Drug treatment in Parkinson’s disease

The new drugs that have become available for treating Parkinson’s disease in the past 20 years have given encouraging results, but many problems remain unsolved. Attention to general measures throughout the illness is as important as ever. We need to encourage physical activity, regular walks, and positive attitudes to counter the malignant apathy which threatens independence, both at work and at home. Personal attention and support are probably as effective as formal physiotherapy and speech therapy in most circumstances. Drugs, however, remain the linchpin of treatment.

At the earliest stage, when signs and disability are minimal, the wisest policy is to withhold drugs and to observe progress. If rigidity, slowness, and tremor become a nuisance anticholinergic drugs such as benzhexol or orphenadrine may be prescribed; these are generally well tolerated, though occasional troublesome side effects may occur including a dry mouth, urinary hesitancy, and glaucoma. Since they deplete the basal nucleus of Meiner and cholinergic neurones known to be affected in dementia, which may occur later in the illness, many physicians withdraw these drugs as the disease advances.

Anticholinergic drugs eventually fail to modify symptoms, and amantadine 100 mg twice a day is then worth a trial (as an addition or an alternative) before levodopa compounds are introduced. Amantadine has the advantages of a standard dose, few side effects, and conferring benefit within a few days. Unfortunately 30-40% of patients fail to maintain this benefit for more than two months, but in those who do the 20-30% improvement in symptoms and disability scores is worth while.

Usually within two to three years of diagnosis bradykinesia, rigidity, stumbling, and falling cause increasing disability that jeopardises the patient’s work. At this juncture dopamine replacement is necessary. Those favouring postponement of levodopa until this stage argue that with time it saturates the brain and forms neurotoxic metabolites (for example, 6-hydroxydopamine) and may contribute to dementia. A former fashion favoured treatment at the time of diagnosis, claiming that replacing the missing neurotransmitter would reverse changes in the postsynaptic neurone responsible for the later fluctuating “on-off” responses. Experimental and clinical evidence remains equivocal, but most experienced clinicians now start a levodopa decarboxylase inhibitor compound (Sinemet or Madopar) at a stage of threatened rather than established disability.

More than three out of four patients are restored to near normal activities with this regimen. A lack of response should arouse the suspicion that the patient is not taking the tablets; that pyridoxine (possibly unrecognized in a tonic) or phenothiazines are interacting; or that the diagnosis is incorrect and the patient has striatogniral degeneration, olivopontocerebellar atrophy, Shy-Drager syndrome, or progressive supranuclear palsy.

After six years of levodopa, however, half the patients fail to maintain benefit or cannot tolerate the drug’s side effects. Half of the remainder still obtain substantial or moderate benefit, and survival is enhanced to almost normal life expectancy in this group.

The toxic effects of levodopa comprise a succession of motor and psychiatric phenomena—“end of dose wearing off,” early morning akinesia, and peak dose dyskinesia. Later, random on-off attacks unrelated to individual doses and painful dystonic cramps of foot or hand may supervene. The most distressing and incapacitating side effects are psychiatric. Depression occurs in half of all patients given levodopa and is best controlled by tricyclic antidepressants. Nightmares and hallucinations are early symptoms of levodopa intolerance; at first these respond to reduction or altered timing of treatment. Daytime agitation and confusion may supervene and merge into a chronic psychosis and ultimately to dementia. Without doubt many of these mental symptoms are due to levodopa acting on an aging brain with concomitant cerebral atrophy in many instances. The contribution of levodopa to dementia is less certain, but since suspicion remains the dose should be kept to the minimum necessary to produce worthwhile improvement of function.

In an attempt to bypass the degenerating nigrostriatal receptor site dopamine agonists were introduced. Bromocriptine, an ergot derivative, stimulates dopamine receptors and has an antiparkinsonian action comparable with levodopa. Its plasma half life is about five hours. The toxic...
effects are similar to those of levodopa, but psychosis is more severe and may be more protracted despite withdrawal of the drug. When levodopa fails to control symptoms adding bromocriptine may allow a modest reduction of the dose of levodopa and produce an appreciable benefit in some patients. Intolerance, however, is not predictable—nor is it necessarily related to dosage.

Pergolide is another potent, long acting postsynaptic dopamine agonist.11 Like bromocriptine it is not effective in patients with primary levodopa failure, but about half the patients with on-off oscillations will derive benefit. Lisuride, a drug with similar potency to bromocriptine, reduces the off phase of on-off swings.16 The toxicity of these three ergot derivatives is similar, and they remain valuable in extending the useful period of active treatment when the benefits of levodopa are waning or the patient's fluctuating performance is causing problems. The suggestion that low doses of bromocriptine should be given early in the disease in place of levodopa has not yet been substantiated and is not recommended. All of these ergot derivatives should be used with extreme caution in the elderly.

A recent, different approach has become possible with 1-deprenyl, a relatively specific inhibitor of monoamine oxidase-B which is claimed to have a selective stimulant action on the dopaminergic system.17 A dose of 5-10 mg a day appears to have a weak potentiating action on levodopa. Used alone the antiparkinsonian action of 1-deprenyl is weak but it may be a mild stimulant of the amphetamine type. Its present place appears to be as an adjuvant in selective cases of advancing resistant disease.

At all stages we should aim to confine treatment to no more than two drugs at a time; these should be frequently reviewed with an eye to timing, duration of benefit, and side effects. Hourly charts of symptoms, activity, and side effects recorded by skilled observers throughout the day may allow fine adjustment and lead to new and useful strategies. Even at a late stage is is often surprising how much improvement results from a short period of hospital admission, simplification of treatment, and attention to detail in the domestic arrangements and mental attitudes to the patient's management.

J M S PEARCE

Consultant Neurologist,
Hull Royal Infirmary,
Hull HU3 2JZ


Parallel imports: a pharmacist's viewpoint

The use of parallel imports is said to be unfair to patients, unfair to the DHSS (since extra profit is generated for pharmacists using these products), and unfair to prescribers. In this article the term parallel imports refers only to medicines manufactured in Britain, exported to a community country where there is a cost differential with the domestic price in Britain, and then reimported. I do not intend to deal with products manufactured in European Economic Community countries and imported to Britain or indeed with counterfeit products, although some of the following remarks may well be applicable in these cases.

Current concern has arisen because of exploitation for commercial reasons of the Medicines (Exemption from Licences) (Importation) Order 1978 (SI 1978/1641)—an exemption intended to apply “in circumstances in which small quantities of medicinal products are imported into Britain, for the purpose of treatment of particular patients.”

Certainly parallel importing of medicines may cause several problems. Patients may be confused—for example, by minor differences in the colour or shape of the product. If, faulty, products may be more difficult to recall to the manufacturer. The product may not have been stored and transported under optimum conditions—so that checks for quality control should be carried out on arrival in Britain. On the other hand, Mr Kenneth Clarke, the Minister of Health, has confirmed that all labelling particulars must be in English; this will mean relabelling by the parallel importer.1 The Pharmaceutical Society Council has published a statement that “any pharmacist who dispenses a medicine not having all requisite information in English, would be guilty of unprofessional conduct.”2

Clearly the issue of parallel imports is of great concern to the profession of pharmacy. Only a few pharmacists are dispensing these medicines, and, though there is little evidence of unsatisfactory products being used, the potential risks are grave. Several suggestions have been put forward for control of the practice, such as a register of pharmacists who do not participate in parallel importing. This suggestion has been rejected on the grounds that it may contravene European Economic Community regulations. Another is that pharmacists should endorse prescriptions (but again this is not favoured because of problems with trade barriers and the Treaty of Rome). A further idea is that parallel importers should be required to notify the DHSS at regular intervals of the names of customers supplied and the quantities.

On the positive side some pharmacies are displaying notices stating: “Important Notice. This pharmacy does not dispense parallel imported medicines.” At least one health authority has warned chemist contractors that, in certain circumstances, they may be in breach of their terms of service by supplying parallel imports on NHS prescriptions.

The national press has given this subject wide coverage, much of it inaccurate, but some points warrant comment. The Price Regulation Scheme operated more tightly in other European Economic Community countries, thus creating this “opportunity.” The market for parallel imports may be around £120m a year. The government may refuse to reimburse contractors at the present rate, thus forcing more to correct the balance by resorting to parallel imports, with a consequent lowering of standards. The pharmaceutical companies may be able to obtain price increases for other products—that is, those not being parallelly imported—so that the DHSS...