

Essential Drugs

Parkinsonism

Parkinson's disease results from focal degeneration of dopaminergic neurones within the striatal system of the brain. This leads to progressive neurological impairment characterized by tremor, muscle rigidity and dyskinesias progressing to akinesia. The cause of the disease, which occurs worldwide, is unknown. It is rare in persons under 45 years of age, but more than 1% of those over 60 are probably affected. Patients usually first notice tremor in a hand at rest and, within 5 years, disabling rigidity results in many becoming bedridden. Speech and swallowing become difficult. Seborrhoeic dermatitis and intercurrent infections are often troublesome. Depression is common, memory is frequently impaired and, ultimately, confusion and dementia may occur. The psychogenic changes often result as much from drug therapy as from the degenerative process.

Less frequently, signs of parkinsonism are a consequence of more diffuse brain damage caused by encephalitis, arteriosclerosis, tumours, diseases of metabolism or degenerative conditions. More selective damage to striatal pathways has been reported following exposure to toxic chemicals, notably — among drug addicts — to methyl-phenyl-tetrahydropyridine (MPTP), a by-product of illicit pethidine production. Acute and transient striatal dysfunction is also sometimes induced by the normal use of prescribed drugs, particularly reserpine, phenothiazines and butyrophenones, which reversibly deplete stores of dopamine or otherwise block dopaminergic transmission. These signs often remit if dosage is reduced, and — provided exposure to the drug has not been prolonged — they resolve within a few weeks once it is withdrawn.

General Management

Underlying disorders should always be sought and treated. Physical exercise, physiotherapy, psychotherapy and speech therapy are each of value as the disease progresses. Supportive attitudes within the family can be of critical importance, but depression may need specific treatment.

Pharmacotherapy

Acute parkinsonism

Anticholinergic drugs such as trihexyphenidyl and biperiden offer relief in acute drug-induced parkinsonism and — to a lesser degree — in the early stages of the chronic disease, presumably by attenuating the disproportion between dopaminergic and cholinergic activity in the basal ganglia. However, the adverse effects that result from cholinergic inhibition can be severe and sometimes dangerous in elderly patients.

Chronic parkinsonism

The ultimate need is to stimulate dopaminergic activity in the striatal system, but drugs are generally first used only when symptoms compromise working capacity and social relationships. It is possible, however, that recently-developed dopaminergic agents may enable treatment to be started, with advantage, during the initial stages of the disease.

Close supervision and frequent adjustments of treatment regimens are required at all stages of the disease to ensure that the prescribed drugs are safely tolerated and that appropriate changes are made as the patient's condition deteriorates.

Levodopa/carbidopa

Levodopa is the physiological precursor of dopamine. Unlike dopamine, it diffuses freely across the blood-brain barrier. It thus repletes stores of dopamine in the central nervous system when administered orally. Taken alone, however, its central effect is attenuated because it is also extensively transformed to dopamine outside the central nervous system. It is more effective if administered together with a decarboxylase inhibitor, either carbidopa or benserazide, that does not cross the blood-brain barrier. This inhibits the peripheral transformation of levodopa which is conserved to pass in greater quantities into the cerebrospinal fluid.

Within a few years of starting treatment the response to levodopa/carbidopa fluctuates, becoming either progressively attenuated or

unpredictably erratic. Dose-related adverse effects including dyskinesias, mental changes, disruption of the sleep cycle, vivid dreams and hallucinations also frequently become troublesome. Amelioration of these effects can sometimes be achieved by administering levodopa in a sustained-release preparation or in a greater number of fractionated doses throughout the day. It has also been suggested that the emergence of these effects might be delayed by postponing treatment with levodopa for as long as is practicable, but this is disputed.

Supplementary dopaminergic drugs

Bromocriptine, which directly stimulates post-synaptic dopamine receptors, and selegiline, a monoamine oxidase B-inhibitor, have been used both to potentiate the effect of levodopa and to permit dosage to be reduced below the threshold at which adverse effects begin to become troublesome. Unfortunately, used in this way, these drugs are unlikely to delay the progression of the disease by more than a few months. Initial reports, however, suggest that administration of selegiline in the earlier phases of the disease may postpone the need for levodopa treatment for at least one year. Further studies are required before firm recommendations can be made on whether newly-diagnosed patients should be started on selegiline rather than low doses of levodopa.

Ultimately all treatment fails, either as a result of progressive loss of dopaminergic neurones or from overstimulation of dopamine receptors. In these circumstances, sudden complete withdrawal of levodopa/carbidopa to restore dopamine receptor sensitivity and subsequent readministration at lower dosage is all that can be offered. This is sometimes temporarily beneficial, but it should only be attempted in hospitalized patients since the inevitable initial intense akinetic reaction during the withdrawal period is potentially lethal.

Other treatment

Surgery has no place in the routine treatment of parkinsonism. Thalamotomy, which became largely obsolescent with the introduction of levodopa, is now reserved for occasional young patients with tremor that is predominantly unilateral and that is resistant to drug treatment. Intraatrial transplants of adrenal or fetal tissue remain investigational techniques.

Levodopa/carbidopa

tablet, 100 mg + 10 mg, 250 mg + 25 mg

Levodopa is metabolized by carboxylase enzymes to dopamine. This conversion is inhibited by carbidopa. However, levodopa penetrates the blood-brain barrier, whereas carbidopa does not. Concurrent administration of the two compounds thus prevents peripheral decarboxylation of levodopa and increases its availability to the central nervous system where its enzymatic conversion to dopamine proceeds unimpaired.

Uses

Treatment of all forms of parkinsonism, except acute, drug-induced cases.

Dosage

Initial dose: 100 mg levodopa + 10 mg carbidopa twice daily increasing, as necessary, by increments of 100 mg + 10 mg every two days to a maximum of 2000 mg levodopa + 200 mg carbidopa daily. The optimum maintenance dose must be determined by careful clinical monitoring.

Contraindications

Known hypersensitivity to levodopa or carbidopa. Patients receiving monoamine oxidase inhibitors. Narrow angle glaucoma. Confirmed or suspected malignant melanoma.

Precautions

All treated patients should remain under close supervision. Particular attention should be accorded to possible mental changes and to cardiac conductivity in patients with atrial, nodal or ventricular dysrhythmias, or with a history of myocardial infarction.

Use in pregnancy

Levodopa/carbidopa is teratogenic in animals. Women of child-bearing age should be treated only when the needs of the mother outweigh the risk to the fetus.

Adverse effects

Nausea, anorexia and vomiting are sometimes troublesome at the outset of treatment, particularly when a large starting dose is used or when dosage is rapidly augmented. This is thought to be caused

by the action of dopamine on the area postrema, which lies outside the blood-brain barrier. Symptoms can sometimes be reduced by administration after meals but, if they are persistent, a peripheral dopamine antagonist, such as domperidone, can be helpful. Metoclopramide and other centrally acting antiemetics should not be used.

Postural hypotension may also occur at the outset of treatment, particularly in elderly patients and those receiving antihypertensive drugs. The mechanism of this effect is unknown. Levodopa, which is a precursor of dopamine and norepinephrine, has also occasionally caused hypertension. It is for this reason that monoamine oxidase inhibitors are contraindicated during dopaminergic therapy.

Cardiac dysrhythmias of various types are common in elderly patients but, except in patients with pre-existing conduction disorders, they rarely present a serious risk.

Levodopa dilates the pupil and for this reason it is contraindicated in narrow angle glaucoma.

Psychiatric and neurological disturbances are the most frequent dose-limiting adverse effects. Neuroleptic therapy should be avoided. About half of all patients treated complain at some time of vivid dreams, hallucinations or delusions. Psychotic symptoms and confusional states are less common.

Mild intermittent dyskinesias which occur within a few months of starting treatment often respond to reduction or fractionation of dosage. Later in the course of the disease, dosage reduction is increasingly likely to result in akinesia.

Painful dystonic spasms and short episodes of akinesia, tremor and rigidity lasting from a few minutes to several hours are characteristic of the later phases of treatment.

Severe generalized dyskinesias are seldom drug-induced and are most likely to occur in patients who have received high dosages over prolonged periods. Sudden withdrawal in these circumstances has resulted in neuroleptic malignant syndrome.

Drug interactions

The effectiveness of levodopa may be impaired by phenothiazines, thioxanthenes, rauwolfia alkaloids, phenytoin and metoclopramide.

Overdosage

Emesis or gastric lavage is of value if undertaken within a few hours of ingestion. Otherwise, management is dependent on general supportive measures.

Storage

Levodopa/carbidopa tablets should be stored in tightly closed containers protected from light.

BIPERIDEN

tablet 2 mg (hydrochloride)

Biperiden is a synthetic, tertiary amine with central and peripheral cholinergic blocking effects. Benztropine, procyclidine and trihexyphenidyl which are also frequently used in this context, are similar in their pharmacological actions.

Biperiden is readily absorbed from the gastrointestinal tract and is excreted in the urine largely unchanged.

Uses

Treatment of parkinsonism induced by drugs and as adjunctive treatment for all other forms of the condition.

Dosage

Initially 2 mg three times daily or 2–4 mg once daily up to a maximum of 16 mg daily depending on response and tolerance.

Contraindications

Known hypersensitivity to biperiden.
Narrow angle glaucoma.
Obstructive uropathy.
Myasthenia gravis.

Precautions

Elderly patients are highly susceptible to the dose-related adverse effects of anticholinergics. Therapy should always be withdrawn gradually to avoid rebound deterioration.

Patients should be warned that their ability to drive or operate machinery may be impaired.

Patients with cardiac dysrhythmias, congestive cardiac failure or coronary heart disease need particularly close supervision since they are at risk of atrioventricular block due to vagal stimulation of the sinoatrial node.

Adverse effects

Drowsiness, dry mouth, constipation, blurred vision, postural hypotension and hesitancy of micturition are common, but dose-related adverse effects diminish as tolerance develops.

Urinary retention, glaucoma, dizziness, tachycardia and dysrhythmias may also occur.

Psychiatric disturbances ranging from mild impairment of recent memory to acute confusional states can be particularly difficult to manage and are most likely to occur in elderly patients.

Drug interactions

An additive effect is sometimes apparent when other compounds with anticholinergic properties,

such as tricyclic antidepressants, antihistamines, disopiramide and terodiline, are used concomitantly.

Overdosage

Gross overdosage results in acute stimulation followed by depression of the central nervous system. Signs of acute psychosis and hypersensitivity to external stimuli may be followed by circulatory collapse, hypotension and coma. Death can result from respiratory failure. Treatment is symptomatic and supportive. Mechanically-assisted respiration may be vital.

Storage

Biperiden tablets should be stored in well-closed containers.