Parkinson's disease

Drugs for Parkinson's disease

A J Lees

Oldies but goodies

It is chastening to reflect that although the portfolio of available drug treatments for Parkinson's disease has multiplied, L-dopa, in its fourth decade of clinical use is still the most potent and effective medication. The newer drugs have refined, rather than revolutionised treatment and no available therapy can do more than temporarily control motor disability. Depression, abulia, severe constipation, pain, and sleep disturbance can all have devastating effects, and the benefits of any new treatment need to be judged on the basis of its impact on quality of life as well as relief of the cardinal motor symptoms. About a quarter of patients will severely dement and at least as many will have visual hallucinations, episodic confusional states, and daytime somnolence.

Systematic reviews have been published recently by the Movement Disorder Society[1]; the Standards Committee of the American Academy of Neurology[2] and the Cochrane Movement Disorders group have also provided reports on a number of therapeutic interventions.[3] However, the available data on which most of these analyses are founded, is often sketchy and incomplete because of the dearth of high quality data.[4] New drug treatments have a headstart because trial design has changed radically over the past 20 years and many of the studies conducted with older drugs are now considered inadequate or insubstantial. This, however, should not be equated with inferiority or inefficacy, and indeed from a safety point of view proven treatments with a long track record have advantages. Serious adverse events, as for example occurred with the COMT inhibitor, tolcapone, may only come to light in the first few years of postmarketing surveillance.

Scrutiny of even the best available evidence, therefore, leaves the physician with doubt and uncertainty in relation to what constitutes best clinical practice. A paradox of the randomised controlled trial is that it may be the best available way to show the efficacy of a drug, but it is not particularly helpful in determining which individuals will benefit most and in which patients a particular treatment should be avoided. Many of the recently published trials were funded, and more importantly, designed by the pharmaceutical industry as part of the process of registration. Stringent exclusion criteria often limit their applicability to everyday clinical practice. For example, relatively few antiparkinsonian drugs have been tested on patients older than 75 years or with coexisting cardiovascular or cerebrovascular disease, diabetes, or treated cancer. Furthermore, negative studies or important postmarketing observational studies find it harder to gain editorial acquiescence and frequently languish unpublished.

Existing knowledge does not permit the adoption of a standardised treatment algorithm for Parkinson's disease. The clinical picture, natural history of Parkinson's disease, and response to drug treatment are all extremely variable. Very few patients have identical drug regimes. Patients are now much better informed about available treatments and expect and demand a partnership with a specialist. If any form of therapeutic success is to be achieved, concordance between patient and physician is a minimum requirement. A 20–30% improvement in disability scales as a result of the placebo response lasting up to six months is a feature of many randomised trials in Parkinson's disease, and the dopamine mesocorticolimbic system has been implicated in the pathogenesis of the placebo effect.[5] In contrast a poor or confrontational doctor-patient relationship may lead to detrimental nocebo effects. Despite these caveats, the judicious and personalised use of the available armamentarium of drugs can lead to significant functional improvements in most patients' lives, and advances in the medical management of Parkinson's disease stand as one of the major successes of clinical neuropharmacology in the twentieth century.

L-DOPA

Four 3–5 year trials in in which dopamine agonists have been compared against L-dopa in previously untreated patients have recently been published. Rascol and colleagues[6] conducted a five year study of ropinirole versus L-dopa in 268 de novo patients. Open label supplementation with L-dopa was allowed in both arms. A higher rate of dyskinesias, but significantly greater motor improvement and fewer hallucinations occurred in the L-dopa arm. The US Parkinson Study Group (PSG) carried out a study on 301 de novo patients using another non-ergolene dopamine agonist, pramipexole. On follow up, dyskinesias were significantly less common (reduced 67% risk) in the group randomised to pramipexole, but more somnolence and visual hallucinations occurred in this arm and there was less motor improvement than seen with the active comparator. One would need to treat four or five patients with pramipexole instead of L-dopa over a two year period to prevent one additional dopaminergic complication.[7] Similar results confirming the greater potency of L-dopa, but its greater proclivity to induce dyskinesias, have been presented for the ergolene agonists cabergoline and pergolide.[8 9]

These trials, therefore, confirm clinical experience that standard L-dopa is the most effective available treatment for relief of motor symptoms, activities of daily living, and quality of life in Parkinson's disease.[7] However, they also emphasise that early dopamine agonist therapy may combine worthwhile symptomatic benefit with a lower incidence of dyskinesias during the early years of symptomatic therapy. This has led to a recommendation by many opinion leaders that dopamine agonists should be the treatment of choice for early Parkinson's disease. Even if this strategy is pursued it is accepted that less than a quarter of patients (probably closer to 15% of patients) will accept to remain on agonist monotherapy for five years. Based on the use of 3D-PET F-dopa studies and SPECT dopamine transporter studies as surrogate markers for dopamine neurone function it has also been claimed that the dopamine agonists ropinirole and pramipexole might slow down nigral dopaminergic degeneration.[10] Even if these findings are eventually proved to correlate with postmortem findings, it remains unclear whether this would have a worthwhile impact on motor handicap or life expectancy. A surprising finding of these functional imaging studies is that a number of patients with clinically diagnosed early Parkinson's disease and an apparent worthwhile response to dopaminergic therapy have normal scans.

The Parkinson's Disease Research Group of the United Kingdom (UKPDRG) has recently published its 10 year results of a randomised trial on 782 de novo patients in which L-dopa was compared against L-dopa in combination with selegiline (10 mg/day) and against high dose bromocriptine monotherapy (approx. 40 mg/day). The patients initially randomised to bromocriptine had significantly worse disability scores throughout the first five years and returned to pretreatment level of disability a year earlier than those randomised to L-dopa (three years as opposed to four years). Those randomised to bromocriptine had a significantly lower incidence

of dyskinesias than either of the two L-dopa arms, but this was not significant at 10 years when only moderate and severely disabling involuntary movements were considered. Initiating therapy with bromocriptine failed to show an improved life expectancy compared with L-dopa treatment over 10 years follow up in both the UKPDRG trial[11] and the smaller Sydney study.[12] The UKPDRG trial also confirmed better initial tolerability of L-dopa over bromocriptine, and fewer withdrawals because of lack of useful therapeutic benefit (less than 30% initial improvement) occurred (15.6% in the bromocriptine arm and only 0.8% of patients in the two randomised L-dopa arms).

In all these trials it is difficult to disentangle whether the lower risk of motor complications with dopamine agonists is an effect of delaying L-dopa or caused by a lower cumulative L-dopa dose. There is available evidence to indicate that using lower doses of L-dopa reduces the incidence of dyskinesias, but there is no convincing evidence that the controlled release L-dopa formulations are more efficacious or reduce the frequency of long term side effects. Most physicians now cap the dose of L-dopa at no more than 600 mg per day, and if possible keep the dose lower than this over the first four or five years of treatment (300–400 mg daily).

Patients' preferences need to be taken into account in deciding which treatment to start, but scaremongering suggesting that L-dopa has toxic effects on the brain, or produces beneficial effects for only a short "honeymoon period", need to be firmly dispelled at the earliest possible opportunity. In most patients who do not dement, L-dopa continues to have therapeutic effects on bradykinesia, rigidity, and tremor for several decades, but unfortunately no available treatment can halt the inexorable progression of the underlying disease process. In a patient under the age of 50 years, an initial trial of high doses of a dopamine receptor agonist may be appropriate and many patients are keen to follow this strategy. However, concerns related to the provocation of drug induced dyskinesias should not be used as an argument for delaying L-dopa so long that a patient's mobility is severely and unnecessarily compromised. Patients tolerate mild dyskinesias well, and it is the family who are more likely to be distressed by adventitious movements and to demand reduction of medication. There is little or no convincing evidence to suggest that initial treatment with an agonist as opposed to low dose L-dopa reduces major motor complications of therapy after 10 years (on-off effects and severe dyskinesias); as patients enter the second decade of disease the overwhelming majority will in any case be receiving both types of drug in combination. Early treatment with low doses of L-dopa, even in a young onset patient with considerable disability, remains good practice.

Clinical equipose exists with respect to whether a dopamine agonist or L-dopa should be the initial treatment of choice in Parkinson's disease, but the fact that more patients will tolerate and respond well initially to L-dopa is an argument in favour of the more traditional but currently increasingly less fashionable approach.

AMANTADINE

Amantadine was first found to be effective for Parkinson's disease in the 1960s, following its introduction as a prophylaxis for influenza. It was traditionally used in doses of 100–300 mg/day as a mild symptomatic therapy, either as an initial treatment of choice in mildly affected patients or as an adjuvant therapy in combination with L-dopa.[13] Concerns about tachyphylaxis lingered in many circles, and this, together with the advent of other therapeutic options, led to a marked reduction in its use. The very few early reports of amantadine's possible antidyskinetic properties were ignored until interest in the possible application of glutamate antagonists to treat L-dopa induced involuntary movements developed. Amantadine has complex pharmaceutical effects, including enhancement of dopamine release and blockade of dopamine reuptake, anticholinergic effects, and blockade of NMDA glutamate receptors. In 1998 Verhagen Metman and colleagues[14] carried out a small controlled trial with amantadine using doses up to 1000 mg/day for three weeks in an intravenous L-dopa infusion paradigm. The antidyskinetic effects observed were subsequently confirmed by both the same authors and others in longer term follow up studies.[15–17] These results have generally been confirmed in routine clinical practice, and all patients with disabling dyskinesias should be given a six week trial of amantadine before consideration of subcutaneous apomorphine pump therapy or functional neurosurgery. It remains unclear exactly what proportion of patients derive a sustained antidyskinetic response, the optimum dose range, and whether amantadine may aggravate parkinsonism at very high doses (300 mg and above). The resurrection of amantadine as an effective antidyskinetic agent has been one of the more useful and still underused therapeutic advances in the past five years.

ANTICHOLINERGIC DRUGS

Plants with anticholinergic properties were recommended in the ancient Ayurvedic texts as treatments for nervous maladies, and Charcot stumbled on belladona's therapeutic antiparkinsonian effects while using it to treat drooling of saliva. In 1945, acetylcholine was proposed as a central nervous system neurotransmitter, and the solanaceous alkaloids, hyoscyamine, stramonium, and atropine were used as the only widely available treatment for Parkinson's disease. Synthetic anticholinergic drugs remained the mainstay of drug treatment until the arrival of L-dopa and amantadine. Although there are very few trials which would fulfil currently accepted design standards, scrutiny of the early literature suggests that they are probably efficacious and may not have beneficial effects restricted to rest tremor and rigidity.

Their use has declined drastically in recent years because of genuine concerns relating to their unwanted but reversible effects on short term memory,[18] and their proclivity to induce delirium, faecal retention and toxic megacolon, severe weight loss, and retention of urine in men with prostatism. However, in young patients, particularly with troublesome dystonia of a foot[19] or prominent rest tremor, they should still be considered as an initial treatment option but doses should be kept low (for example, benzhexol 2 mg three times daily). A spectacular response to anticholinergic drugs in a patient with juvenile or young onset Parkinson's syndrome raises the strong possibility of a dopa responsive dystonia. If deterioration of disability following drug withdrawal is a good marker of therapeutic potency, the effects of anticholinergics may have been underestimated in the past as catastrophic motor deterioration can occur with sudden discontinuation.

Anticholinergics also remain important in the management of neuroleptic induced Parkinson's syndrome. L-dopa is ineffective as long as the antipsychotic drug is prescribed, although it is now clear that a number of elderly patients, initially thought to have iatrogenic parkinsonism, have underlying additional Lewy body pathology. The greater use of the newer antipsychotics such as clozapine and quetiapine, and the greater awareness of the dangers of long term prochlorperazine and metaclopramide therapy, is reducing the frequency of drug induced Parkinson's syndrome.

APOMORPHINE

Apomorphine was first shown to have potent antiparkinsonian effects 50 years ago,[20] and it remains the prototype dopamine receptor agonist for preclinical studies. In clinical practice it is the only antiparkinsonian drug which has been shown to have comparable potency to L-dopa in improving motor performance.[21] The availability of the peripheral dopamine receptor antagonist, domperidone facilitated its clinical

introduction by markedly reducing nausea, vomiting, and postural hypotension, and a clinical trial in 1984[22] showed that intermittent subcutaneous injections of 1 mg could consistently relieve refractory off period disability. Although it is now increasingly used in many parts of the world as an effective treatment for on-off motor fluctuations and disabling interdose chorea,[23 24] it is still underused[16] and awaits registration in the United States.[25] Continuous waking day steady state subcutaneous infusion of apomorphine by means of a specially designed automated minipump has proved extremely effective for the treatment of young onset Parkinson's disease. Provided both patient and family are fully instructed in what the therapy entails and are agreeable and enthusiastic to proceed, comparable benefits to those reported with bilateral subthalamic nucleus stimulation can be achieved with lower morbidity. Success depends on a committed and enthusiastic multidisciplinary team and regular and conscientious ongoing support from physicians and nurse specialists.[26]

WHAT ELSE IS THERE?

Selegiline[27] and the catechol-o-methyl transferase inhibitor, entacapone[28] are both useful in treating early end of dose deterioration in L-dopa treated patients. Both drugs are well tolerated and may also possibly have useful effects on drive, motivation, and depression, but further work is needed to confirm this in clinical trials. Entacapone is only useful in combination with L-dopa; 200 mg should be given with each L-dopa dose. In contrast, selegiline has weak, mild symptomatic effects and may be considered as an initial treatment in mildly disabled patients. The new buccal formulation of selegiline (Zelapar) does not produce significant quantities of amphetamine catabolites, but it remains unclear whether this confers safety or efficacy benefits over standard selegiline.

Controlled release formulations of L-dopa are still in vogue for treating nocturnal disability, but there is no evidence they are clearly superior in this regard to standard L-dopa. Dispersible formulations of L-dopa may be useful for delayed morning start up time, usually working after 20–30 minutes compared with 30–60 minutes for standard L-dopa. Dopamine agonist drugs are extremely useful and important L-dopa sparing agents, reducing motor complications and benefiting off period disabilities. There is very little to choose between them in efficacy, and it is likely that most of the reported adverse events are class effects.

Cost should be an important consideration in the choice of an agonist. Pleuropulmonary infiltrates and retroperitoneal fibrosis may prove to be more frequent with the ergolenes, and there is still concern that excessive daytime sleepiness is more frequent with ropinirole and pramipexole than with bromocriptine, pergolide, or cabergoline. In patients with severe ischaemic heart disease or peripheral vascular disease, a non-ergolene may be the best initial choice, whereas the once a day administration of cabergoline is attractive to many patients.

Many patients are taking complementary therapies in the hope that they may slow disease progression, but as yet no definite clinical evidence exists to support this practice.[29] The current favourites are coenzyme Q10, NADH, vitamin E, and vitamin C. Caffeine may be helpful for "psychic dips", and the separation of dopa intakes away from mealtimes and modest dietary protein restriction can sometimes improve the treatment response considerably.

Depression is common and may precede motor symptoms in a proportion of patients. In patients not responding to antidepressants, unilateral electroshock therapy can be considered and transmagnetic stimulation is under review.[30] Clozapine and probably quetiapine are useful antipsychotic drugs which do not aggravate motor symptoms in Parkinson's disease at low doses. Paranoid delusions invariably settle after a few weeks and the neuroleptic can then be withdrawn.[31] Macrogol 3350 (Movicol) has developed a recent reputation for being particularly effective for the almost invariable refractory constipation.[32]

Deep cerebral stimulation with implantation of electrodes into both subthalamic nuclei is the currently favoured procedure by most of the world's neurosurgeons. In very carefully selected patients (probably no more than 1% of the total number of people with Parkinson's disease), spectacular results can occur. The effect of optimum high frequency electrical stimulation is comparable to that seen with the maximum L-dopa response with respect to relief of the cardinal motor symptoms. Ideal candidates are young, non-demented patients with no psychopathology and with severe refractory motor fluctuations who have received L-dopa for a minimum period of seven years.[33]

THE FUTURE

Falls, deteriorating bulbar function, and dementia remain the major therapeutic challenges in Parkinson's disease. None of these are likely to be solved by surgical implants or striatal neurotrophin infusion, even if perfect dopamine cell systems can eventually be achieved. Greater understanding of protein misfolding through research in genetics and molecular biology hold out more promise, with the tantalising therapeutic possibilities of immunisation and gene therapy. Realistically, however, trials in this area are probably at least five years away. It is to be hoped that controlled trials with the central cholinesterase inhibitors will confirm promising anecdotal experience suggesting useful short term benefit for memory loss, levels of arousal, and visual hallucinations.[34] Clozapine and probably quetiapine are useful antipsychotic drugs which do not aggravate motor symptoms in Parkinson's disease at low doses. Paranoid delusions invariably settle after a few weeks and the neuroleptic can then be withdrawn.[31] These drugs can also be helpful for the dopamine dysregulation syndrome in which inappropriate hyperlibidinous behaviour, pathological gambling, or punding may have disastrous social and marital consequences.[35]

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