THE MANAGEMENT OF IDIOPATHIC PARKINSON'S DISEASE

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INTRODUCTION

The management of patients with idiopathic Parkinson's Disease can be both rewarding and exasperating. Patients vary in their response to treatment and also deteriorate as the years progress. Parkinson's disease is, however, unique in being a neurodegenerative disease which responds to drug therapy sometimes quite dramatically. It is common, with a prevalence of 1.5 per thousand in the general population, and 19 per thousand in the population over 85[1].

The diagnosis of Parkinson's disease is a clinical one and is often best made by watching the patient walk. One can get used to how a patient looks and behaves and it is often a person seeing the patient for the first time who makes the diagnosis. Remember Parkinson's disease when screening elderly patients, as it is common, does not need any fancy tests, and is treatable. In elderly patients the diagnosis is often delayed, particularly in those with bradykinesia as the main feature, as the patient and their carer may accept that their problems are part of ageing.

PATHOLOGY AND PHYSIOLOGY

The neuropathological criteria for the diagnosis hinge on the presence of multiple specific intraneuronal inclusion bodies (Lewy bodies) and the loss of at least 60% of the neuromelanin containing nerve cells of the substantia nigra. Dopamine depletion occurs in all cases of Parkinson's disease and symptoms do not normally appear until the loss of 80% of dopamine production. Dopamine and acetylcholine operate as antagonistic transmitters in the corpus striatum. The reduction of dopaminergic function in Parkinsonism disturbs the normal balance.

EPIDEMIOLOGY

The epidemiology of idiopathic Parkinson's disease is of interest to both doctors and patients. Ten to 15% of patients have relatives similarly affected but twin studies demonstrate that simple Mendelian inheritance is unlikely[2]. Some people are probably much more susceptible to environmental toxins than others and it is likely that Parkinson's disease is multi-factorial. Parkinson's disease occurring at a young age has a positive association with living the first two decades of life in areas with vegetable farming, wood pulping mills, and drinking well water[3,4]. The indigenous population served by the Kendal and Lancaster hospitals have frequently been exposed to such activities although the paper mills in Kendal and Beetham buy in pulp rather than processing it on site, and therefore produce less chemical pollution than pulping mills. There is a negative association with smoking as in Alzheimer's disease.

The interest in environmental toxins was fuelled by the discovery that syndromes similar to Parkinson's disease could be induced by methylphenyltetra-hydropyridine (MPTP) given intravenously or inhaled[5]. Primates seem to be particularly sensitive to MPTP especially with increasing age. The MPTP is metabolised to methylphenylpyridinium (MPP) which is the active toxin and the metabolism to MPP can be blocked by a monamine oxidase B inhibitor such as selegiline. However, MPTP is not the whole story as it does not produce Lewy bodies which are classically found in Parkinson's disease. The search for environmental toxins goes on and also the ability to predict which people are more sensitive to the toxins and might benefit from prophylactic treatment with drugs such as selegiline.

CLINICAL FEATURES AND DIAGNOSIS

The features necessary to make a diagnosis of Parkinson's disease are listed in Table 1. **Bradykinesia** is the most disabling part of the disease and it may be the least obvious to the untrained observer. There is slowness in the initiation and execution of voluntary motor activity and a poverty of automatic and associated movements, and it may be unilateral initially. Bradykinesia is responsible for many of the symptoms and signs listed in Table 2. **Tremor** can frequently be the presenting complaint as it seems much more noticeable than the other problems. It usually affects distal muscles and is often unilateral. It is usually present at rest and made worse by nervousness, tiredness or excitement. Involuntary movement may momentarily inhibit the tremor. The patient presenting with tremor confined to the head has probably not got the disease. Parkinson's disease should not be diagnosed in patients presenting with tremor in the absence of rigidity or bradykinesia. **Rigidity** is common and may be unilateral. It often occurs in the musculature of the neck producing the characteristic flexed posture. **Postural immobility with impaired righting reflexes** is the cause of falls which are a frequent presenting feature.

The diagnosis of Parkinson's disease is best made by looking at the patient at rest and noting any tremor and the appearance of their face, and then by asking them to get up

BRADYKINESIA and at least one of the following:-

1. Coarse (4-8 cycles/sec) resting tremor of limbs
2. Muscular rigidity (cogwheel or lead pipe)
3. Postural immobility with impaired righting reflexes (not due to primary sensory deficits).

Table 1. The Diagnosis of Parkinson's Disease

out of a chair to assess their general posture and walking ability. Patients frequently have difficulty getting up and tend to freeze when they get to obstacles such as furniture, changes in floor covering, or doorways, and they also have difficulty turning. Rocking the patient gently from side to side between two people may well abolish the freezing and allow the patient to walk on. Patients can learn to "get going" by rocking back on their heels and some count to maintain their walking speed or pretend to step over objects. Patients frequently find it easier to climb stairs or step over things than to walk normally.

Unexplained falls
Lack of facial expression
Difficulty turning round
Hesitation + "stuttering" at obstacles
Difficulty rolling in bed
Monotonous/quiet voice
Difficulty eating
Stooped posture
Dribbling
General and mental slowness
Rest tremor
Constipation
Weight loss

Table 2. Signs and Symptoms of Parkinson's Disease

Some people present with symptoms other than immobility, such as constipation. This is related to reduced mobility and may be aggravated if a patient has already been diagnosed as Parkinsonian and given anticholingeric drugs. Weight loss is probably due to a combination of difficulty eating, due to the flexed posture, and increased energy requirements which have been found in patients with Parkinson's disease. Dribbling of saliva is not due to an increase in saliva production but due to the immobility of the facial muscles and should improve with treatment. Dementia has an increased incidence in Parkinson's disease but is rare in young patients[6].

MANAGEMENT OF THE DISEASE

The diagnosis of Parkinson's disease comes as a great blow to patients and their families. It is important to approach the situation with optimism and explain that the disease is treatable. Many people choose to join the Parkinson's Disease Society which provides information and has local support groups both in Kendal and Lancaster (Table 3).

Physiotherapy should be combined with drug treatment. The aim is to improve the patient's mobility and give them tips which will help them to improve their walking, such as counting or pretending to step over things, and it will also increase their muscle strength which may have deteriorated considerably prior to the diagnosis being made.

Occupational therapy helps patients to regain independence and cope with activities of daily living which they may find difficult, in particular dressing and cooking. The therapist can also advise about equipment and adaptations which will be helpful at home. In patients with advanced disease the occupational therapist will be able to advise about aids for eating and drinking, which may become difficult. A Pat Saunders' straw which has a non-return valve is helpful for patients with a very flexed posture who need to use a straw but cannot suck hard enough to get fluid into their mouth with one suck.

The Speech Therapist can advise the patient how to increase their voice volume and also help with general communication tips. Communication aids are occasionally required in advanced disease.

The Dietitian may be needed to advise on a high calorie diet to increase weight if the patient has increased energy requirements, particularly if they have very severe tremor or rigidity. Low protein diets may be required to avoid competition of neutral amino acids with levodopa absorption both in the gut and for entry into the brain.

The Social Worker can support the patient and carer, providing counselling and practical help within the home, and advise about benefits and allowances such as disability living allowance and attendance allowance. Help with applications for housing or residential care may be required in advanced disease.

A multidisciplinary approach to a patient is important as frequently the therapist as well as the patient's carer can highlight problem areas and fluctuations in a patient's ability which may be amenable to changes in treatment.

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Parkinson's Disease Society Kendal Branch Monica Tarring Coat Faw Dent Nr Sedbergh LA10 7RQ Tel: 05875 252
Parkinson's Disease Society Lancaster Branch Anne Brotheridge 18 Covedale Road Lancaster Tel: 0524 35578

Table 3. Support Groups

DRUG TREATMENT

Patients vary greatly in their response to medication both in the early stages and later on. It is necessary to reassess the patient regularly and alter the medication, trying different doses and formulations, particularly of levodopa. There is no simple regime which suits all patients and it is important to tell the patient this at the beginning of the treatment and they can then participate in monitoring their good and bad periods, to make alteration of their drug regime as straight forward as possible. Intercurrent illnesses such as urinary tract infections can temporarily affect control of symptoms. The main groups of drugs available are listed in Table 4 and their main areas of action are shown in Figure 1.

Drug	Dosage
MAO-B Inhibitor	
Selegiline	5-10 mg in morning
Dopamine precursors	- see Table 5
Sinemet Madopar	50 mg t.d.s. - lg levodopa in divided doses
Dopamine agonists	- see Table 6
Bromocryptine	Start 1 mg nocte
Lysuride	Start 200 mcg nocte
Pergolide	Start 50 mcg nocte
Anticholinergics	
Benhexol	Start 1 mg daily. Maintenance 3-15 mg
Orphenadrine	Start 50 mg daily. Maintenance 150-400 mg
Other	
Amanatadine	100-200 mg in one or two doses

Table 4. Drug Treatment

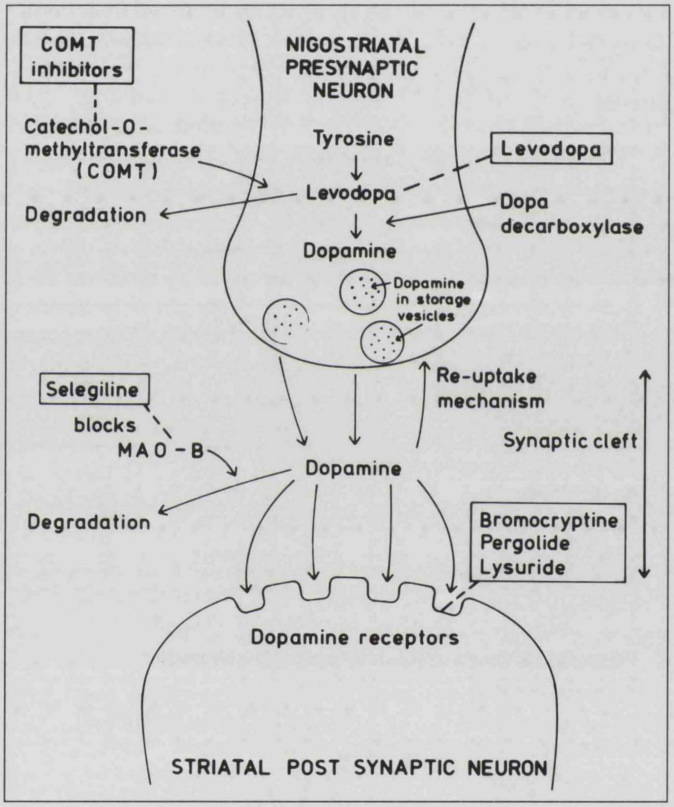

Fig 1 – Modes of action of drugs at the nigrostriatal synapse

SELEGILINE

Selegiline, an inhibitor of mono-amine oxidase B (MAOB) decreases the oxidation of dopamine and therefore conserves this transmitter. This improves symptoms and it has also been suggested that this reduces the likelihood of nigral damage by toxic free radicals and therefore delays the progression of the disease[7]. Selegiline should be given to all patients at the time of diagnosis as in early cases it can be sufficient to use selegiline and it delays the requirement for levodopa. In more advanced cases it is best to start both selegiline and levodopa simultaneously, remembering if selegiline is added to an existing levodopa regime that the dose of levodopa may need to be reduced, as selegiline can increase adverse effects.

LEVODOPA

Levodopa is a precursor of dopamine and is converted to this by the action of dopamine decarboxylase. Levodopa should always be given with a **dopa-decarboxylase inhibitor (DCI)** such as carbidopa or benserazide. They do not cross the blood brain barrier so levodopa, which enters the CNS can still be converted to dopamine in the striatum, but the conversion to dopamine at peripheral sites is slowed down, minimising the peripheral side effects and allowing more levodopa to reach the brain. Methylation of levodopa by catechol-O-methyltransferase (COMT) in the brain reduces the amount of dopamine formed. Several COMT inhibitors are being researched and in the future these should play a large part in treatment.

Levodopa/DCI is available as Sinemet and Madopar in a variety of formulations (Table 5). Madopar is produced both as a standard tablet and a dispersible one, which is helpful in those patients with swallowing difficulties and where a quick rise in dopamine levels is required. Both Sinemet and Madopar come as controlled release formulations (CR) but Madopar CR tablets contain 100 mg and Sinemet CR contains 200 mg of levodopa. Madopar and Sinemet CR give reduced and delayed peak concentrations with a prolonged plateau concentration of levodopa. This reduces peaks and troughs in the plasma concentration if it is given regularly throughout the day. Peak levels occur about one hour after the administration of standard levodopa and 2.5 hours after CR, so it is necessary to give patients standard levodopa first thing in the morning with their first CR capsule to get them going. When changing from standard tablets to controlled release medication it is usually necessary to increase the dose as the CR preparations have a reduced bio-availability of about 60%. CR capsules must be swallowed whole and the administration of antacids may decrease the absorption. They are also contra-indicated in narrow angle glaucoma.

Levodopa/DCI Combination	Levodopa	DCI
Sinemet LS	50 mg	12.5 mg
Sinemet 110	100 mg	10 mg
Sinemet Plus	100 mg	25 mg
Sinemet 275	250 mg	25 mg
Sinement CR	200 mg	50 mg
Madopar 62.5*	50 mg	12.5 mg
Madopar 125*	100 mg	25 mg
Madopar 250	200 mg	50 mg
Madopar CR	100 mg	25 mg

DCI = dopa decarboxylase inhibitor

* dispersible formulation

Table 5. Levodopa Preparations

Levodopa improves all the clinical features of Parkinsonism, particularly bradykinesia. About 30% of patients get substantial benefit and a further 30% some improvement. Some patients cannot tolerate levodopa because of adverse effects such as nausea, diarrhoea, dyskinesia or postural hypotension. Some patients, particularly elderly patients with an element of confusion, may develop hallucinations or delusions. Levodopa tends to have a minimal effect on tremor.

PROBLEMS WITH LEVODOPA

Patients on long term levodopa can develop problems and it is thought that with progression of the disease there is diminished storage capacity of the degenerating neurones to buffer fluctuating levodopa concentrations. The patient first notices a decline in the response to individual doses of treatment with unpredictable periods of **akinesia**. Some then develop **on/off phenomena** with sudden changes in their symptoms going from relative mobility to almost complete immobility due to bradykinesia. It is important to explain to carers that the patient is not being "difficult". **Dyskinesi**a in the early stages of the disease tends to be related to peak concentrations of levodopa.

In advanced disease the dyskinesias are much more closely linked to the therapeutic response so that the dose required to mobilise the patients may produce involuntary movements.

Problems of end of dose akinesia, on/off phenomena, and dyskinesias may be helped by reducing fluctuations in drug levels. This can be achieved by either giving levodopa in smaller quantities more frequently, changing to a controlled release preparation, and administering the levodopa between meals well after protein intake, to avoid competition of amino acids with levodopa for absorption and entry into the CNS. The addition of small booster doses of either dispersible or standard levodopa, or the addition of a dopamine agonist may be helpful. If a patient is not already on selegiline then this should be added.

Diphasic dyskinesias, which are usually slow repetitive movements of the limbs, tend to occur at the beginning and end of the dose and may well deteriorate using CR preparations. Patients may benefit from larger less frequent doses of standard levodopa.

DOPAMINE AGONISTS

Bromocryptine, lysuride and **pergolide** are all dopamine agonists which directly stimulate dopamine receptors. Pergolide stimulates both D1 and D2 receptors and bromocryptine and lysuride D2 receptors. The clinical relevance of these differing actions is unclear. The features and problems of these drugs are listed in Table 6. Overall the adverse effects and anti-Parkinsonian activity of the three drugs seems to be quite similar but bromocryptine is considerably cheaper. They are probably of more use in younger patients, as in the elderly confusion and hallucinations are extremely common. Monotherapy with dopamine agonists in early disease produces a satisfactory response in a small number of patients and most patients initially treated only with dopamine agonists and selegiline require the addition of levodopa after a few years. The combination of a dopamine agonist and low dose levodopa can reduce disability during long term treatment compared to levodopa alone, with fewer end of dose failures and dyskinesias. This is probably due to the slowing down of dopamine storage failure mechanisms as the dose of levodopa is smaller. In advanced disease the addition of a dopamine agonist can improve end of dose deterioration and help on/off phenomena to some extent. However, these benefits tend to wane after about two years. **Apomorphine** is a dopamine agonist used rarely because of nausea and vomiting. It is, however, useful as a subcutaneous injection or infusion in patients with severe on/off phenomenon.

OTHER DRUGS

Amantadine stimulates dopamine release but its efficacy is lost after a few months of treatment.

Anticholinergics such as benzhexol should only be used when tremor is disabling, as the problems of glaucoma, constipation, and urinary retention can be severe particularly in the elderly.

	Bromocryptine	Lysuride	Pergolide
Plasma half life	5 hours	2 hours	15-42 hours
Pharmacokinetics	– metabolised in liver – erythromycin increases drug levels – tolerance to drug reduced with alcohol	– extensive first pass metabolism in liver	– 90% protein bound – 45% metabolised by liver 55% excreted by kidneys
Levodopa reduction required	30%	30%	50%
Initial dose	1-1.25 mg nocte	200 mcg nocte	50 mcg nocte
Maintenance dose (in 3 divided doses)	3-80 mg with food	600 mcg – 4mg with food	1-4 mg with food
Contraindications	– confusion – ischaemic heart disease (at high concentrations)	– confusion	– confusion – ischaemic heart disease – peripheral vascular disease
Side effects	– pleural effusions – retroperitoneal fibrosis	– Raynauds, rashes, – headaches	– insomnia, dyspnoea, rhinitis, – tachycardia, bowel disturbance
All cause nausea, vomiting, postural hypotension, dyskinesias, drowsiness, malaise and confusion. Titrate carefully			

Table 6. Dopamine Agonists

	Initial treatment	Alternative treatment
Early Disease		
Mild symptoms	– Selegiline	
Disability	– add levodopa/DCI standard 62.5 – 125 mg tds	– Low dose levodopa and bromocryptine
	– or CR 125 mg tds + standard 62.5 mg morning	– or bromocryptine alone
Advanced Disease		
End of dose deterioration	– fractionate dose of levodopa eg six to eight times daily	– change to CR levodopa – or add bromocryptine
	– eat main meal in evening	– try lysuride or pergolide – low protein diet
Peak dose dyskinesias	– reduce or fractionate dose of levodopa	– change to CR levodopa
On-off phenomenon	– fractionate dose of levodopa or CR	– add bromocryptine, lysuride or pergolide
	– eat main meal in evening	– low protein diet and avoid food within 2 hours of medication
Diphasic dyskinesias	– change to standard from CR levodopa	– stop levodopa and start bromocryptine

Table 7. Treatment Strategies

TREATMENT STRATEGIES

Selegiline should be given to all patients at the time of diagnosis, unless the patients is confused and also has a severe disability in which case it may be better to commence levodopa in a low dose to get maximum improvement in physical symptoms first. It should be given as 5 or 10 mg in the morning as if given at night it can cause insomnia. Table 7 outlines possible strategies for drug treatment in Parkinson's disease. There is considerable debate about drug regimes. In younger people it would seem appropriate to use a dopamine agonist such as bromocryptine, either alone or with low dose levodopa/DCI, rather than levodopa/DIC alone. In elderly patients who usually become quite confused with dopamine agonists treatment with low dose levodopa/DCI would be appropriate, either using standard levodopa or CR, with a small dose of levodopa in the morning to get them going. A dopamine agonist may be required in addition to levodopa later on in treatment.

In late Parkinson's disease, when a patient is experiencing end of dose akinesia and on/off phenomena, a number of strategies can be tried and are discussed earlier and shown in Table 7. It is important to monitor the patient's fluctuations and times when they are having difficulties and keep altering the drug regime to get maximum improvement.

CONCLUSION

New drugs and different formulations of presently used drugs are appearing quite frequently and it is likely that further developments such as COMT inhibitors and possibly surgery will improve the treatment of patients with Parkinson's disease. Drug treatment and multidisciplinary assessment of the newly diagnosed patient can be initiated by the general practitioner but if there is any doubt about the diagnosis then I think the patient should be referred for a second opinion, prior to starting treatment. Occasionally a therapeutic trial of levodopa is indicated which should be done with objective assessment of the patient, usually by a physiotherapist. Those with advanced disease may require specialist advice when they are experiencing problems with their medication, perhaps after long term levodopa treatment.

Patients with Parkinson's disease are a challenge but are rewarding to treat as they can experience marked improvement in their well being and activities, whether they are young or old.

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