts (w/w)
- Co-careldopa *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of carbidopa and levodopa, respectively
- Co-careldopa (*PEN*)—carbidopa and levodopa

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Levodopa). A white or slightly cream-coloured, crystalline powder. Slightly soluble in water; freely soluble in 1M hydrochloric acid but sparingly soluble in 0.1M hydrochloric acid; practically insoluble in alcohol. A 1% suspension in water has a pH of 4.5 to 7.0. Protect from light.

USP 31 (Levodopa). A white to off-white, odourless, crystalline powder. In the presence of moisture, it is rapidly oxidised by atmospheric oxygen and darkens. Slightly soluble in water; freely soluble in 3N hydrochloric acid; insoluble in alcohol. Store in a dry place in airtight containers at a temperature not exceeding 40°. Protect from light.

Stability. Extemporaneously prepared oral liquid dosage forms may be unstable and manufacturers' formulations should be used where possible.[1] Water dispersible formulations of levodopa with benserazide are available in some countries but a method that can be used by patients to prepare daily solutions of levodopa with carbidopa has been suggested:[2] one litre of a solution in potable water may be prepared with ten crushed standard tablets of levodopa 100 mg with carbidopa 25 mg and 2 g of ascorbic acid added to stabilise the levodopa.

1. Walls TJ, *et al.* Problems with inactivation of drugs used in Parkinson's disease. *BMJ* 1985; **290:** 444–5.
2. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.

Adverse Effects

Gastrointestinal effects, notably nausea, vomiting, and anorexia are common early in treatment with levodopa, particularly if the dosage is increased too rapidly. Gastrointestinal bleeding has been reported in patients with a history of peptic ulcer disease.

The commonest cardiovascular effect is orthostatic hypotension, which is usually asymptomatic, but may be associated with faintness and dizziness. Cardiac arrhythmias have been reported and hypertension has occasionally occurred.

Psychiatric symptoms occur in a high proportion of patients, especially the elderly, and include agitation, anxiety, euphoria, nightmares, insomnia or sometimes drowsiness, and depression. More serious effects, usually requiring a reduction in dosage or withdrawal of levodopa, include aggression, paranoid delusions, hallucinations, delirium, severe depression, with or without suicidal behaviour, and unmasking of psychoses. Psychotic reactions are more likely in patients with postencephalitic parkinsonism or a history of mental disorders. Excessive daytime sleepiness and sudden onset of sleep have been reported very rarely.

Abnormal involuntary movements or dyskinesias are the most serious dose-limiting adverse effects of levodopa and are very common at the optimum dose required to control parkinsonism; their frequency increases with duration of treatment. Involuntary movements of the face, tongue, lips, and jaw often appear first and those of the trunk and extremities later. Severe generalised choreoathetoid and dystonic movements may occur after prolonged use. Muscle twitching and blepharospasm may be early signs of excessive dosage. Exaggerated respiratory movements and exacerbated oculogyric crises have been reported in patients with postencephalitic parkinsonism. Bradykinesia and akinesia, in the form of 'end-of-dose' deterioration and the 'on-off' phenomenon, may reemerge in patients with parkinsonism as a complication of long-term treatment, but may be due to progression of the disease rather than to levodopa (see also Parkinsonism, p.791).

A positive response to the direct Coombs' test may occur, usually without evidence of haemolysis although auto-immune haemolytic anaemia has occasionally been reported. Transient leucopenia and thrombocytopenia have occurred rarely. The effects of levodopa on liver and kidney function are generally slight; transient increases in liver enzymes, and in blood-urea nitrogen and serum-uric acid concentrations, have been reported. Levodopa may cause discoloration of the urine; reddish at first then darkening on standing. Other body fluids may also be discoloured.

Some of the adverse effects reported may not be attributable directly to levodopa, but rather to the use of antimuscarinics, to increased mobility, or to the unmasking of underlying conditions as parkinsonism improves. Use with a peripheral dopa-decarboxylase inhibitor may reduce the severity of peripheral symptoms such as gastrointestinal and cardiovascular effects, but central effects such as dyskinesias and mental disturbances may occur earlier in treatment.

Incidence of adverse effects. The major adverse effects of levodopa are dyskinesia in 75% of patients and psychiatric disturbances in 25%.[1] Nausea and vomiting in 40 to 50% gradually regress and hypotension in 25 to 30% is generally asymptomatic. Less common adverse effects include cardiac arrhythmias, particularly atrial and ventricular ectopic beats and less commonly atrial flutter and fibrillation; palpitations and flushing often accompanied by excessive sweating; hypertension; polyuria, incontinence, and urinary retention, although antimuscarinic drugs often contribute to problems with micturition; and dark coloration of the urine and saliva. Rare adverse effects include abdominal pain, constipation, and diarrhoea; mydriasis, blurred vision, diplopia, and precipitation of glaucoma; headache; stridor; tachypnoea; and paraesthesias.

1. Calne DB, Reid JL. Antiparkinsonian drugs: pharmacological and therapeutic aspects. *Drugs* 1972; **4:** 49–74.

Abnormal coloration. Black pigmentation of rib cartilage has been noted at necropsy in patients treated with levodopa.[1,2] Abnormal pigmentation is generally not seen at other sites[2] but there have been isolated reports[2,3] of patients who also had pigmentation of the intervertebral discs. Although the pigmentation appears to be irreversible it was considered to be probably harmless.[2] It has been suggested that the pigmentation was due to deposition of dihydroxyphenylalanine (DOPA) in the cartilage.[1] It is known that DOPA will readily auto-oxidise *in vitro* in the presence of oxygen to a black pigment and this can also happen *in vivo* since black urine is a well known adverse effect of levodopa. Dark sweat and pigmentation of the skin and teeth are also known adverse effects.

See also Effects on the Skin and Hair, below.

1. Connolly CE, *et al*. Black cartilage associated with levodopa. *Lancet* 1986; **i:** 690.
2. Rausing A, Rosén U. Black cartilage after therapy with levodopa and methyldopa. *Arch Pathol Lab Med* 1994; **118:** 531–5.
3. Keen CE. *BMJ* 1998; **316:** 240.

Dysgeusia. A change in taste sensation was reported[1] in 23 of 514 patients treated with levodopa and a peripheral dopa-decarboxylase inhibitor; 2 of the 23 had total loss of taste initially. The altered taste, often described as insipid, metallic, or plastic, was first observed 3 to 32 weeks after beginning treatment, and lasted for 2 to 40 weeks. In an earlier report, 22 of 100 patients receiving levodopa alone had experienced changes in taste.[2]

1. Siegfried J, Zumstein H. Changes in taste under L-DOPA therapy. *Z Neurol* 1971; **200:** 345–8.
2. Barbeau A. L-DOPA therapy: past, present and future. *Ariz Med* 1970; **27:** 1–4.

Effects on the blood. Reports of effects of levodopa on the blood are mostly confined to individual case reports. A study in 365 patients, receiving levodopa in a mean daily dosage of 4.04 g, found that 32 developed a positive direct Coombs' test, the majority after between 3 and 12 months of therapy, but none developed haemolytic anaemia.[1] However, occasional cases of auto-immune haemolytic anaemia have been reported;[2-4] in one case, dosage reduction and addition of a peripheral dopa-decarboxylase inhibitor largely abolished haemolysis,[3] but in another, haemolysis recurred on re-institution of levodopa with carbidopa and required corticosteroid treatment.[4] A case of severe acute non-haemolytic anaemia related to levodopa therapy has also been reported.[5]

Although levodopa is widely stated to produce leucopenia in some patients, there are few published reports. However transient minor decreases in total leucocyte counts were reported in 3 of a group of 80 patients receiving levodopa.[6]

Severe thrombocytopenia has been reported in 2 patients who had received levodopa for 3 and 2 years respectively;[7,8] the condition was apparently an auto-immune response and responded to prednisone therapy and withdrawal of levodopa.

1. Joseph C. Occurrence of positive Coombs test in patients treated with levodopa. *N Engl J Med* 1972; **286:** 1401–2.
2. Territo MC, *et al*. Autoimmune hemolytic anemia due to levodopa therapy. *JAMA* 1973; **226:** 1347–8.
3. Lindström FD, *et al*. Dose-related levodopa-induced haemolytic anaemia. *Ann Intern Med* 1977; **86:** 298–300.
4. Bernstein RM. Reversible haemolytic anaemia after levodopa-carbidopa. *BMJ* 1979; **1:** 1461–2.
5. Alkalay I, Zipoli T. Levodopa-induced acute non-hemolytic anemia. *Ann Allergy* 1977; **39:** 191.
6. Barbeau A. L-Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Can Med Assoc J* 1969; **101:** 791–800.
7. Wanamaker WM, *et al*. Thrombocytopenia associated with long-term levodopa therapy. *JAMA* 1976; **235:** 2217–19.
8. Giner V, *et al*. Thrombocytopenia associated with levodopa treatment. *Arch Intern Med* 2003; **163:** 735–6.

Effects on the cardiovascular system. There have been conflicting reports on the effects of peripheral dopa-decarboxylase inhibitors on orthostatic hypotension attributed to levodopa therapy. In a study,[1] supine and erect systolic blood pressure was found to be significantly higher in parkinsonian patients given levodopa with carbidopa than in those receiving levodopa alone, suggesting that the peripheral actions of dopamine contribute to levodopa-induced hypotension. However, another study[2] found no change in the incidence and degree of orthostatic hypotension after giving levodopa with carbidopa and, similarly, no difference in the frequency of ventricular arrhythmias.

See also Effects on Kidney Function, below and Cardiovascular Disorders, under Precautions, below.

1. Calne DB, *et al*. Action of -α-methyldopahydrazine on the blood pressure of patients receiving levodopa. *Br J Pharmacol* 1972; **44:** 162–4.
2. Leibowitz M, Lieberman A. Comparison of dopa decarboxylase inhibitor (carbidopa) combined with levodopa and levodopa alone on the cardiovascular system of patients with Parkinson's disease. *Neurology* 1975; **25:** 917–21.

Effects on electrolytes. See Effects on Kidney Function, below.

Effects on the endocrine system. Single doses of levodopa given to healthy subjects cause an increase in plasma concentrations of glucose, insulin, and glucagon, as well as of growth hormone[1] and there has been concern over the potential endocrine effects of levodopa therapy in patients with Parkinson's disease.[2] A study of carbohydrate metabolism in 24 patients with Parkinson's disease indicated that these patients had abnormally low rates of **glucose utilisation** when untreated, apparently due to impaired insulin release, and this was not altered when levodopa therapy was given.[3] However, a similar study completed by 19 patients[2] noted increased impairment of glucose utilisation after levodopa therapy for 1 year with a delayed hypersecretion of insulin in response to a glucose load similar to the metabolic changes of acromegaly. It was considered that patients given levodopa for parkinsonism should be monitored for evidence of diabetes mellitus or frank acromegaly.[2]

Postmenopausal bleeding occurred in varying degrees in 12 of 47 women treated with levodopa.[4] In one case bleeding was severe enough to warrant interrupting treatment and subsequent dosage reduction.

1. Rayfield EJ, *et al*. -Dopa stimulation of glucagon secretion in man. *N Engl J Med* 1975; **293:** 589–91.
2. Sirtori CR, *et al*. Metabolic responses to acute and chronic -dopa administration in patients with parkinsonism. *N Engl J Med* 1972; **287:** 729–33.
3. Van Woert MH, Mueller PS. Glucose, insulin, and free fatty acid metabolism in Parkinson's disease treated with levodopa. *Clin Pharmacol Ther* 1971; **12:** 360–7.
4. Wajsbort J. Post-menopausal bleeding after -dopa. *N Engl J Med* 1972; **286:** 784.

Effects on the eyes. Both miosis[1] and mydriasis[2] have been reported with levodopa.

For a report of the exacerbation of oculogyric crises by levodopa, see Extrapyramidal Effects, below.

1. Spiers ASD, *et al*. Miosis during -dopa therapy. *BMJ* 1970; **2:** 639–40.
2. Weintraub MI, *et al*. Pupillary effects of levodopa therapy: development of anisocoria in latent Horner's syndrome. *N Engl J Med* 1970; **283:** 120–3.

Effects on the gastrointestinal tract. Although gastrointestinal bleeding has more commonly been reported in patients with a history of peptic ulceration, there is a rare report[1] of acute melaena and non-specific gastritis associated with levodopa therapy in a 56-year-old man without any previous evidence of a gastric disorder.

See also Dysgeusia, above.

1. Riddoch D. Gastritis and -dopa. *BMJ* 1972; **1:** 53–4.

Effects on kidney function. Levodopa 1 to 2 g given to 7 patients with idiopathic or postencephalitic Parkinson's disease produced significant increases in renal plasma flow, glomerular filtration rate, and sodium and potassium excretion.[1] It was considered that the natriuretic effects could contribute to the orthostatic hypotension commonly seen in patients receiving levodopa. There is a report of a patient who developed hyponatraemia when given levodopa with carbidopa.[2] The patient had previously had a similar reaction with amantadine. On each occasion symptoms disappeared when dopaminergic medication was withdrawn and recurred on rechallenge. Inappropriate secretion of antidiuretic hormone was suggested as a possible mechanism.

Levodopa has also been reported to have a kaliuretic effect, resulting in hypokalaemia, in some parkinsonian patients;[3] the effect could be prevented by also giving a peripheral dopa-decarboxylase inhibitor.

1. Finlay GD, *et al*. Augmentation of sodium and potassium excretion, glomerular filtration rate and renal plasma flow by levodopa. *N Engl J Med* 1971; **284:** 865–70.
2. Lammers GJ, Roos RAC. Hyponatraemia due to amantadine hydrochloride and L-dopa/carbidopa. *Lancet* 1993; **342:** 439.
3. Granérus A-K, *et al*. Kaliuretic effect of -dopa treatment in parkinsonian patients. *Acta Med Scand* 1977; **201:** 291–7.

Effects on mental function. Psychiatric complications were the single commonest reason for stopping levodopa treatment in a follow-up study of 178 patients with idiopathic Parkinson's disease, 81 of whom were still taking levodopa after 6 years.[1] Within 2 years, levodopa was withdrawn because of toxic confusional states (21 patients), paranoid psychosis (6), unipolar depression (2), and mania (1). The incidence of visual hallucinations increased as treatment continued but, as with toxic confusional states, patients generally improved when levodopa was withdrawn. Before treatment, 40 patients had suffered severe depression and levodopa produced sustained improvement in only 2. After 6 years, 20 of the 81 patients remaining were moderately or severely depressed and were rarely improved by withdrawal or reduction in dosage of levodopa. Increasing dementia affected 26 of the 81 patients after 6 years; withdrawal of levodopa in 5 failed to improve cognitive disabilities, but increased parkinsonism.

Another study[2] reported that 141 of 400 patients being treated for Parkinson's disease developed mental disorders. In this study certain acute states, particularly anxiety, on-off hallucinations, and fits of delirium were linked to treatment with levodopa, whereas dementia and depression were not.

Long-term use of levodopa and dopamine agonists has been associated with a number of **behavioural disturbances**, including hypersexuality (see Effects on Sexual Function, below), punding (purposeless repetitive acts), excessive gambling or shopping (see below), and other obsessive behaviour such as compulsive eating.[3] Reduction in dopaminergic therapy can lead to cessation or improvement in symptoms. Some patients may develop dopamine dysregulation syndrome (see Abuse, under Precautions, below).

A 12-month study of 1281 patients in the USA treated with dopamine agonists for Parkinson's disease found that 9 were suffering from **excessive gambling**.[4] All patients had received levodopa, 8 pramipexole, and the remaining patient pergolide. The rate of pathological gambling was 1.5% in the 529 patients taking pramipexole. The authors considered that this was not unexpected given the general availability of casinos in the local area and an incidence in the general US population of 0.3 to 1.3%. An analysis[5] of 11 patients who began pathological gambling after starting therapy with pramipexole (9 cases) or ropinirole (2 cases) found that in 8 patients such behaviour resolved when the

drug was tapered or stopped; follow-up was not available in the other 3. In 7 patients the symptoms had developed within 1 to 3 months of achieving maintenance dose or after dose increases of dopamine agonist therapy. Of the 11 patients, 3 had not received levodopa. Cabergoline therapy has also been associated with pathological gambling.[6] Similar behaviour described as being markedly increased in "on" periods has been reported in other patients treated with levodopa.[7] Pathological gambling has also been associated with misuse of dopaminergics.[8]

Sleep-related complaints have occurred and were reported by 74 of 100 patients with Parkinson's disease.[9] All 74 were on levodopa and the prevalence of symptoms increased with the duration of treatment. Symptoms included insomnia, excessive daytime somnolence, altered dream phenomena, nocturnal vocalisation, involuntary myoclonic movements, and rarely, sleepwalking. Sleep fragmentation, which includes insomnia and somnolence, was the most common symptom overall. It has been suggested[10] that in patients with mild to moderate disease levodopa and dopamine agonists could cause sleep disruption. However, these drugs produce beneficial effects on nocturnal disabilities in patients with more severe disease. Reports[11-17] of daytime somnolence or sudden onset of sleep with various other dopamine agonists, including apomorphine, bromocriptine, cabergoline, lisuride, pergolide, piribedil, pramipexole, quinagolide, and ropinirole, suggest that this is a class effect of dopaminergic antiparkinsonian therapy, and patients should be warned of the possible risks (see Precautions, below). The risk of somnolence may be increased in those patients taking combinations of dopaminergics.[15,18]

1. Shaw KM, *et al.* The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980; **49:** 283–93.
2. Rondot P, *et al.* Mental disorders in Parkinson's disease after treatment with -Dopa. *Adv Neurol* 1984; **40:** 259–69.
3. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 2004; **17:** 172–80.
4. Driver-Dunckley E, *et al.* Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 2003; **61:** 422–3.
5. Dodd ML, *et al.* Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005; **62:** 1377–81.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Pathological gambling with cabergoline. *Aust Adverse Drug React Bull* 2005; **24:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0508.pdf (accessed 16/02/06)
7. Molina JA, *et al.* Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov Disord* 2000; **15:** 869–72.
8. Gschwandtner U, *et al.* Pathologic gambling in patients with Parkinson's disease. *Clin Neuropharmacol* 2001; **24:** 170–2.
9. Nausieda PA, *et al.* Psychiatric complications of levodopa therapy of Parkinson's disease. *Adv Neurol* 1984; **40:** 271–7.
10. van Hilten B, *et al.* Sleep disruption in Parkinson's disease: assessment by continuous activity monitoring. *Arch Neurol* 1994; **51:** 922–8.
11. Frucht S, *et al.* Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999; **52:** 1908–10.
12. Schapira AHV. Sleep attacks (sleep episodes) with pergolide. *Lancet* 2000; **355:** 1332–3.
13. Ferreira JJ, *et al.* Sleep attacks and Parkinson's disease treatment. *Lancet* 2000; **355:** 1333–4.
14. Pirker W, Happe S. Sleep attacks in Parkinson's disease. *Lancet* 2000; **356:** 597–8.
15. Committee on Safety of Medicines/Medicines and Healthcare Products Regulatory Agency. Dopaminergic drugs and sudden sleep onset. *Current Problems* 2003; **29:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)
16. Houmann CN. *et al.* Sleep attacks in patients taking dopamine agonists: review. *BMJ* 2002; **324:** 1483–7.
17. Plowman BK, *et al.* Sleep attacks in patients receiving dopamine-receptor agonists. *Am J Health-Syst Pharm* 2005; **62:** 537–40.
18. Etminan M, *et al.* Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomised controlled trials. *Drug Safety* 2001; **24:** 863–8.

Effects on respiration. Respiratory crises, including attacks of gasping, panting, sniffing, puffing, and breath-holding, occurred in 12 of 25 patients with postencephalitic parkinsonism during treatment with levodopa.[1] A further 8 developed respiratory and phonatory tics, including sudden deep breaths, yawns, coughs, giggles, sighing, grunting, and moaning. All 20 patients also suffered tachypnoea, bradypnoea, and asymmetrical movement of both sides of the chest, paradoxical diaphragmatic movements, and reversal of inspiratory and expiratory phases. The induction of respiratory crises may be prompt or greatly delayed; 3 patients only developed crises after more than 9 months of treatment with levodopa. Crises were readily precipitated by psychophysiological arousals such as rage and exertion. Most of the patients who developed marked respiratory disorders had shown slight irregularities of respiratory rhythm, rate, and force before receiving levodopa.

In another report a distressing dose-related irregularity in the rate and depth of breathing occurred when a patient with Parkinson's disease was given levodopa with benserazide.[2] The respiratory abnormality was completely suppressed by use of tiapride, with no reduction in the efficacy of levodopa.

1. Sacks OW, *et al.* Side-effects of L-dopa in postencephalitic parkinsonism. *Lancet* 1970; **i:** 1006.
2. De Keyser J, Vincken W. -Dopa-induced respiratory disturbance in Parkinson's disease suppressed by tiapride. *Neurology* 1985; **35:** 235–7.

Effects on sexual function. An increase in libido, over and above the effects of improved mobility and well-being, has been reported in parkinsonian patients receiving levodopa or dopamine agonists. One report noted increased libido but no improvement in sexual performance in 4 of 80 patients receiving levodopa[1] while another reported a moderate increase in sexual interest in 4 of 7 male patients.[2] There have also been reports of hypersexuality and deviant sexual behaviour in patients with Parkinson's disease receiving levodopa or dopamine agonists.[3-6] In some cases this was associated with increased dosage and possibly abuse of the drugs. Symptoms often improved on dosage reduction or withdrawal. Hypersexual behaviour and hypergenitalism have also been reported in a pre-pubertal boy given levodopa for behavioural disturbances.[7]

Some workers[8] have commented that dopaminergics such as cabergoline are being promoted illegally on the Internet for male sexual enhancement and warn of the potential for abuse and serious adverse effects.

Clitoral tumescence and increased libido has been noted in a woman receiving bromocriptine to suppress lactation[9] but there has been a report of sexual dissatisfaction and decreased libido in 3 women receiving bromocriptine for hyperprolactinaemia.[10]

1. Barbeau A. -Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Can Med Assoc J* 1969; **101:** 791–9.
2. Brown E, *et al.* Sexual function and affect in parkinsonian men treated with -dopa. *Am J Psychiatry* 1978; **135:** 1552–5.
3. Vogel HP, Schiffter R. Hypersexuality—a complication of dopaminergic therapy in Parkinson's disease. *Pharmacopsychiatry* 1983; **16:** 107–10.
4. Jiménez-Jiménez FJ, *et al.* Possible zoophilia associated with dopaminergic therapy in Parkinson disease. *Ann Pharmacother* 2002; **36:** 1178–9.
5. Kaňovský P, *et al.* Penile erections and hypersexuality induced by pergolide treatment in advanced, fluctuating Parkinson's disease. *J Neurol* 2002; **249:** 112–14.
6. Berger C, *et al.* Sexuelle Delinquenz und Morbus Parkinson. *Nervenarzt* 2003; **74:** 370–5.
7. Korten JJ, *et al.* Undesirable prepubertal effects of levodopa. *JAMA* 1973; **226:** 355.
8. Pinero A, *et al.* Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med* 2005; **353:** 1976–7.
9. Blin O, *et al.* Painful clitoral tumescence during bromocriptine therapy. *Lancet* 1991; **337:** 1231–2.
10. Saleh AK, Moussa MAA. Sexual dysfunction in women due to bromocriptine. *BMJ* 1984; **289:** 228.

Effects on the skin and hair. Two women who were given levodopa, up to 3 g daily, developed diffuse alopecia in addition to other adverse effects.[1] Repigmentation of hair has occurred in a white-bearded man after being treated with levodopa 1.5 g daily for 8 months.[2] Vitiligo has been reported[3] in a patient with Parkinson's disease following addition of tolcapone to his levodopa/carbidopa regimen. The development of vitiligo was attributed to the increase in plasma-levodopa concentrations brought about by concomitant use of tolcapone.

See also Melanoma, under Precautions, below.

1. Marshall A, Williams MJ. Alopecia and levodopa. *BMJ* 1971; **2:** 47.
2. Grainger KM. Pigmentation in Parkinson's disease treated with levodopa. *Lancet* 1973; **i:** 97–8.
3. Sabaté M, *et al.* Vitiligo associated with tolcapone and levodopa in a patient with Parkinson's disease. *Ann Pharmacother* 1999; **33:** 1228–9.

Extrapyramidal effects. Choreiform movements were the major dose-limiting complication of long-term treatment with levodopa in a follow-up study of 178 patients with idiopathic Parkinson's disease, 81 of whom were still taking levodopa after 6 years.[1] Dyskinesias usually appeared in the first year and became more severe and generalised with time. Certain distinctive patterns of involuntary movements occurred as follows:

- peak-dose movements affected 65 of the 81 patients and were dose-related. Movements were usually choreic, affecting the face and limbs, but dystonic and ballistic movements were also seen; characteristically they began 20 to 90 minutes after an oral dose and lasted from 10 minutes to 4 hours with a tendency to be more severe mid-way through the interdose period
- biphasic movements presenting as 2 distinct episodes of chorea or dystonia within each interdose period occurred in only 3 patients
- early morning and 'end-of-dose' dystonia was present in 15 patients after 6 years of treatment with levodopa, but rarely developed during the first 3 years
- nocturnal myoclonus occurred in 12 patients

The frequency, intensity, and complexity of spontaneous fluctuations in performance were greatly enhanced by long-term levodopa therapy. Two clinically distinct types of fluctuation, 'end-of-dose' deterioration and the 'on-off' phenomenon, were related to treatment. 'End-of-dose' deterioration or the 'wearing-off' effect affected 52 patients after 6 years of treatment and was characterised by progressive reduction in the duration of benefit from each dose with a gradual return of nocturnal and early morning disability in some patients. The 'on-off' phenomenon affected 14 patients who experienced completely unpredictable swings from relative mobility, usually accompanied by involuntary movements, to periods of profound bradykinesia and hypotonia. In addition, 'freezing episodes' and abrupt falls became increasingly common and affected 50 patients after 6 years compared with 33 before therapy.

1. Shaw KM, *et al.* The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980; **49:** 283–93.

Oculogyric crisis. After initial remission, oculogyric crises in 5 of 25 patients with postencephalitic parkinsonism recurred and were subsequently severely exacerbated during treatment with levodopa.[1] One patient, who previously had not had oculogyric crises, developed severe crises in the fourth month of therapy with levodopa. During these crises forced gaze deviation was always accompanied by severe neurological and mental symptoms, some of which were scarcely tolerable.

1. Sacks OW, Kohl M. -Dopa and oculogyric crises. *Lancet* 1970; **ii:** 215–16.

Gout. There have been reports of elevated serum uric acid concentrations in patients receiving levodopa, but some of these are of doubtful significance since levodopa has been shown to give falsely-elevated uric acid concentrations by colorimetric methods.[1] However, hyperuricaemia as measured by more specific methods,[2,3] with a few cases of overt gout,[2,3] has also been reported.

1. Cawein MJ, Hewins J. False rise in serum uric acid after -dopa. *N Engl J Med* 1969; **281:** 1489–90.
2. Honda H, Gindin RA. Gout while receiving levodopa for parkinsonism. *JAMA* 1972; **219:** 55–7.
3. Calne DB, Fermaglich J. Gout induced by -dopa and decarboxylase inhibitors. *Postgrad Med J* 1976; **52:** 232–3.

Hypersensitivity. Reports of hypersensitivity reactions to levodopa have included a vasculitis characterised by neuromyopathy, periarteriolitis with eosinophilia,[1] and a lupus-like auto-immune syndrome.[2]

1. Wolf S, *et al.* Neuromyopathy and periarteriolitis in a patient receiving levodopa. *Arch Intern Med* 1976; **136:** 1055–7.
2. Massarotti G, *et al.* Lupus-like autoimmune syndrome after levodopa and benserazide. *BMJ* 1979; **2:** 553.

Overdosage. Adverse effects after ingestion of 80 to 100 g of levodopa over a 12-hour period by a parkinsonian patient included hypertension initially, followed by hypotension of a few hours' duration, sinus tachycardia, and symptomatic orthostatic hypotension for more than a week.[1] Marked confusion, agitation, insomnia, and restlessness were the most prominent clinical symptoms and did not disappear completely for over a week; severe anorexia and insomnia persisted for 2 to 3 weeks. After the overdose the patient had virtually no signs of parkinsonism and received no levodopa or antimuscarinic medication for 6 days; rigidity and akinesia began to recur on the fourth day.

1. Hoehn MM, Rutledge CO. Acute overdose with levodopa: clinical and biochemical consequences. *Neurology* 1975; **25:** 792–4.

Withdrawal syndromes. Withdrawal of antiparkinsonian drugs, particularly levodopa, has been implicated in the development of a syndrome resembling the neuroleptic malignant syndrome,[1-6] characterised by fever, muscle rigidity, profuse sweating, tachycardia, tachypnoea, and elevated muscle enzyme values.[1] Several fatalities have occurred.[1,2] It has been suggested that the neuroleptic malignant syndrome is associated with blockade of dopamine receptors in the striatum, leading to increased rigidity and heat production, and in the hypothalamus, resulting in impaired thermoregulation[7] and it seems reasonable that withdrawal of levodopa might have a similar effect in patients with depleted central dopamine concentrations. Thus, the use of a 'drug holiday' to manage fluctuations in response to levodopa (see Parkinsonism, p.791) is no longer recommended.

Fever, extrapyramidal symptoms and raised creatine kinase concentrations, resembling a very mild form of the neuroleptic malignant syndrome, have also been reported in parkinsonian patients exposed to stress such as dehydration or infection but without any change in medication.[8]

1. Friedman JH, *et al.* A neuroleptic malignantlike syndrome due to levodopa therapy withdrawal. *JAMA* 1985; **254:** 2792–5.
2. Sechi GP, *et al.* Fatal hyperpyrexia after withdrawal of levodopa. *Neurology* 1984; **34:** 249–51.
3. Figà-Talamanca L, *et al.* Hyperthermia after discontinuance of levodopa and bromocriptine therapy: impaired dopamine receptors a possible cause. *Neurology* 1985; **35:** 258–61.
4. Gibb WRG, Griffith DNW. Levodopa withdrawal syndrome identical to neuroleptic malignant syndrome. *Postgrad Med J* 1986; **62:** 59–60.
5. Serrano-Dueñas M. Neuroleptic malignant syndrome-like, or—dopaminergic malignant syndrome—due to levodopa therapy withdrawal: clinical features in 11 patients. *Parkinsonism Relat Disord* 2003; **9:** 175–8.
6. Mizuno Y, *et al.* Malignant syndrome in Parkinson's disease: concept and review of the literature. *Parkinsonism Relat Disord* 2003; **9** (suppl 1): S3–S9.
7. Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? *Neurology* 1981; **31:** 132–7.
8. Mezaki T, *et al.* Benign type of malignant syndrome. *Lancet* 1989; **i:** 49–50.

Treatment of Adverse Effects

Reduction in dosage reverses most of the adverse effects of levodopa. Nausea and vomiting may be diminished by increasing the dose of levodopa gradually, and/or by taking with or after meals, although taking

levodopa on a full stomach may lead to lower plasma concentrations. Gastrointestinal effects may also be reduced by giving an antiemetic such as cyclizine or domperidone but not a phenothiazine (see Antipsychotics, under Interactions, below). Use with a peripheral dopa-decarboxylase inhibitor reduces peripheral but not central adverse effects. Orthostatic hypotension may respond to the use of elastic stockings.

The benefits of gastric decontamination are uncertain. However, activated charcoal should be considered in adults who have ingested more than 2 g (or more than the total daily dose, whichever is greater), and in children who have taken more than 200 mg, if they present within 1 hour of ingestion. Supportive measures should also be instituted. Pyridoxine may increase the metabolism of levodopa (see Nutritional Agents, under Interactions, below) but its value in overdosage has not been established; it does not reduce the effects of levodopa given with a peripheral dopa-decarboxylase inhibitor.

Nausea and vomiting. For reference to the use of domperidone in the management of nausea and vomiting associated with levodopa in patients with Parkinson's disease, see under Uses and Administration of Domperidone, p.1727.

Psychosis. Atypical antipsychotics such as clozapine (p.985) have been tried in the management of psychosis occurring as a complication of parkinsonism and of drugs such as levodopa used in its treatment.

Precautions

Levodopa is contra-indicated in patients with angle-closure glaucoma and should be used with caution in open-angle glaucoma. Caution is also required in patients with cardiovascular disease, pulmonary disease, endocrine disorders, psychiatric disturbances, osteomalacia, hepatic or renal disease, or a history of peptic ulceration. Periodic evaluations of hepatic, psychiatric, haematological, renal, and cardiovascular functions have been advised.

Since an association between levodopa and activation of malignant melanoma has been suspected (although not confirmed), it is generally recommended that levodopa should not be given to patients with (or with a history of) the disease or with skin disorders suggestive of it.

Parkinsonian patients who benefit from levodopa therapy should be warned to resume normal activities gradually to avoid the risk of injury. Treatment with levodopa should not be stopped abruptly.

Excessive daytime sleepiness and sudden onset of sleep may occur with levodopa 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.

Levodopa inhibits prolactin secretion and may therefore interfere with lactation.

Food interferes with the absorption of levodopa, though levodopa is usually given with or immediately after meals to reduce nausea and vomiting. However, patients experiencing the 'on-off' phenomenon may benefit from dosage on an empty stomach (see Parkinsonism, p.791).

Abuse. Abuse of levodopa and dopamine agonists in patients with Parkinson's disease has been reported.[1-6] The term dopamine dysregulation syndrome, has been used to describe a condition where there is a compulsive and dysregulated use of dopaminergic drugs beyond that needed to achieve relief of motor symptoms and which is harmful to the patient.[7] Patients have progressively increased the dosage of levodopa to obtain psychotropic effects such as euphoria despite accompanying dystonia and other extrapyramidal adverse effects. Withdrawal often led to craving, drug-seeking behaviour, and mood disturbances such as depression, features resembling a psychological dependence syndrome. Abuse in patients without parkinsonism has also occurred.[8]

See also Effects on Sexual Function under Adverse Effects, above.

1. Nausieda PA. Sinemet "abusers". *Clin Neuropharmacol* 1985; **8:** 318–27.
2. Soyka M, Huppert D. L-dopa abuse in a patient with former alcoholism. *Br J Addict* 1992; **87:** 117–18.
3. Spigset O, von Schéele C. Levodopa dependence and abuse in Parkinson's disease. *Pharmacotherapy* 1997; **17:** 1027–30.
4. Merims D, *et al.* Is there addiction to levodopa in patients with Parkinson's disease? *Mov Disord* 2000; **15:** 1014–16.
5. Müller U, *et al.* Levodopa-Abhängigkeit bei Parkinsonkrankheit: Fallbericht und Literaturübersicht. *Nervenarzt* 2002; **73:** 887–91.
6. Borek LL, Friedman JH. Levodopa addiction in idiopathic Parkinson disease. *Neurology* 2005; **65:** 1508.
7. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 2004; **17:** 172–80.
8. Steiner I, Wirguin I. Levodopa addiction in non-parkinsonian patients. *Neurology* 2003; **61:** 1451.

Cardiovascular disorders. A high incidence of cardiovascular adverse effects was reported in early studies of levodopa, but both Parkinson's disease and heart disease are common in the elderly and adverse cardiac effects of levodopa may be less prevalent than was first thought. A study in 40 patients[1] concluded that, apart from those with severe orthostatic hypotension or unstable coronary disease, levodopa may be used safely in parkinsonian patients with heart disease. Others[2] noted that levodopa and bromocriptine cause cardiac arrhythmias in less than 1% of all patients, the incidence for levodopa with a peripheral dopa-decarboxylase inhibitor being lower still. Nevertheless, caution is advised in patients with cardiovascular disease.

1. Jenkins RB, *et al.* Levodopa therapy of patients with parkinsonism and heart disease. *BMJ* 1972; **3:** 512–14.
2. Parkes JD, *et al.* Amantadine-induced heart failure. *Lancet* 1977; **i:** 904.

Diabetes mellitus. For reference to concern over the potential of levodopa to impair glucose utilisation, see Effects on the Endocrine System under Adverse Effects, above.

Melanoma. There has been concern over the effects of levodopa on melanoma in view of the ability of malignant melanoma cells to convert levodopa to melanin and isolated reports of melanoma developing or being exacerbated during levodopa therapy continue to appear. However, in a survey of 1099 patients with primary cutaneous malignant melanoma only one had taken levodopa.[1] It was concluded that levodopa therapy is not an important factor in the induction of malignant melanoma. Furthermore, use of levodopa in daily doses of up to 4 g with carbidopa in 17 patients with metastatic melanoma failed to provide any evidence that levodopa accelerated the progression of the disease.[2] Reviews[3,4] of these and later reports concluded that the purported link between levodopa and malignant melanoma was tenuous.

For a report of antineoplastic chemotherapy used for the treatment of melanoma reducing the efficacy of levodopa, see under Interactions, below.

1. Sober AJ, Wick MM. Levodopa therapy and malignant melanoma. *JAMA* 1978; **240:** 554–5.
2. Gurney H, *et al.* The use of L-dopa and carbidopa in metastatic malignant melanoma. *J Invest Dermatol* 1991; **96:** 85–7.
3. Siple JF, *et al.* Levodopa therapy and the risk of malignant melanoma. *Ann Pharmacother* 2000; **34:** 382–5.
4. Fiala KH, *et al.* Malignant melanoma and levodopa in Parkinson's disease: causality or coincidence? *Parkinsonism Relat Disord* 2003; **9:** 321–7.

Pregnancy. Levodopa alone and with carbidopa has been associated with fetal abnormalities in *animals* given high doses; no teratogenic effect has been noted with carbidopa alone. However, 2 women with parkinsonism who received levodopa with carbidopa or levodopa alone throughout their pregnancies gave birth to normal infants.[1]

1. Cook DG, Klawans HL. Levodopa during pregnancy. *Clin Neuropharmacol* 1985; **8:** 93–5.

Withdrawal. For adverse effects associated with withdrawal of levodopa, see under Adverse Effects, above.

Interactions

The therapeutic or adverse effects of levodopa may be affected by interactions with a variety of drugs. Mechanisms may include effects on catecholamine metabolising enzymes, neurotransmitters, or receptor sites, effects on the endocrine system, and effects on gastrointestinal absorption. Drugs that modify gastric emptying may affect the absorption of levodopa.

Antibacterials. A study[1] in 7 healthy subjects showed that use of *spiramycin* with levodopa and carbidopa resulted in reduced plasma-levodopa concentrations and an increase in its peripheral metabolism.

A hypertensive reaction and severe tremor occurred when *isoniazid* was given to a patient receiving levodopa;[2] it was not certain whether isoniazid was acting as an MAOI.

1. Brion N, *et al.* Effect of a macrolide (spiramycin) on the pharmacokinetics of -dopa and carbidopa in healthy volunteers. *Clin Neuropharmacol* 1992; **15:** 229–35.
2. Morgan JP. Isoniazid and levodopa. *Ann Intern Med* 1980; **92:** 434.

Antidementia drugs. Increasing the dose of *tacrine* worsened parkinsonian symptoms in an elderly woman with Alzheimer's disease and mild parkinsonism; symptoms responded to levodopa with carbidopa, but recurred when the dose of tacrine was again increased.[1]

1. Ott BR, Lannon MC. Exacerbation of parkinsonism by tacrine. *Clin Neuropharmacol* 1992; **15:** 322–5.

Antidepressants. ***BUPROPION.*** Caution has been advised with bupropion because of reports of a higher incidence of adverse effects during use with levodopa.

MAOIS. Giving levodopa with non-specific MAOIs such as *phenelzine*, *pargyline*, *nialamide*, or *tranylcypromine* may cause dangerous hypertension;[1-4] it is recommended that levodopa should not be given with, or within at least 14 days of stopping, an MAOI. Hypertensive reactions to levodopa with tranylcypromine were inhibited by carbidopa,[5] but licensed product information for preparations containing levodopa with carbidopa or benserazide still contra-indicates their use with MAOIs. The incidence of adverse effects may be increased if levodopa is used with *moclobemide*, a monoamine oxidase type A inhibitor (see Dopaminergics, p.411). *Selegiline*, a monoamine oxidase type B inhibitor, is used to enhance the antiparkinsonian effect of levodopa, see p.818.

1. Hunter KR, *et al.* Monoamine oxidase inhibitors and -dopa. *BMJ* 1970; **3:** 388.
2. Hodge JV. Use of monoamine oxidase inhibitors. *Lancet* 1965; **i:** 764–5.
3. Friend DG, *et al.* The action of L-dihydroxyphenylalanine in patients receiving nialamide. *Clin Pharmacol Ther* 1965; **6:** 362–6.
4. Sharpe J, *et al.* Idiopathic orthostatic hypotension treated with levodopa and MAO inhibitor: a preliminary report. *Can Med Assoc J* 1972; **107:** 296–300.
5. Teychenne PF, *et al.* Interactions of levodopa with inhibitors of monoamine oxidase and -aromatic amino acid decarboxylase. *Clin Pharmacol Ther* 1975; **18:** 273–7.

SSRIS. There was some evidence from a prescribing study that SSRIs might exacerbate parkinsonism resulting in increased doses of levodopa or addition of adjunctive drugs.[1]

1. van de Vijver DAMC, *et al.* Start of a selective serotonin reuptake inhibitor (SSRI) and increase of antiparkinsonian drug treatment in patients on levodopa. *Br J Clin Pharmacol* 2002; **54:** 168–70.

TRICYCLIC ANTIDEPRESSANTS. Although tricyclic antidepressants have generally been used safely with levodopa,[1] hypertensive crises have occurred in some rare cases. Such events have been reported in patients receiving *amitriptyline* or *imipramine* and levodopa with carbidopa.[2,3] Imipramine has been reported to impair the rate of levodopa absorption,[4] presumably due to its antimuscarinic properties (for the effect of antimuscarinics on the absorption of levodopa, see below).

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Rampton DS. Hypertensive crisis in a patient given Sinemet, metoclopramide, and amitriptyline. *BMJ* 1977; **2:** 607–8.
3. Edwards M. Adverse interaction of levodopa with tricyclic antidepressants. *Practitioner* 1982; **226:** 1447–8.
4. Morgan JP, *et al.* Imipramine-mediated interference with levodopa absorption from the gastrointestinal tract in man. *Neurology* 1975; **25:** 1029–34.

TRYPTOPHAN. See Amino Acids under Nutritional Agents, below.

Antiepileptics. *Phenytoin* has been shown to diminish the therapeutic effect of levodopa in patients with parkinsonism or chronic manganese poisoning.[1] The mechanism of the interaction was considered uncertain.

1. Mendez JS. Diphenylhydantoin: blocking of levodopa effects. *Arch Neurol* 1975; **32:** 44–6.

Antihypertensives. Use of levodopa with *guanethidine* may cause increased hypotension.[1] *Clonidine* has been reported to inhibit the therapeutic effect of levodopa, possibly by stimulating central alpha-adrenoceptors.[2] *Methyldopa* and levodopa may enhance each other's therapeutic or adverse effects, although there has been mention of the inhibitory effect of methyldopa on the therapeutic response to levodopa.[3,4] *Reserpine and other rauwolfia alkaloids* may oppose the antiparkinsonian effects of levodopa by central depletion of dopamine; UK licensed product information advises that use together should be avoided.

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Shoulson I, Chase TN. Clonidine and the anti-parkinsonian response to -dopa or piribedil. *Neuropharmacology* 1976; **15:** 25–7.
3. Cotzias GC, *et al.* -Dopa in Parkinson's syndrome. *N Engl J Med* 1969; **281:** 272.
4. Kofman O. Treatment of Parkinson's disease with -dopa: a current appraisal. *Can Med Assoc J* 1971; **104:** 483–7.

Antimuscarinics. Antimuscarinic antiparkinsonian drugs may enhance the therapeutic effects of levodopa but by delaying gastric emptying they may also reduce its absorption.[1]

1. Algeri S, *et al.* Effect of anticholinergic drugs on gastro-intestinal absorption of L-dopa in rats and in man. *Eur J Pharmacol* 1976; **35:** 293–9.

Antineoplastics. A patient with Parkinson's disease noted[1] that the efficacy of levodopa was reduced each time he received *dacarbazine* for the treatment of melanoma. As serum-dopamine

concentrations were unchanged it was suggested[1] that dacarbazine might compete with levodopa at the blood-brain barrier.

1. Merello M, *et al.* Impaired levodopa response in Parkinson's disease during melanoma therapy. *Clin Neuropharmacol* 1992; **15:** 69–74.

Antipsychotics. The therapeutic effects of levodopa may be diminished by CNS dopamine inhibitors including phenothiazine derivatives[1] such as *prochlorperazine*.[2] Butyrophenones such as *haloperidol* and thioxanthenes such as *flupentixol* might be expected to have a similar effect due to their antidopaminergic properties.

1. Yahr MD, Duvoisin RC. Drug therapy of parkinsonism. *N Engl J Med* 1972; **287:** 20–4.
2. Duvoisin RC. Diphenidol for levodopa induced nausea and vomiting. *JAMA* 1972; **221:** 1408.

Anxiolytics. Reversible deterioration of parkinsonism has been reported in patients receiving levodopa who were also given *benzodiazepines* such as *diazepam*,[1,2] *nitrazepam*[1] (although the evidence was equivocal), or *chlordiazepoxide*.[3] In one case parkinsonian symptoms resolved without alteration in the medication.[1]

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Wodak J, *et al.* Review of 12 months' treatment with L-dopa in Parkinson's disease, with remarks on unusual side effects. *Med J Aust* 1972; **2:** 1277–82.
3. Yosselson-Superstine S, Lipman AG. Chlordiazepoxide interaction with levodopa. *Ann Intern Med* 1982; **96:** 259–60.

Baclofen. Adverse effects including hallucinations, confusion, headache, and nausea and worsening of symptoms have been reported[1,2] in patients with Parkinson's disease taking levodopa when also given baclofen.

1. Skausig OB, Korsgaard S. Hallucinations and baclofen. *Lancet* 1977; **i:** 1258.
2. Lees AJ, *et al.* Baclofen in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1978; **41:** 707–8.

Gastrointestinal drugs. ***ANTACIDS.*** Some studies have suggested that taking an antacid before a dose of levodopa enhances the absorption of levodopa, apparently by enhancing gastric emptying and reducing metabolism of levodopa in the stomach.[1,2] This was particularly marked in a case report in a patient with prolonged gastric emptying time.[1] However, another study in 8 patients with presumably normal gastric motility, only 3 of whom had Parkinson's disease, found no significant increase in overall absorption of levodopa when given with an antacid although there was some evidence of increased absorption in some of the patients.[3] UK licensed product information (*Madopar CR; Roche*) states that antacids reduce the absorption of levodopa from the modified-release preparation by 32%.

1. Rivera-Calimlim L, *et al.* -Dopa treatment failure: explanation and correction. *BMJ* 1970; **4:** 93–4.
2. Pocelinko R, *et al.* The effect of an antacid on the absorption and metabolism of levodopa. *Clin Pharmacol Ther* 1972; **13:** 149.
3. Leon AS, Spiegel HE. The effect of antacid administration on the absorption and metabolism of levodopa. *J Clin Pharmacol* 1972; **12:** 263–7.

ANTIEMETICS. *Metoclopramide* is a dopamine antagonist and may cause extrapyramidal symptoms including parkinsonism; however, it accelerates gastric emptying and has been reported[1] to increase the rate of levodopa absorption. The importance of timing has been noted[2] since levodopa delays gastric emptying and metoclopramide antagonises this effect. Licensed product information advises caution when using metoclopramide with levodopa. *Domperidone* has been reported to increase the bioavailability of levodopa slightly.[3]

1. Morris JGL, *et al.* Plasma dopa concentrations after different preparations of levodopa in normal subjects. *Br J Clin Pharmacol* 1976; **3:** 983–90.
2. Berkowitz DM, McCallum RW. Interaction of levodopa and metoclopramide on gastric emptying. *Clin Pharmacol Ther* 1980; **27:** 414–20.
3. Shindler JS, *et al.* Domperidone and levodopa in Parkinson's disease. *Br J Clin Pharmacol* 1984; **18:** 959–62.

PROKINETICS. Maximum plasma concentrations of levodopa are increased by *cisapride*.[1]

See also Metoclopramide and Domperidone, under Antiemetics, above.

1. Neira WD, *et al.* The effects of cisapride on plasma -dopa levels and the clinical response in Parkinson's disease. *Mov Disord* 1995; **10:** 66–70.

General anaesthetics. The general anaesthetics *cyclopropane* and *halothane* lower the threshold for ventricular arrhythmias to sympathomimetic amines, including dopamine, and should probably not be used within 6 to 8 hours of levodopa.[1,2] Although other general anaesthetics are now usually preferred, it was suggested that, in any case, levodopa could safely be taken before surgery when given with a peripheral dopa-decarboxylase inhibitor.[3]

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* 1971; **12:** 376–82.
2. Bianchine JR, Sunyapridakul L. Interactions between levodopa and other drugs: significance in the treatment of Parkinson's disease. *Drugs* 1973; **6:** 364–88.
3. Anonymous. Surgery and long-term medication. *Drug Ther Bull* 1984; **22:** 73–6.

Nutritional agents. ***AMINO ACIDS.*** The transport of levodopa into the brain is subject to competition from chemically related L-amino acids, especially the other aromatic amino acids *phenylalanine*, *tyrosine*, *tryptophan*, and *histidine*.[1] A high-protein diet or the large neutral amino acids phenylalanine, *leucine*, or *isoleucine* have been shown to reduce the therapeutic effect of levodopa given by intravenous infusion to parkinsonian patients; such alterations in the absorption and transport of levodopa may contribute to the fluctuating responses seen in Parkinson's disease, the so-called 'on-off' phenomenon[2] (see also Parkinsonism, p.791). In contrast, a study in healthy subjects[3] found that while a low-protein meal appeared to cause a small reduction in levodopa absorption, a high-protein meal had no such effect. Other reported interactions with amino acids include *methionine*-antagonism of the therapeutic effect of levodopa in parkinsonism[4] and *tryptophan*-reduced blood concentrations of levodopa.[5]

1. Daniel PM, *et al.* Do changes in blood levels of other aromatic aminoacids influence levodopa therapy? *Lancet* 1976; **i:** 95.
2. Nutt JG, *et al.* The "on-off" phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med* 1984; **310:** 483–8.
3. Robertson DRC, *et al.* The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. *Br J Clin Pharmacol* 1991; **31:** 413–17.
4. Pearce LA, Waterbury LD. L-methionine: a possible levodopa antagonist. *Neurology* 1974; **24:** 640–1.
5. Weitbrecht W-U, Weigel K. Der Einfluß von -Tryptophan auf die -Dopa-Resorption. *Dtsch Med Wochenschr* 1976; **101:** 20–2.

IRON SALTS. Levodopa forms complexes with iron salts and ferrous sulfate has reduced bioavailability of levodopa by about 50% in healthy subjects.[1] Giving *ferrous sulfate* to 9 patients with Parkinson's disease receiving levodopa with carbidopa reduced the area under the curve for levodopa by 30%; the reduction was greater than 75% for carbidopa. Although this was associated with deterioration in some patients' disability, the average reduction in efficacy of therapy did not achieve statistical significance.[2]

1. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* 1991; **31:** 251–5.
2. Campbell NRC, *et al.* Sinemet-ferrous sulphate interaction in patients with Parkinson's disease. *Br J Clin Pharmacol* 1990; **30:** 599–605.

PYRIDOXINE. The enzyme responsible for the decarboxylation of levodopa, L-amino acid decarboxylase, is dependent on pyridoxine and pyridoxine supplements have been reported to enhance the peripheral metabolism of levodopa to dopamine leaving less available to cross the blood-brain barrier for central conversion to dopamine;[1-4] pyridoxine therefore inhibits the action of levodopa but this can be stopped by use of a peripheral dopa-decarboxylase inhibitor.[3,4]

1. Carter AB. Pyridoxine and parkinsonism. *BMJ* 1973; **4:** 236.
2. Leon AS, *et al.* Pyridoxine antagonism of levodopa in parkinsonism. *JAMA* 1971; **218:** 1924–7.
3. Cotzias GC, Papavasiliou PS. Blocking the negative effects of pyridoxine on patients receiving levodopa. *JAMA* 1971; **215:** 1504–5.
4. Yahr MD, Duvoisin RC. Pyridoxine, levodopa, and -α-methyldopa hydrazine regimen in parkinsonism. *JAMA* 1971; **216:** 2141.

Papaverine. Antagonism of the beneficial effects of levodopa in parkinsonism has been reported when patients were also given papaverine,[1,2] and it was recommended that the combination should be avoided. However, a later study[3] in 9 patients receiving levodopa with a peripheral dopa-decarboxylase inhibitor found no changes in the control of Parkinson's disease when they were also given papaverine for 3 weeks.

1. Duvoisin RC. Antagonism of levodopa by papaverine. *JAMA* 1975; **231:** 845.
2. Posner DM. Antagonism of levodopa by papaverine. *JAMA* 1975; **233:** 768.
3. Montastruc JL, *et al.* Does papaverine interact with levodopa in Parkinson's disease? *Ann Neurol* 1987; **22:** 558–9.

Penicillamine. Isolated case reports suggest that penicillamine increases plasma-levodopa concentrations.[1]

1. Mizuta E, *et al.* Effect of -penicillamine on pharmacokinetics of levodopa in Parkinson's disease. *Clin Neuropharmacol* 1993; **16:** 448–50.

Sympathomimetics. It has been suggested that sympathomimetics such as *adrenaline* or *isoprenaline* may enhance the cardiac adverse effects of levodopa.[1]

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* 1971; **12:** 376–82.

Pharmacokinetics

Levodopa is rapidly absorbed from the gastrointestinal tract by an active transport system. Most absorption takes place in the small intestine; absorption is very limited from the stomach, and since decarboxylation may take place in the stomach wall, delays in gastric emptying may reduce the amount of levodopa available for absorption. Peak plasma concentrations are achieved within 2 hours of oral doses. Levodopa is about 10 to 30% bound to plasma proteins.

Levodopa is rapidly decarboxylated by the enzyme aromatic L-amino acid decarboxylase, mostly in the gut, liver, and kidney, to dopamine, which is metabolised in turn, principally to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Other routes of metabolism include *O*-methylation, transamination, and oxidation, producing a variety of minor metabolites including noradrenaline and 3-*O*-methyldopa; the latter may accumulate in the CNS due to its relatively long half-life. The elimination half-life of levodopa itself is reported to be about 30 to 60 minutes.

Unlike dopamine, levodopa is actively transported across the blood-brain barrier, but because of the extent of peripheral decarboxylation very little is available to enter the CNS unless it is given with a peripheral dopa-decarboxylase inhibitor. In the presence of a peripheral dopa-decarboxylase inhibitor the major route of metabolism of levodopa becomes the formation of 3-*O*-methyldopa by the enzyme catechol-*O*-methyltransferase.

About 80% of an oral dose of levodopa is excreted in the urine within 24 hours, mainly as dihydroxyphenylacetic and homovanillic acids. Only small amounts of levodopa are excreted unchanged in the faeces.

Levodopa crosses the placenta and is distributed into breast milk.

◊ General references.

1. Nutt JG, Fellman JH. Pharmacokinetics of levodopa. *Clin Neuropharmacol* 1984; **7:** 35–49.
2. Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. *Clin Pharmacokinet* 1987; **13:** 141–78.
3. Robertson DRC, *et al.* The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa. *Br J Clin Pharmacol* 1989; **28:** 61–9.
4. Robertson DRC, *et al.* The influence of levodopa on gastric emptying in man. *Br J Clin Pharmacol* 1990; **29:** 47–53.

Uses and Administration

Levodopa, a naturally occurring amino acid, is the immediate precursor of the neurotransmitter dopamine. The actions of levodopa are mainly those of dopamine (p.1273).

Unlike dopamine, levodopa readily enters the CNS and is used in the treatment of conditions, such as Parkinson's disease, that are associated with depletion of dopamine in the brain. Levodopa is rapidly decarboxylated by peripheral enzymes so that very little unchanged drug is available to cross the blood-brain barrier for central conversion into dopamine. Consequently, levodopa is usually given with a peripheral dopa-decarboxylase inhibitor such as benserazide (p.796) or carbidopa (p.803) to increase the proportion of levodopa that can enter the brain. This enables the dosage of levodopa to be reduced and may diminish peripheral adverse effects, such as nausea and vomiting and cardiac arrhythmias, by blocking the peripheral production of dopamine. It may also provide a more rapid response at the start of therapy.

The majority of patients with Parkinson's disease benefit from levodopa therapy, but after 2 years or more, improvement in disability is gradually lost as the disease progresses and fluctuations in mobility emerge. Postencephalitic parkinsonism responds to levodopa, but a higher incidence of adverse effects has been reported than in the idiopathic form so smaller doses are generally used. Levodopa has also been used to control the neurological symptoms of chronic manganese poisoning, which resemble those of parkinsonism. It should not be used in antipsychotic-induced parkinsonism.

Levodopa has an effect on pituitary function as a result of its conversion to dopamine. It may enhance growth hormone secretion and has been used diagnostically as a provocative test for growth hormone deficiency. Levodopa also inhibits prolactin secretion.

Response to levodopa varies considerably between patients. **Treatment of parkinsonism** should begin with small doses increased gradually, ideally to a dose that improves mobility without producing adverse effects. Levodopa should be taken with or after meals, although in later disease, it may be preferable to take it on an empty stomach (see Precautions, above). Once established, maintenance doses may need to be re-

duced as the patient ages. When given **without a peripheral dopa-decarboxylase inhibitor** (which is rare) a suggested initial oral dose is 125 mg twice daily increased gradually every 3 to 7 days, according to response, to up to 8 g daily in divided doses. The intervals between doses should be adjusted to meet individual needs; many patients find 4 or 5 divided doses daily to be satisfactory although some may require smaller, more frequent doses in order to control fluctuations in mobility. Maximum improvement may take up to 6 months or longer to occur.

When given **with a peripheral dopa-decarboxylase inhibitor** lower doses of levodopa are used. As high central dopamine concentrations can be achieved more quickly, both beneficial and adverse effects tend to occur more rapidly than with levodopa alone and patients should be monitored carefully. In those already receiving levodopa the drug should be stopped and benserazide or carbidopa with levodopa started on the next day or after 24 hours if the patient was receiving a modified-release preparation of levodopa.

Benserazide is given as the hydrochloride but doses are expressed in terms of the base. Benserazide hydrochloride 28.5 mg is equivalent to about 25 mg of benserazide. Benserazide is usually given with levodopa in the ratio of 1 part of benserazide base to 4 parts of levodopa (co-beneldopa) and the doses for co-beneldopa that follow are expressed in terms of the levodopa component.

- An initial oral dose for *patients not previously treated with levodopa* is levodopa 50 mg three or four times daily increased gradually in increments of levodopa 100 mg once or twice weekly, according to response. If the disease is at an advanced stage, the initial starting dose may be increased to levodopa 100 mg three times daily. For some elderly patients, an initial dose of levodopa 50 mg once or twice daily, increased by 50 mg every third or fourth day, may be suitable. Maintenance doses usually lie within the range of levodopa 400 to 800 mg daily in divided doses, although most patients require no more than 600 mg daily. If optimal improvement has not been achieved after several weeks at the average dose, further increases may be made with caution; it is rarely necessary to give more than 1 g of levodopa daily.
- The initial dose of levodopa given with benserazide in *patients previously treated with levodopa alone* should be about 10 to 15% of the dose previously being taken, thus levodopa 300 mg would be appropriate for a patient previously taking levodopa 2 g daily. For *patients previously treated with other levodopa/dopa-decarboxylase inhibitor combinations* an initial dose is levodopa 50 mg given three or four times daily. In either situation, the dose may then be adjusted in a similar manner as described for previously untreated patients.
- Modified-release capsules containing the equivalent of benserazide 25 mg with levodopa 100 mg are available to reduce fluctuations in response to immediate-release preparations. For *patients not already receiving levodopa* the initial dose is one capsule three times daily adjusted every 2 to 3 days according to response; it is recommended that initial dosages should not exceed 600 mg of levodopa daily. For *patients already receiving an immediate-release preparation* of levodopa with benserazide, initially one capsule should be substituted for every 100 mg of levodopa and should be given at the same dosage frequency as before; increases in dosage can then be made every 2 to 3 days according to response. An average of 50% more levodopa may be required compared with previous therapy and titration may take up to 4 weeks. *Supplementary doses* of an immediate-release preparation of benserazide with levodopa may also be required with the first morning dose.

Carbidopa is usually given with levodopa (co-careldopa) as tablets in the ratio of 1 to 4 or 1 to 10, which allows dosage adjustments of either drug for individual patients. Carbidopa is given as the hydrous base although doses are expressed in terms of the anhydrous base; hydrous carbidopa 10.8 mg is equivalent to about 10 mg of anhydrous carbidopa. Full inhibition of peripheral dopa-decarboxylase is reported to be achieved with 70 to 100 mg of carbidopa daily.

- A suggested initial oral dose for *patients not previously treated with levodopa* is carbidopa 25 mg with levodopa 100 mg three times daily, increased gradually, in increments of carbidopa 12.5 mg with levodopa 50 mg or carbidopa 25 mg with levodopa 100 mg every day or on alternate days, as necessary. The usual maintenance dosage range is carbidopa 75 to 200 mg with levodopa 750 mg to 2 g daily in divided doses. Carbidopa doses greater than 200 mg daily are not generally exceeded.
- The initial dose of levodopa with carbidopa in *patients previously treated with levodopa alone* should be about 20 to 25% of the dose previously being taken, thus for patients taking less than 1.5 g of levodopa daily a suggested initial dose is carbidopa 25 mg with levodopa 100 mg given three or four times daily; a suggested initial dose for patients taking more than 1.5 g of levodopa daily is carbidopa 25 mg with levodopa 250 mg given three or four times daily. For *patients previously treated with other levodopa/dopa-decarboxylase inhibitor combinations* an initial dose should provide a similar daily amount of levodopa.
- Modified-release tablets containing carbidopa with levodopa in the ratio of 1 to 4 are available to reduce fluctuations in response to immediate-release preparations. For *patients not already receiving levodopa* therapy, or for *those currently receiving levodopa alone*, the initial dose is carbidopa 50 mg with levodopa 200 mg twice daily, adjusted according to response, at intervals of not less than 3 days. It is recommended that for patients who are not already receiving levodopa initial dosages should not exceed 600 mg of levodopa daily. For *patients already receiving an immediate-release preparation* of carbidopa with levodopa, the initial dose of the modified-release preparation should provide a similar daily amount of levodopa, but the dosing intervals should be prolonged and are normally between 4 to 12 hours. The initial substitution dose of the modified-release preparation should provide no greater than 10% more levodopa than was previously given for doses of levodopa exceeding 900 mg daily. Doses and intervals may then be altered according to clinical response, allowing at least 3 days between adjustments. Up to 30% more levodopa may be required in the modified-release preparation than was previously given in the immediate-release preparation. Average maintenance doses of modified-release preparations lie within the range of carbidopa 100 mg with levodopa 400 mg to carbidopa 400 mg with levodopa 1.6 g daily in divided doses. *Supplementary doses* of an immediate-release preparation of carbidopa with levodopa may be required in some patients.

Combination preparations of levodopa with carbidopa and the catechol-*O*-methyltransferase (COMT) inhibitor **entacapone** are also available; each tablet contains levodopa and carbidopa in a ratio of 4 to 1 with entacapone 200 mg. Such preparations are indicated for patients with end-of-dose motor fluctuations not stabilised on levodopa/peripheral dopa-decarboxylase inhibitor treatment. Patients should only take one combination tablet for each dose.

- *Patients previously treated with an immediate-release preparation of levodopa with a peripheral dopa-decarboxylase inhibitor and separate entacapone* should be transferred to the combination preparation at a dose that provides similar or slightly higher amounts of levodopa.
- For *patients not currently taking entacapone*, the dose of the combination preparation should normally provide a similar or slightly lower dose of levodopa to that previously taken. However, patients with *dyskinesia* or taking *levodopa in doses above 800 mg daily* should start entacapone as a separate medication before being transferred to the combination preparation, as a 10 to 30% reduction in their levodopa dose may be needed when starting combination therapy, especially if levodopa is being given with benserazide.

In some countries a gel formulation of levodopa 20 mg/mL with carbidopa 5 mg/mL is available for continuous infusion by an ambulatory pump into the duodenum. It is indicated for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations when other available combination therapy has not been satisfactory. A positive test of the clinical response via a temporary nasoduodenal tube is required before a permanent tube is inserted into the duodenum or upper jejunum. The total daily dose comprises of 3 individually-adjusted doses, which are expressed in terms of the levodopa component as follows:

- the *morning bolus dose*, based on the patient's previous morning intake of levodopa, is usually 100 to 200 mg infused over 10 to 30 minutes and should not exceed 300 mg
- the *continuous maintenance dose*, based on the patient's previous daily intake of levodopa, is usually 40 to 120 mg/hour infused over 16 hours, adjustable in steps of 2 mg/hour to within a range of 20 to 200 mg/hour; higher doses may be needed in exceptional cases
- *extra bolus doses*, given when required, are usually between 10 to 40 mg/hour although higher doses may be needed in exceptional cases; the maintenance dose should be increased if more than 5 bolus doses are needed daily

After the initial dose setting, further dose adjustments should be made over a few weeks. If medically justified, it may be administered during the night.

Melevodopa, the methyl ester of levodopa, has been used orally as the hydrochloride with carbidopa in some countries for parkinsonism. The ethyl ester of levodopa, etilevodopa, is under study.

Administration. A small crossover study involving 24 patients with severe Parkinson's disease found that intraduodenal infusion of a levodopa and carbidopa gel preparation for 3 weeks was clinically superior to individually optimised conventional regimens.[1] Long-term experience (up to 7 years) in a limited number of patients has suggested that intraduodenal infusion is a good alternative for those with advanced disease and disabling motor fluctuations.[2] A gel formulation of levodopa 20 mg/mL with carbidopa 5 mg/mL is available in some countries for intraduodenal infusion.

1. Nyholm D, *et al.* Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; **64:** 216–23.
2. Nilsson D, *et al.* Duodenal levodopa infusion in Parkinson's disease: long-term experience. *Acta Neurol Scand* 2001; **104:** 343–8.

Drug-induced extrapyramidal disorders. The management of drug-induced extrapyramidal disorders is discussed under the Adverse Effects of Chlorpromazine on p.971. Although the use of dopamine agonists, especially levodopa, to overcome antipsychotic-induced blockade of dopamine receptors might appear rational, levodopa has generally been reported to be ineffective or to increase psychiatric symptoms.

Dysphagia. Results of a small study[1] have suggested that levodopa may improve the impaired swallowing reflex in patients with basal ganglia infarctions and thereby help to prevent aspiration pneumonia.

1. Kobayashi H, *et al.* Levodopa and swallowing reflex. *Lancet* 1996; **348:** 1320–1.

Dystonias. A dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures; it may also have additional myoclonic or tremulous components. Typically it starts as a focal dystonia localised in one part of the body and to begin with may appear only during a specific motor act (action dystonia). If the syn-

drome is progressive the dystonias may become apparent at rest and spread first to more than one part of the body (segmental dystonia) and may eventually affect most or all of the body (generalised dystonia). Progression of the dystonia appears to be related to age of onset. Dystonia beginning in childhood usually starts in the legs and progresses to become segmental or generalised, whereas in adults the dystonia usually starts in other parts of the body and rarely becomes generalised. Examples of focal dystonias are blepharospasm (affecting the eye and surrounding facial muscles), writer's cramp (hand and arm), spasmodic torticollis (neck), spasmodic dysphonia, or dystonic dysphagia (larynx or pharynx), and leg dystonias. Some dystonias may be associated with metabolic disorders such as Wilson's disease or Lesch-Nyhan syndrome; with neurological disorders such as Huntington's disease; or with other causes including head trauma, manganese or carbon disulfide toxicity, or the adverse effects of antipsychotics or antiparkinsonian drugs. However, in the majority of cases the disease is idiopathic.

There are no cures for most types of dystonia, but with appropriate **management** symptomatic relief is possible in many patients.[1-5]

- It has been suggested that all children and adolescents presenting with dystonia, particularly starting in the legs, should first be given a trial with *levodopa*.[1,3,5] Although not licensed for children in the UK, the *BNFC* states that children aged 3 months and older with dopamine-sensitive dystonias, including dystonic cerebral palsy, may be given 250 micrograms/kg of levodopa (with carbidopa in the ratio of 4 to 1) two to three times daily increased according to response every 2 to 3 days to a maximum of 1 mg/kg of levodopa three times daily. Another suggested regimen is to gradually build up to a dose of levodopa 200 mg with carbidopa 50 mg given three times daily and to maintain this dose for 3 months; if there is no useful response in this period the drug is withdrawn.[1] Where there is benefit it is usually dramatic and is sustained as long as the drug is taken, which may be more than 10 years in some cases, in general without the long-term problems associated with levodopa for parkinsonism (see p.791).
- In children and adolescents who fail to respond to levodopa an *antimuscarinic* such as trihexyphenidyl is second choice; the *BNFC* also suggests using benzatropine or procyclidine. Adverse effects are minimised by starting with a low dose which is then gradually increased. General experience indicates that about half of all children and adolescents benefit from antimuscarinics; adults tolerate the drug less well and only about a fifth of adult patients with focal dystonia benefit.
- In patients who do not respond to levodopa or high-dose antimuscarinics other drugs may be used. Many benefit from *benzodiazepines* such as diazepam; a few have responded to *baclofen* or *carbamazepine*. *Antipsychotics* are sometimes useful but carry the risk of inducing tardive dyskinesia. *Tetrabenazine* carries less risk of tardive dyskinesia but may induce depression. In very severe dystonia combination therapy may be required: tetrabenazine with pimozide and trihexyphenidyl is sometimes effective.
- In patients refractory to oral therapy *intrathecal* baclofen, or surgery may be tried.
- The response in patients with adult onset focal dystonia is usually poor. However, the use of *botulinum A toxin* can produce relief in blepharospasm, spasmodic torticollis, and spasmodic dysphonia, and is under investigation for writer's cramp and other occupational dystonias. In some patients with generalised and segmental dystonia, botulinum A toxin injected into the most disabling or painful muscles has been used as adjunctive therapy. Local injections into the affected muscles produce weakness over the next week or so, thereby reducing or abolishing dystonic spasms. The effect lasts some 2 to 4 months. *Botulinum B toxin* has also been used in the management of spasmodic torticollis.

Further details of the management of blepharospasm and spasmodic torticollis can be found under Botulinum Toxins on p.1891. For a discussion of the management of antipsychotic-induced dystonic reactions, see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p.971.

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.
2. Williams A. Consensus statement for the management of focal dystonias. *Br J Hosp Med* 1993; **50:** 655–9.
3. Bressman SB. Dystonia update. *Clin Neuropharmacol* 2000; **23:** 239–51.
4. Tarsy D, Simon DK. Dystonia. *N Engl J Med* 2006; **355:** 818–29.
5. Jankovic J. Treatment of dystonia. *Lancet Neurol* 2006; **5:** 864–72.

Hepatic encephalopathy. For the view that the evidence does not support the use of dopaminergics such as levodopa in the management of hepatic encephalopathy see p.1697.

Neuroleptic malignant syndrome. There have been isolated reports[1-4] that levodopa used alone or with bromocriptine has been successful in the treatment of patients with neuroleptic malignant syndrome (p.972). However, bromocriptine is usually preferred when a dopaminergic is required for the treatment of this condition.

1. Knezevic W, *et al.* Neuroleptic malignant syndrome. *Med J Aust* 1984; **140:** 28–30.
2. Clarke CE, *et al.* Clinical spectrum of neuroleptic malignant syndrome. *Lancet* 1988; **ii:** 969–70.
3. Lo TCN, *et al.* Neuroleptic malignant syndrome: another medical cause of acute abdomen. *Postgrad Med J* 1989; **65:** 653–5.
4. Shoop SA, Cernek PK. Carbidopa/levodopa in the treatment of neuroleptic malignant syndrome. *Ann Pharmacother* 1997; **31:** 119.

Parkinsonism. Levodopa is the mainstay in the treatment of Parkinson's disease (p.791) but opinion varies on when it should be used in the course of the disease. Most patients respond to levodopa initially but after a few years benefit may be reduced. There may be problems with dyskinesias and psychiatric effects and fluctuations in mobility necessitating careful dosage adjustment or the use of adjunctive drugs. 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. Levodopa should be given with a peripheral dopa-decarboxylase inhibitor; a peripheral catechol-*O*-methyltransferase (COMT) inhibitor may also be necessary for patients experiencing fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations. The various methods used for the pharmacokinetic optimisation of levodopa therapy as Parkinson's disease progresses include timing of doses, the use of modified-release formulations, oral solutions (but see Stability, p.804) and dispersible formulations for immediate absorption, the timing of food intake, and the use of other drugs to increase the absorption of levodopa. In some countries a gel formulation of levodopa with carbidopa is available for intraduodenal infusion.

References.

1. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.
2. Contin M, *et al.* Pharmacokinetic optimisation in the treatment of Parkinson's disease. *Clin Pharmacokinet* 1996; **30:** 463–81.
3. Murer MG, *et al.* Levodopa in Parkinson's disease: neurotoxicity issue laid to rest? *Drug Safety* 1999; **21:** 339–52.
4. Furlanut M, *et al.* Monitoring of L-dopa concentrations in Parkinson's disease. *Pharmacol Res* 2001; **43:** 423–7. Correction. *ibid.*; **44:** 149.
5. Carlsson A. Treatment of Parkinson's with L-DOPA: the early discovery phase, and a comment on current problems. *J Neural Transm* 2002; **109:** 777–87.
6. Katzenschlager R, Lees AJ. Treatment of Parkinson's disease: levodopa as the first choice. *J Neurol* 2002; **249** (suppl 2): II19–II24.
7. van Laar T. Levodopa-induced response fluctuations in patients with Parkinson's disease: strategies for management. *CNS Drugs* 2003; **17:** 475–89.
8. LeWitt PA, Nyholm D. New developments in levodopa therapy. *Neurology* 2004; **62** (suppl 1): S9–S16.
9. Stocchi F, Olanow CW. Continuous dopaminergic stimulation in early and advanced Parkinson's disease. *Neurology* 2004; **62** (suppl 1): S56–S63.
10. Nyholm D, *et al.* Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; **64:** 216–23.

Pituitary and hypothalamic disorders. ***DIAGNOSIS AND TESTING.*** Diminished growth hormone reserve is one of the earliest functional abnormalities in anterior pituitary failure and, since dopamine is believed to stimulate growth hormone secretion, levodopa has been used as a provocative test for the diagnosis of growth hormone deficiency.[1,2] Levodopa 500 mg has been given orally after an overnight fast and serum concentrations of growth hormone measured hourly at 0 to 3 hours; children may be given 10 mg/kg to a maximum of 500 mg. Transient nausea, vomiting, vertigo, and hypotension may occur and the patient should be kept recumbent during the test. A normal response is an increase in serum concentration of growth hormone of more than 5 nanograms/mL or to a level of more than 10 nanograms/mL, although 10 to 15% of normal subjects may not respond. However, there is some dispute as to whether stimulated growth hormone secretion tests are superior to measurements of circulating somatomedins in detecting growth hormone deficiency.[3-5] For a discussion of the management of growth retardation, including the problems of accurate diagnosis, see p.1798.

1. Abboud CF. Laboratory diagnosis of hypopituitarism. *Mayo Clin Proc* 1986; **61:** 35–48.
2. Müller EE, *et al.* Involvement of brain catecholamines and acetylcholine in growth hormone deficiency states: pathophysiological, diagnostic and therapeutic implications. *Drugs* 1991; **41:** 161–77.
3. Hoffmann DM, *et al.* Diagnosis of growth-hormone deficiency in adults. *Lancet* 1994; **343:** 1064–8. Correction. *ibid.*, **344:** 206.
4. de Boer H, *et al.* Diagnosis of growth hormone deficiency in adults. *Lancet* 1994; **343:** 1645–6.
5. Rosenfeld RG, *et al.* Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. *J Clin Endocrinol Metab* 1995; **80:** 1532–40.

Sleep-associated movement disorders. The aetiology of *restless legs syndrome* and *periodic limb movements in sleep* is obscure and treatment has been largely empirical (p.958). Few of the treatments tried in these often co-existent disorders have been studied in a controlled manner but small controlled studies[1-6] have reported beneficial effects such as improved sleep quality and reduced leg movements from levodopa used with a peripheral dopa-decarboxylase inhibitor. Most patients received a bedtime dose of 50 to 200 mg of levodopa with possible additional doses during the night. A 1-year open-label extension study[7] confirmed the continued efficacy and safety of levodopa in patients with restless legs syndrome; the authors recommended a maximum daily dose of 400 mg levodopa to decrease the risk of exacerbation or rebound symptoms during the day. However, long-acting dopaminergic agonists are preferred in order to avoid the complications associated with levodopa.

Levodopa has also been reported to have been of benefit in a study of 10 patients with *sleep bruxism*.[8]

1. von Scheele C. Levodopa in restless legs. *Lancet* 1986; **ii:** 426–7.
2. Brodeur C, *et al.* Treatment of restless legs syndrome and periodic movements during sleep with -dopa: a double-blind controlled study. *Neurology* 1988; **38:** 1845–8.
3. Kaplan PW, *et al.* A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep* 1993; **16:** 717–23.
4. Trenkwalder C, *et al.* L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind crossover trial. *Sleep* 1995; **18:** 681–8.
5. Beneš H, *et al.* Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. *Sleep* 1999; **22:** 1073–81.
6. Janzen L, *et al.* An overview of levodopa in the management of restless legs syndrome in a dialysis population: pharmacokinetics, clinical trials, and complications of therapy. *Ann Pharmacother* 1999; **33:** 86–92.
7. Trenkwalder C, *et al.* One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? *Mov Disord* 2003; **18:** 1184–9.
8. Lobbezoo F, *et al.* The effect of the catecholamine precursor -dopa on sleep bruxism: a controlled clinical trial. *Mov Disord* 1997; **12:** 73–8.

Strabismus. Experimental studies have shown that centrally acting drugs such as levodopa may improve vision in patients with amblyopia (see Strabismus, p.1874). However, their role in clinical practice remains to be established.[1]

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; **2:** 91–100.

Tourette's syndrome. Levodopa has been studied in the management of Tourette's syndrome (see Tics, p.954). A small pilot study[1] has produced encouraging results.

1. Black KJ, *et al.* Response to levodopa challenge in Tourette syndrome. *Mov Disord* 2000; **15:** 1194–8.

Preparations

BP 2008: Co-beneldopa Capsules; Co-careldopa Tablets; Dispersible Co-beneldopa Tablets; Levodopa Capsules; Levodopa Tablets;
USP 31: Carbidopa and Levodopa Tablets; Levodopa Capsules; Levodopa Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Prikap; ***Ger.:*** Dopaflex; Restex; ***Hung.:*** Dopaflex†; ***India:*** Levopa†; ***Ital.:*** Levomet†; ***Jpn:*** Dopar‖; ***Pol.:*** Nakom; ***USA:*** Dopar†; Larodopa†.

Multi-ingredient: ***Arg.:*** Lebocar; Lecarge; Madopar; Nervocur; Parkinel; Sinemet; Stalevo; ***Austral.:*** Kinson; Madopar; Sinemet; Stalevo; ***Austria:*** Dopamed; Levobens; Levocar; Madopar; Restex; Sinemet; ***Belg.:*** Prolopa; Sinemet; Stalevo; ***Braz.:*** Carbidol; Cronomet; Duodopa; Levocarb; Parkidopa; Parklen; Prolopa; Sinemet; Stalevo; ***Canad.:*** Apo-Levocarb; Novo-Levocarbidopa; Nu-Levocarb; Prolopa; Sinemet; ***Chile:*** Grifoparkin; Levofamil†; Melitase; Prolopa; Protonis; Saniter Compuesto; Sinemet; Stalevo; ***Cz.:*** Dopalux; Duodopa; Isicom; Lecardop; Madopar; Nakom; Sinemet; Stalevo; ***Denm.:*** Duodopa; Madopar; Sinemet; Stalevo; ***Fin.:*** Kardopal; Madopar; Sinemet; Stalevo; ***Fr.:*** Duodopa; Modopar; Sinemet; Stalevo; ***Ger.:*** Dopadura C; Isicom; Levo-C; Levobeta C; Levocarb; Levocomp; Levodop; Levodopa Comp; Levodopa comp B; Levodopa comp C; Levodopa-Carbi†; Levopar; Madopar; Nacom; NeyDop N (Revitorgan-Dilutionen N Nr 97)†; PK-Levo; Stalevo; Striaton; Tremopar†; ***Gr.:*** Madopar; Sinemet; Sinemet-CR; Stalevo; Zimox; ***Hong Kong:*** Apo-Levocarb; Levomed; Levomet; Madopar; Sinedopa; Sinemet; Stalevo; ***Hung.:*** Duellin; Madopar; Sinemet; Stalevo; ***India:*** Levopa-C†; Syndopa; ***Indon.:*** Leparson; Levazide; Levopar; Madopar; Pardoz; Stalevo; ***Irl.:*** Half Sinemet; Madopar; Sinemet; Stalevo; ***Israel:*** Dopicar; Levopar Plus; Sinemet; Stalevo; ***Ital.:*** Duodopa; Madopar; Sinemet; Sirio; Stalevo; ***Malaysia:*** Apo-Levocarb; Levomed; Madopar; Sinemet; Stalevo; ***Mex.:*** Cloisone; Lemdopa; Madopar; Racovel; Sinemet; Stalevo; Ternovag; ***Neth.:*** Duodopa; Madopar; Modopar; Sinemet; Stalevo; ***Norw.:*** Duodopa; Madopar; Sinemet; Stalevo; ***NZ:*** Apo-Levocarb; Madopar; Sindopa; Sinemet; ***Philipp.:*** Ledocar; Madopar; Sinemet; Stalev; Tidomet; ***Pol.:*** Madopar; Sinemet; Stalevo; ***Port.:*** Duodopa; Ledopsan; Madopar; Sinemet; Stalevo; ***Rus.:*** Duellin (Дуэллин); Madopar (Мадопар); Nakom (Наком); Stalevo (Сталево); Syndopa (Синдопа); Tidomet (Тидомет); Tremonorm (Тремонорм); ***S.Afr.:*** Carbilev; Madopar; Sinemet; ***Singapore:*** Cardopar; Levomet; Madopar; Sinemet; Stalevo; Tidomet; ***Spain:*** Duodopa; Ledopsan; Madopar; Sinemet; Stalevo; ***Swed.:*** Duodopa; Madopark; Sinemet; Stalevo; ***Switz.:*** Madopar; Sinemet; Stalevo; ***Thai.:*** Cenparkin†; Levomed†; Levomet; Madopar; Sinemet; Stalevo; Syndopa; Vopar; ***Turk.:*** Madopar; Sinemet; Stalevo; ***UK:*** Duodopa; Half Sinemet; Madopar; Sinemet; Stalevo; Tilolec†; ***USA:*** Atamet; Parcopa; Sinemet; Stalevo; ***Venez.:*** Madopar; Sinemet; Stalevo.

Lisuride Maleate *(BANM, rINNM)*

Lisurid Maleat; Lisuride, Maléate de; Lisuridi Hydrogenomaleas; Lisuridi Maleas; Lisuridivetymaleaatti; Lisuridvätemaleat; Lysuride Maleate; Maleato de lisurida; Methylergol Carbamide Maleate. 3-(9,10-Didehydro-6-methylergolin-8α-yl)-1,1-diethylurea hydrogen maleate; 8-Decarboxamido-8-(3,3-diethylureido)-D-lysergamide maleate.

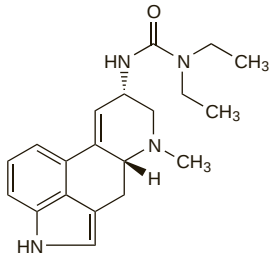
Лизурида Малеат

$C_{20}H_{26}N_4O,C_4H_4O_4$ = 454.5.

CAS — 18016-80-3 (lisuride); 19875-60-6 (lisuride maleate).

ATC — G02CB02; N02CA07.

ATC Vet — QG02CB02; QN02CA07.



(lisuride)

Adverse Effects and Precautions

As for Bromocriptine, p.798. Infusion of lisuride in parkinsonian patients has been associated with severe psychiatric adverse effects.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including lisuride, see under Adverse Effects of Levodopa, p.805.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including lisuride, see under Adverse Effects of Bromocriptine, p.799.

Porphyria. Lisuride maleate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

As for Bromocriptine, p.800.

Pharmacokinetics

◊ Plasma concentrations varied widely after a single oral dose of lisuride maleate 300 micrograms in 11 patients with Parkinson's disease.[1] Absorption was rapid and the mean plasma elimination half-life was 2.2 hours. Only a mean of 0.05% of the dose was excreted unchanged in the urine in 24 hours. The mean oral bioavailability of lisuride maleate has been reported[2] to be 10% after a 100-microgram dose and 22% after a 300-microgram dose.

A single dose of lisuride 25 micrograms given by intravenous, intramuscular, or subcutaneous injection reduced plasma-prolactin concentrations by up to 60% in 11 of 12 healthy subjects, the effect lasting for about 10 hours.[3] Plasma-lisuride concentrations after intravenous injection fell in 2 phases with half-lives of 14 minutes and 1.5 hours, respectively. Peak plasma concentrations after subcutaneous and intramuscular injection were obtained after 12 and 15 minutes, respectively.

1. Burns RS, *et al*. Disposition of oral lisuride in Parkinson's disease. *Clin Pharmacol Ther* 1984; **35:** 548–56.
2. Hümpel M, *et al*. Radioimmunoassay of plasma lisuride in man following intravenous and oral administration of lisuride hydrogen maleate; effect on plasma prolactin level. *Eur J Clin Pharmacol* 1981; **20:** 47–51.
3. Krause W, *et al*. The pharmacokinetics and pharmacodynamics of lisuride in healthy volunteers after intravenous, intramuscular, and subcutaneous injection. *Eur J Clin Pharmacol* 1991; **40:** 399–403.

Uses and Administration

Lisuride maleate, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p.798). It is also reported to have serotonergic activity. It is used similarly in the management of Parkinson's disease and has been used in disorders associated with hyperprolactinaemia. It is also used to suppress puerperal lactation for medical reasons; it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that can be adequately relieved with simple analgesics and breast support. Lisuride has been used in some countries for the treatment of acromegaly, and for the prophylaxis of migraine.

In the management of **Parkinson's disease** lisuride maleate has been given alone or added to treatment in patients having 'on-off' fluctuations in control with levodopa. It is normally given orally; doses should be taken with food. Initially 200 micrograms is taken at bedtime and additional doses of 200 micrograms may be added, at intervals of one week, first at midday and then in the morning. Further increases are made, until an optimum response is obtained, by adding 200 micrograms each week using the same sequence of increases, starting with the bedtime dose; dosage should not normally exceed 5 mg daily in divided doses.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p.1798). While bromocriptine has been the main dopamine agonist used, lisuride has been used in some countries, typically in a dose of 100 micrograms three times daily.

Hyperprolactinaemia and prolactinomas. Dopamine agonists have been widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p.2079). Lisuride has been used as an alternative to bromocriptine. There is a report of plasma-prolactin concentrations being reduced to normal in 4 female patients with macroprolactinomas given lisuride 400 to 800 micrograms daily for 2 years.[1] Subsequent dosage reduction in 3 was followed by a rise in prolactin values. In the fourth patient prolactin remained in the normal range when the dose was progressively reduced from 400 to 50 micrograms daily, although complete withdrawal was followed by an increase in prolactin concentration within 3 months.

Vaginal dosage of lisuride has been studied in an attempt to avoid adverse effects associated with oral therapy. In a study[2] involving 40 women with hyperprolactinaemia a 200-microgram standard oral tablet placed in the vagina at night produced a similar reduction in prolactin concentrations to that obtained with 400 micrograms taken orally and was better tolerated.

1. Liuzzi A, *et al*. Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. *N Engl J Med* 1985; **313:** 656–9.
2. Tasdemir M, *et al*. Vaginal lisuride for hyperprolactinaemia. *Lancet* 1995; **346:** 1362.

Lactation inhibition. Lisuride is used in some countries for the prevention of puerperal lactation (p.2003). However, the routine use of dopaminergics is not recommended for the suppression of physiological lactation.

References.

1. Venturini PL, *et al*. Effects of lisuride and bromocriptine on inhibition of lactation and on serum prolactin levels: comparative double-blind study. *Eur J Obstet Gynecol Reprod Biol* 1981; **11:** 395–400.

Mastalgia. In a small placebo-controlled study,[1] lisuride 200 micrograms daily was effective in the treatment of cyclical mastalgia. However, since mastalgia (p.2092) can improve spontaneously, treatment should rarely be considered unless pain has been present for about 6 months.

1. Kaleli S, *et al*. Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study. *Fertil Steril* 2001; **75:** 718–23.

Migraine. Although lisuride has been used in some countries for the prophylaxis of migraine (p.616) it is not usually considered to be the drug of choice or even one of the main alternatives.

Parkinsonism. While some neurologists use dopamine agonists such as lisuride early in the treatment of parkinsonism (p.791) in an attempt to delay therapy with levodopa, others reserve them for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. They are sometimes useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations in mobility in the later stages of the disease.

References.

1. Rinne UK. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. *Neurology* 1989; **39:** 336–9.
2. Clarke CE, Speller JM. Lisuride for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
3. Clarke CE, Speller JM. Lisuride versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
4. Allain H, *et al.* Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. *Eur Neurol* 2000; **44:** 22–30.

ADMINISTRATION. Lisuride has been of benefit when given by continuous intravenous or subcutaneous infusion in patients having fluctuations in mobility with levodopa therapy[1-4] but severe psychiatric effects have been associated with the use of these routes.[3] Transdermal lisuride is also being investigated for the treatment of Parkinson's disease and restless legs syndrome.[5,6]

1. Obeso JA, *et al.* Intravenous lisuride corrects oscillations of motor performance in Parkinson's disease. *Ann Neurol* 1986; **19:** 31–5.
2. Obeso JA, *et al*. Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. *Lancet* 1986; **i:** 467–70.
3. Critchley P, *et al.* Psychosis and the lisuride pump. *Lancet* 1986; **i:** 349.
4. Stocchi F, *et al.* Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. *Brain* 2002; **125:** 2058–66.
5. Woitalla D, *et al.* Transdermal lisuride delivery in the treatment of Parkinson's disease. *J Neural Transm Suppl* 2004; **68:** 89–95.
6. Benes H. Transdermal lisuride: short-term efficacy and tolerability study in patients with severe restless legs syndrome. *Sleep Med* 2006; **7:** 31–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dopagon†; ***Austria:*** Dopergin; Prolacam†; ***Fr.:*** Arolac; Dopergine; ***Ger.:*** Cuvalit†; Dopergin; ***Gr.:*** Dipergon; ***Ital.:*** Dopergin; ***Mex.:*** Dopergin; ***Neth.:*** Dopergin; ***NZ:*** Dopergin; ***Spain:*** Dopergin; ***Switz.:*** Dopergin†; ***Thai.:*** Dopergin†; ***Turk.:*** Dopergin.

Metixene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de metixeno; Methixene Hydrochloride *(USAN)*; Methixene Hydrochloride Monohydrate; Metikseenihydrokloridi; Metikseno hidrochloridas; Métixène, chlorhydrate de; Metixén-hidroklorid; Metixen-hydrochlorid monohydrát; Metixenhydroklorid; Metixeni hydrochloridum; Metixeni Hydrochloridum Monohydricum; NSC-78194; SJ-1977. (*RS*)-9-(1-Methyl-3-piperidylmethyl)thioxanthene hydrochloride monohydrate.

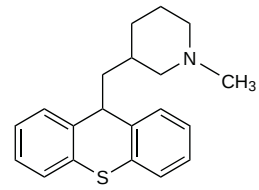
Метиксена Гидрохлорид

$C_{20}H_{23}NS,HCl,H_2O$ = 363.9.

CAS — 4969-02-2 (metixene); 1553-34-0 (anhydrous metixene hydrochloride); 7081-40-5 (metixene hydrochloride monohydrate).

ATC — N04AA03.

ATC Vet — QN04AA03.



(metixene)

Pharmacopoeias. In *Eur.* (see p.vii)

Ph. Eur. 6.2 (Metixene Hydrochloride). A white or almost white, crystalline or fine crystalline powder. Soluble in water, in alcohol, and in dichloromethane. A 1.8% solution in water has a pH of 4.4 to 5.8. Protect from light.

Profile

Metixene hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p.1219); it also has antihistaminic and direct antispasmodic properties.

It is used for the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. The usual oral dose of metixene hydrochloride is 2.5 mg three times daily initially, gradually increased according to response to a total of 15 to 60 mg daily in divided doses.

Metixene hydrochloride has also been used in preparations to relieve gastrointestinal spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Tremarit; ***Hung.:*** Tremaril; ***Ital.:*** Tremaril; ***Swed.:*** Tremoquil†.

Multi-ingredient: ***Philipp.:*** Spasmo-Canulase; ***Port.:*** Espasmo Canulase; ***S.Afr.:*** Spasmo-Canulase; ***Switz.:*** Spasmo-Canulase.