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Pharmacological Management of Parkinson's Disease

Robert Iansek

ABSTRACT

Parkinson's disease is an incurable neurodegenerative disease of the elderly. Although symptoms can be ameliorated by drugs, optimum management requires a multidisciplinary approach. Pharmacotherapy is usually initiated with levodopa using gradual dosage titration. Initial therapy with dopamine agonists such as cabergoline can be considered in younger patients. Cabergoline can also be used to reduce levodopa dosage in patients who develop dyskinesia. End-of-dose effects may require more frequent levodopa administration and the addition of a catechol-O-methyl transferase inhibitor such as entacapone. In mid-stage disease a degree of dyskinesia may be accepted in order to maintain movement capacity. Cabergoline can also be used for levodopa sparing. In advanced disease, fluctuations between on and off states become rapid and disabling. Levodopa dosage can be further refined with a liquid formulation and apomorphine may be used to overcome sudden off periods.

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INTRODUCTION

Parkinson's disease (PD) is the only neurodegenerative disorder for which effective symptomatic treatment exists. Parkinson's is a disease of the elderly with a maximum incidence and prevalence in the 75 to 85 year old age groups.¹ The impact of PD in this age group is greater because of their limited functional reserve and pre-existing co-morbidities. Therefore, changes in severity of symptoms will not only reflect medication effects but also co-morbidities, such as urinary tract infection. Any new complaint needs to be assessed in its own right rather than assume it is due to PD.

There is no cure for the underlying neurodegenerative basis of PD. It is a multidimensional disease and management needs to be holistic, incorporating the patient and family, utilising a multidisciplinary team and addressing both medical as well as rehabilitation issues from diagnosis to advanced disease (Table 1).

DIAGNOSIS

The newly diagnosed patient requires education and support to understand the nature of the disease and its impact on their life. The decision to initiate treatment is based on the results of regular observation of the patient and frequent discussion with the patient and family as to their particular needs and functional capacity. Controversy exists in regard to which medicine should be used. To some degree this is influenced by the patient's age at the onset of disease, co-morbidities and patient expectations.²⁻⁴

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Table 1. Progression of Parkinson's disease

Time (years)	Stage	Impairment
0	disease onset	asymptomatic
6	symptom onset	minimal
8	diagnosis	mild
10	early onset	moderate
15	end-of-dose effects	3.5-4 hours/dose
20	mid-stage	2.5-3 hours/dose 10-20 mg window slow change predictable
25	advanced	1.5-2 hours/dose 6-8 mg window sudden change unpredictable

The level of impairment is directly related to the duration of action of a single dose of levodopa, the degree of narrowing of the therapeutic window of benefit, the rapidity of change from the on to off state and the predictability of change.

The majority of patients can be started on levodopa and a decarboxylase inhibitor. The dosage schedule is three times a day usually at 5-hourly intervals starting at 50 mg twice daily, increasing by 50 mg every 4 to 5 days, up to 450 mg per day. At this dose, maximum clinical benefit may take a further month, probably through the loading of dopamine brain stores. Sometimes adjustments need to be made according to response and adverse effects. In some situations the dosage may need to be increased up to 600 or 750 mg per day or reduced to 300 mg per day. It is vital that an adequate dose of levodopa is administered for at least 4 to 6 weeks to load dopamine brain stores. Once this occurs patients are able to function without any fluctuation throughout the day. This is in contrast to a single oral dose of levodopa which has a half-life of 1.5 to 2 hours.⁵ If inadequate doses of levodopa are administered, dopamine brain stores will not be loaded adequately and patients will demonstrate fluctuations and inadequate motor response throughout the day.

Patients below 60 years of age may be initially treated with a dopamine agonist; introducing a dopamine agonist should delay the onset of motor fluctuations. However, in reaching this decision one must balance the prospect of producing an inadequate motor response and a need to add levodopa at a later stage.² The dopamine agonists (cabergoline 6 mg, pergolide 3 mg, bromocriptine 30 mg) provide half the effect of levodopa (300 mg equivalence).

Cabergoline is the most suitable because of its long half-life (>60 hours).⁶ It is administered once-daily and the benefit is seen over a 24-hour period. It is started at 1 mg daily and increased weekly by 1 mg, up to 6 to 8 mg per day. Due to its long half-life, the benefits of cabergoline may not be seen for several weeks after a target dosage

has been reached. There is a lag (2–3 weeks) between dosage attainment and maximum benefit. Overall, this process can take 3 to 4 months before the maximum benefit is seen. Non-ergot derived agonists, such as pramipexol and ropinirole are currently unavailable in Australia.

EARLY-ONSET DYSKINESIA

Rarely, some patients develop early-onset dyskinesia when levodopa is introduced. This is usually mild and may involve any body part and is not usually disruptive to the patient. This may be overcome by reducing levodopa by 25 mg per dose. Most patients are able to function with minimal dyskinesia with these minor alterations.

For patients who continue to experience dyskinesia it may be appropriate to add a dopamine agonist. Cabergoline is started at 1 mg daily and increased weekly by 1 mg, up to 4 to 6 mg per day. Due to the long lag between introducing cabergoline and development of motor benefit, patients need to reduce levodopa by the minimum amount (25 mg/dose), once they develop more dyskinesia. In this manner it is possible to maintain a constant level of benefit and exchange control of motor symptoms from levodopa over to cabergoline. Patients are eventually able to reduce their levodopa by 50 to 75% in this exchange program. Once they are stabilised on cabergoline as the predominant drug, the dyskinesia seems to settle considerably.

END-OF-DOSE EFFECTS

End-of-dose effects manifest from three to seven years after starting levodopa.⁷ The time of onset varies and is more likely to occur in younger patients at an earlier age. These symptoms signal the impending loss of the buffering capacity of dopamine storage within the neurones of the substantia nigra. This effect first manifests overnight because of the long period between the last dose and the first dose in the day. It then occurs during the day.

Initially the levodopa doses are brought closer together. When medication failure occurs, controlled-release levodopa can be administered prior to retiring at night. The bioavailability of the controlled-release dose is approximately 60% of the standard-release dose; therefore, to give an equivalent dose to the daily dose, the controlled-release dose needs to be almost doubled.⁶

Once four or five doses are administered during the day and end-of-dose effects exist, then a catechol-O-methyl transferase (COMT) inhibitor is introduced.^{8,9} Entacapone prolongs the duration of action of each levodopa dose and is introduced after the individual dose of levodopa is optimised. Entacapone is added to the first levodopa dose of the day and the patient either self monitors or is monitored for the duration of action of the drug combination. Once the dose has worn off the next dose is given in a similar combination. An estimate of duration of action is achieved after a number of doses and a dosing interval is then established. Observation over two to seven days is necessary to determine the appropriateness of the dosing schedule and reduce the likelihood of adverse effects such as dyskinesia or lack of effectiveness. Entacapone has a tendency to lose efficacy and this typically occurs within the first four weeks. It may be necessary to reduce the timing interval to try and avoid re-occurrence of end-of-dose effects. Tolcapone may be considered in those who do not respond to entacapone and is administered in a similar manner. Tolcapone has a longer half-life and is administered 6 to 8-hourly for three doses in the day. In Australia, tolcapone is available on

the Special Access Scheme, is expensive and requires regular monitoring of liver function because of rare hepatic dysfunction.¹⁰

Some patients can be refractory to entacapone and tolcapone, and are difficult to manage. One approach is to use controlled-release levodopa with entacapone. Due to the continual release of levodopa from the controlled-release preparation it is possible to extend the interval between dosing to approximately four hours. The first dose of the day is standard-release levodopa in conjunction with entacapone administered first thing in the morning as there is a lag between administration of the controlled-release levodopa and its peak effect (2–3 hours). This combination has a tendency to increase the likelihood of dyskinesia towards the end of the day because of the difficulty in optimising the dosing interval.

MID-STAGE DISEASE

At mid-stage of the disease, patients develop a shorter duration of response to levodopa (1.5–2.5 hours) which reflects the half-life of levodopa in the blood following a single dose.⁵ This implies that the storage capacity within the neurones of the substantia nigra is markedly reduced. The therapeutic window of benefit narrows and is variable (levodopa 5–10 mg). Therefore, it is difficult to enter the therapeutic window of benefit under these circumstances as the minimum amount of levodopa available in tablet form is 25 mg. This combination of responses to levodopa leads to motor fluctuations throughout the day. At mid-stage disease these are predictable and develop slowly to warn patients of an incipient change in motor state.

In this setting it is imperative to monitor patients closely in order to optimise motor control. With close monitoring it is possible to identify a dose which will enable approximation into the therapeutic window of benefit. The patient will experience some minor dyskinesia in order to be able to move reasonably well.

Attempts are then made to prolong the duration of action of each dose of levodopa by introducing a COMT inhibitor. This approach is similar to that described for the management of end-of-dose effects. In mid-stage disease the increase in duration of action of levodopa with a COMT inhibitor may only be 15 to 30 minutes.

If patients continue to experience end-of-dose effects prior to a 3-hourly interval with this combination then controlled-release levodopa and a COMT inhibitor may be trialled. It is important to be aware of the reduced bioavailability of controlled-release levodopa and to overlap the dosages because of the long levodopa plasma build-up and fall-off time from peak dose. Patients are able to tolerate 4-hourly intervals with controlled-release levodopa and a COMT inhibitor. An initial dose of standard-release levodopa is needed with the first dose to prevent the long delay of clinical effect.

As optimisation of levodopa at this stage of the disease will invariably lead to further difficulties, it is important to try and optimise control in the long term. One approach is to introduce cabergoline; the dose is increased slowly, by 0.5 or 1 mg per week, up to 6 to 8 mg per day, depending on the patient's response and adverse effects (Table 2). As cabergoline levels slowly build up, patients develop dyskinesia and this is the signal to reduce levodopa by a minimal amount for each of the doses. In this manner, over three to four months, it is possible to exchange benefit from levodopa to cabergoline. In some patients the benefits of reducing levodopa can be dramatic and those who are

Table 2. Practical use of cabergoline for levodopa sparing

Main issues
It is not as potent as levodopa. It has a long half-life (>60 hours). Clinical benefit is delayed by 2-3 weeks after dosage adjustment. Dose may need to be increased to show significant improvement.
Titration schedule
Start at 0.5 or 1 mg per day depending on patient and symptoms. Dosage may be administered after breakfast or the evening meal. Increase by the same amount every week up to 4 mg per day. Monitor for dyskinesia over a 2 to 4-week period. Decrease levodopa by 25 to 50 mg to control dyskinesia. Increase to 6 to 8 mg per day by same dose on a weekly basis. Continue to decrease levodopa according to dyskinesia for 1 month post peak dose of cabergoline.

sensitive to levodopa may be able to eliminate levodopa completely. In the long term, this approach reduces the likelihood of dyskinesia, produces a stable motor response and theoretically reduces and eliminates dyskinesia attributable to constant dopamine stimulation.

ADVANCED DISEASE

Advanced disease is characterised by a very short duration of action of levodopa with a very narrow therapeutic window of benefit (levodopa 4–6 mg). The fluctuations are unpredictable and very rapid from the on to the off state and vice versa. Because of this unpredictability, quality of life deteriorates considerably as it is difficult to predict when one would be able to function adequately or require assistance.

Advanced disease is also complicated by cognitive decline, neuropsychiatric complications to medication and non-basal ganglia disease progression and associated symptoms such as hypotension, bladder disturbance and sleep disturbance.

Optimisation of medication is similar to that described for mid-stage disease. The presence of a very narrow therapeutic window of benefit with severe dyskinesia or severe immobility requires different approaches to control symptoms. One approach is to use the liquid form of levodopa (Table 3) and the dosage is titrated during the day on an hourly basis according to need. It is possible to vary the dosages by 1 mg if necessary to enter the therapeutic window of benefit. Higher doses are required in the morning because of the long period overnight without levodopa and the dosage is then adjusted downwards during the day according to the level of dyskinesia. Because of the interaction with protein it may be necessary to increase the dose prior to mealtimes. If patients are undertaking any extra physical activity the dose will need to be increased to anticipate the increased need for levodopa.

Once this technique has been mastered, the levodopa load can be reduced by a COMT inhibitor. The sole benefit is to reduce the levodopa dosage rather than have an effect on the duration of action. In a similar manner it is possible to introduce a dopamine agonist. The dosage builds over a 3-month period so patients reduce their levodopa dose according to the level of dyskinesia that they experience.

Subcutaneous apomorphine is useful in some patients to overcome the sudden off periods that can occur and to smooth out the fluctuations.¹¹ Apomorphine requires the concomitant use of oral domperidone to avoid nausea or vomiting. Rarely infusions delivered by a pump are used.

Table 3. Levodopa, carbidopa, ascorbic acid solution (LCAS)

Composition: Solution prepared daily with 10 x 100/25 levodopa/carbidopa tablets and 2 g ascorbic acid in 1 litre water. It is stable for 24 hours and provides 1 mg/mL of levodopa.

Target population: Advanced disease with a very narrow therapeutic window with severe dyskinesia or off periods.

Dosage: Total the daily levodopa dosage and divide by total hours of use to estimate hourly dose of LCAS. This is the starting dose in the morning. All tablet forms of levodopa are ceased.

Storage: No special conditions are necessary. Appropriate sized containers are needed and a syringe can be used to make accurate measures of dosage volume.

Titration: Doses are administered hourly; if ineffective it is increased and if it causes dyskinesia it is reduced at the next dose. Higher doses are needed for the first two doses in the morning. The dose is gradually reduced as the day progresses, making adjustments on motor response. Initially dosage changes are bigger and as the window of benefit becomes apparent the dosage steps are gradually reduced. The window is usually of 4 to 10 mg of LCAS. A bigger dose is to be given at mealtimes in anticipation of the interaction with protein or if undertaking extra physical activities. Slow-release preparations are given overnight.

Education: Patients will require admission and titration is performed by trained nursing staff. Patients are monitored to decide on dosage adjustments. The patient/carer are trained under nursing supervision. They are asked to decide on a dose and to explain the reasons. It is important mistakes are made in order to learn to deal with different circumstances. They are encouraged to practise in different settings (shopping, driving).

Minimisation of levodopa load: Once a stable regimen is established it is important to reduce the levodopa load by introducing a catechol-O-methyl transferase inhibitor. This drug does not affect the dosing interval but tends to reduce the total amount of levodopa per dose. Entacapone is given 4-hourly for four doses in the day. Tolcapone is given 6-hourly for three doses in the day. Cabergoline can be introduced and increased over a 2-month period. This will result in the development of dyskinesia. Patients then reduce the LCAS dose. These techniques can reduce the levodopa dosage quite significantly.

In recent years, amantadine has been reintroduced because of possible benefit in reducing dyskinesia.¹² It is a glutamate blocker which may theoretically also have a neuroprotective effect. The dosage for management of dyskinesia is 200 to 500 mg per day. Amantadine is started at 100 mg daily and increased by 100 mg weekly, up to the desired dose on a 6 to 8-hourly interval. Patients may find it difficult to tolerate the high doses because of adverse effects such as confusion, nausea or (rarely) rash.

RARELY USED DRUGS

Anticholinergic agents are rarely used because of their high adverse effect profile. Their efficacy is minimal for hypokinesia and akinesia but may provide some benefit for the tremor. Selegiline is also rarely used because of the possibility of adverse cardiovascular effects.¹³ There is no evidence that it is neuroprotective or that it can delay disease progression. Some of these potential benefits were attributed to symptomatic effects of the drug itself.¹⁴ Similarly, the possible benefits on motor control of selegiline have been superseded by the COMT inhibitors.

COMPLICATIONS

Nausea

Nausea is uncommon and the use of decarboxylase inhibitors has reduced its prevalence considerably. It has also reduced the total amount of levodopa that is required to produce a symptomatic response. Nevertheless, there

are still individuals who experience nausea when levodopa is introduced. The first-line approach is to swap the decarboxylase inhibitor. Alternatively, domperidone, a peripheral dopamine blocker that does not cross the blood brain barrier, may be used. A dose of 10 to 20 mg is administered 3 to 4-hourly or with each levodopa dose.

Postural Hypotension

Postural hypotension is common because of the peripheral dopamine effects of levodopa. Most patients can tolerate a 5 to 10 mmHg drop in blood pressure on the assumption of erect posture but if it exceeds 20 mmHg or if the systolic blood pressure falls below 80 mmHg they typically develop symptoms. Swapping the decarboxylase inhibitor can produce substantial improvement. If ineffective, domperidone may be introduced at a similar dose as described for nausea. If it persists then it is more likely to be autonomic neuropathy and although this can occur with idiopathic PD it may represent an atypical parkinsonian syndrome. Management becomes difficult and requires other strategies, such as fludrocortisone. Fludrocortisone is administered in the evening because of renal excretion of salt overnight in the supine position. Tilting the head up when asleep can also reduce the salt excretion by the kidneys. High salt intake and use of compression stockings may also be necessary. Sympathetic agents (ephedrine, midodrine) which cause peripheral vasoconstriction provide a variable response. They are administered early in the day as they can cause nocturnal hypertension.¹⁵

Neuropsychiatric

Neuropsychiatric manifestations tend to occur in the elderly with mild cognitive impairment or dementia. An inverse relationship exists between the severity of cognitive impairment and the total dose of dopaminergic medication required to induce psychosis.¹⁶ Symptoms can occur in much younger individuals but the dopamine levels required to produce these symptoms are much higher.

Drug-induced psychosis is difficult to diagnose because the manifestations are varied and subtle, such as anxiety, hypomania, stimulus-orientated behaviour, confusion, hallucinations and paranoia. Behavioural disturbance of an aggressive type can also occur in combination with paranoia and confusion. All of the drugs used in the management of PD have a capacity to induce psychosis. When this occurs, anticholinergic agents, selegiline, dopamine agonists and COMT inhibitors are weaned. The last drug to be withdrawn is levodopa and at times this may need to be reduced substantially until the tranquilliser is able to control the symptoms. Levodopa can then be reintroduced up to its previous level or to a level which enables mobility to return towards normal.

A major issue is the use of major tranquillisers (pimozide, thioridazine, chlorpromazine) which produce dopaminergic blockade and worsening of mobility. Atypical antipsychotics (risperidone, olanzapine) which have less basal ganglia adverse effects are an obvious choice. However, even they can worsen mobility and are best avoided. Although clozapine has minimal effects on mobility, it is difficult to prescribe because of its adverse effect profile, monitoring requirements and cost.¹⁷

Quetiapine is the most suitable as it has no basal ganglia adverse effects¹⁸ and the dose is very small (25–50 mg in the evening or 12.5 to 25 mg in the morning). As it can cause sedation, daytime doses are best avoided. The sedative effects may be beneficial to assist sleep at night.

Dementia

Elderly patients with dementia pose a special problem. Levodopa is started at 6 am and finishes at 2 or 3 pm. The dose is increased by 25 mg every two or three days up to a dose that improves mobility (450–600 mg per day). Neuropsychiatric complications always develop or worsen in the late afternoon, evening and night. If levodopa is given earlier in the day this will minimise the side effect and enable enough drug to be available to improve mobility.

CONCLUSION

Currently, therapeutic options exist to optimise management at all stages of the disease. However, it requires the clinician to be experienced, knowledgeable and to use a scientific approach. It is imperative to work with an experienced team whose role is to monitor the outcomes and adverse effects of any intervention which, in the latter stages of the disease, are best undertaken on an inpatient basis. The future may add new tools to the therapeutic armamentarium in the form of more potent dopamine agonists, adenosine, glutamate or gamma amino butyric acid modulating agents.

Competing interests: None declared

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