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What Is Required When Developing a New Application for an Older Medication -Using Parkinson's Disease as An Example

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Abstract

Introduction: 'Off licence' medication usage is less formal than clinical trials relying on doctors' attitudes, as shown with Parkinson's disease (PD).

Background: Delayed introduction of L-dopa in PD is unnecessary but does not address starting levodopa very early, with very low dosage and slowly titrating to need, adding other PD medications as required when efficacy is diminished.

Discussion: Accepting genetic causes and environmental provocateurs of PD, this paper examines idiopathic PD which may represent aging with early diagnosis heralding age degeneration of both dopamine production and receptors. Delayed use of levodopa may be less efficient, with fewer receptors. Bradykinesia is almost universal in geriatrics translating to the diagnosis of idiopathic PD only requiring one of the remaining 3 characteristics. This should generate treatment with subsequent unfettered audit to confirm benefit. The algorithm comprises: levodopa with either carbidopa (Sinemet®) or benserazide (Madopar®); adding MAO A and B inhibitor, [either selegiline (Eldepryl®), rasagiline (Azalect®) or safinamide (Xadago®)], again titrated to need; followed by dopamine agonist, such as pramipexole (Sifrol ER®); and concluding with L-dopa/carbidopa/entacapone (Stalevo®). This algorithm is novel and examines what is required when developing a new application for older medications.

Conclusion: This review confirmed efficacy of the approach of early initiation of low doses and slowly escalating with addition of different medications, also slowly titrated to need when treating PD.

Keywords: Clinical trials; Parkinsonian features; Alternative approaches; Idiopathic Parkinson's Disease; Diagnostic Dilemma

Abbreviations: PD: Parkinson's Disease; DP: Dopamine

Introduction

New drug/medication development requires a long and tested road to be travelled. The passage starts with a concept that is tested in animal models to prove that the concept has validity [1]. Despite the enormous costs involved in drug/medication development, there remains an inordinately low success rate for these medications to reach bedside usage [2]. The choice of appropriate animal to use in the preclinical experimentation may provide one explanation for this low yield which dictates the need to develop the correct *"...design and conduct of an animal model, including the recommendation of assessing both efficacy and safety endpoints..."* to produce the optimal translational outcome [2].

Once the animal models have produced the suitable results, the drug/medication development progresses into phases I – III stages of development within the human model, subject to suitable ethics committee approval of correct study designs [3]. Post marketing the medication moves into Phase IV, when the medication has wide exposure to determine any unforeseen issues that did not emerge during the development period [4]. Thus, by this stage, the novel agent has been fully evaluated and independently approved by the regulatory authority, such as the Food and Drug Administration, in the US, the EU Medicines Agency or the Therapeutic Goods Administration, in Australia,

to be prescribed for use in the target population of patients for whom the initial proof of concept has been confirmed, the safety established and those licenced to safely prescribe the medication, be it the family physician or the specialist consultant.

When it comes to 'off licence' use of medications, there is far less formality or regimentation, and the rules are far less rigid with much of the impetus coming from medical professionals who hold the view that there is a better way to do things. This concept was one of the reasons why some doctors have adopted the approach to manage Parkinson's disease (PD) by starting the treatment, with L-dopa, much sooner than is generally accepted by the bulk of neurologists [5-7], starting very low and going very slow. This paper reviews this approach with the idea of sharing the concept with others who may wish to follow suit. It is accepted that the medications used have been well tested and are specifically prescribed for the treatment of PD, but the algorithm adopted is not that which most accept as standard treatment.

Background

PD has been recognised, in one form or another, long before the classical report, provided by James Parkinson, in his publication, "Essay on the Shaking Palsy" more than 200 years ago, in 1817, acknowledging that it was eponymously named after him, upon the suggestion of Charcot in 1872. Features of PD date back to ancient times, in Babylon, Greece, China and India [8], which indicates that it has withstood the test of time and that it has been a fairly ubiquitous condition, without respect for race or religion or society. The fundamental treatment only came to the fore in the late 1960s [9] and then was using high dose L-dopa with consequent ill effects, as portrayed in the Hollywood movie, "Awakenings" [10]. As stated by Hornykiewicz [9], *"Today, the concept of DA (dopamine) replacement with levodopa is uncontested, with levodopa being the "gold standard" of modern drug treatment of PD"*. There has been the widely accepted philosophy that DA replacement, with levodopa, should be withheld or minimised, until the expression of the PD features was so truly evident for all to see, and it should not be started too early to avoid the motor complications [11,12]. There has since been a revision of that approach with clinicians accepting that the idea of using L-dopa sparing agents, such as dopamine agonists, was unnecessary as it did not change the natural progression of the PD [12]. This did not address the question of starting the levodopa at a very low dosage and very slowly titrating to the patient's needs, with the addition of other classes of PD medications being added, when the efficacy of the L-dopa was less apparent [5,7,13]. This was the basis of the approach adopted by Beran when starting levodopa, in combination with either carbidopa or benserazide, starting at a tiny dose of 100/25 a half twice daily and titrating from there [5,7,13,14]. This approach is based on the concept that idiopathic PD may be a simple expression of aging, rather than a definitive pathophysiological entity [6].

Discussion

There are unequivocal exceptions to the rule that idiopathic PD is a disease of the elderly, especially with genetically inherited forms. There are several monogenic forms of PD with additional genetic risk factors which enhance the risk of developing PD. Monogenic forms, caused by a single mutation in a dominantly or recessively inherited gene, collectively account for about 30% of the familial and 3%–5% of the sporadic cases of PD [15]. Appreciation of the potential genetic basis of idiopathic PD emerged with Gowers [16] who recognised that 15% of his PD patients had a familial history thereof. Some of the genes and genetic basis of PD include PARK 1; PARK 2; PARK 3; PARK 4; PARK 5; PARK 6; PARK 7; PARK 8; mitochondrial inheritance; with gene inheritance interactions; and genetic anticipation which results in earlier expression of the PD all of which contribute to the evolution of PD [17]. What follows does not deal with these forms of PD and is specifically directed towards idiopathic PD.

Accepting the genetic causes of PD and also some of the environmental provocateurs, such as MPTP [18], these will not be further canvassed in the discussion to follow. What follows is specifically directed towards idiopathic PD and the argument that this may represent a form of aging, specifically directed towards the degeneration of the cells of the substantia nigra, with subsequent loss of dopamine in the basal ganglia, thalamus and cortex [19], rather than a definitive pathophysiological diagnostic entity [6,14,20-22].The reason for adopting this philosophy is that, with the early diagnosis of idiopathic PD, being an expression of the aging process, it may represent the earliest features of that process associated with the loss dopamine within the substantia nigra and hence the start of aging degeneration for not only the production of dopamine but also the dopamine receptors. Without the dopamine, stimulating the dopamine receptors, it is reasonable to assume that, with time, they too will be lost. Delaying the use of levodopa, to be converted to dopamine after crossing the blood brain barrier [23], will result in reduced capacity for the dopamine to achieve success as the receptors will be less efficient, with fewer of them. This provides a good argument to start treatment with levodopa as soon as the diagnosis is clinically made on the basis of at least 2 of the 4 cardinal features of bradykinesia, rigidity and tremor and postural instability, of which bradykinesia is mandatory [24].

When dealing with the geriatric population, bradykinesia is almost universal which translates to the clinical diagnosis of idiopathic PD only requiring one of the remaining 3 characteristics. It is imperative that the rigidity of idiopathic PD is that of an increase in resting tone, rather than during active movement, which means that the patient needs to be distracted, when testing for tone [7], to overcome any subconscious attempt, on the part of the patient, to assist the clinician, that the patient may exert during the examination of tone [7]. To appreciate this, the tone should be tested both without and with distraction, in that order,

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and the increased tone should only be apparent during distraction, in the very early stages of the expression of idiopathic PD [7]. Postural instability should be assessed before starting treatment because levodopa may itself cause postural hypotension which would unequivocally cause 'postural instability' [25]. The popular explanation for the instability is that of vestibular disfunction [26] but an alternative explanation for the 'postural instability' may relate to the failed righting reflexes. These are found in patients with PD and result from the 'lead-pipe rigidity' which impairs the capacity to correct for any loss of balance, limiting the ability to spread the centre of gravity, because the rigidity maintains stiff, rather than loose, muscles preventing their being moved rapidly, as is required for the righting reflex [27].

Once idiopathic PD has been registered, on the radar screen of the clinician, who deals with geriatric patients, on the basis of the above criteria, it will become apparent that most of these patients will display the diagnostic criteria required for the clinical diagnosis of idiopathic PD. If levodopa is started, at this point in time, it should translate to initiating the treatment while the receptors to the DA are still present and active. This will be long before many clinicians have even contemplated the diagnosis, let alone commenced treatment. Having adopted this approach to the management of PD [5,7], it behoved the wider medical community to undertake an audit of the practice, of starting low and going slow, to ensure that it realised the benefits claimed. This was completed and it withstood the critical review from an independent scientist who was given unfettered access to patient records within the practice and given free rein to employ whatever critical evaluation she chose, thus constituting an arm's length appraisal without interference [13].

The algorithm comprised: starting with levodopa in combination with either carbidopa (Stemetil®) or benserazide (Madopar®), at a dosage of 100/25mg, a half twice daily and increasing to need, until reaching either one, twice daily, or one, thrice daily, depending on the patient's response [5,7,13,14]; then adding an MAO A and B inhibitor to the levodopa already in place, using either selegiline (Eldepryl®), rasagiline (Azalect®) or safinamide (Xadago®), again titrated to the patient's need and starting with a half 5mg selegiline twice daily and titrating to need, based on clinical status, building up to one twice daily and only considering the other MAO A and B inhibitors should there be unwanted adverse effects from the selegiline [5,7,13,14]; when it was apparent that the patient required further adjunctive therapy, added to the levodopa and MAO A and B inhibitor, dopamine agonists, such as long acting pramipexole (Sifrol ER®) was added and again introduced at a minimum dosage and that dosage titrated to requirement, up to 1.5mg daily and occasionally higher to 3mg dialy [5,7,13,14]; followed by the replacement of the L-dopa/carbidopa or L-dopa/beserazide combination medications, maintaining the MAO A and B inhibitor (assuming it is well tolerated) and the dopamine agonist, with the triple combination medication of L-dopa/carbidopa/entacapone (Stalevo®), also introduced at allow one, twice daily, of the 100/25/200 mg initial dosage and increased in incremental fashion and titrated to need but rarely, if ever, above four daily [5,7,13,14].

Having described the above algorithm, it is clear that this represents a novel approach to the management of PD, especially idiopathic PD, and the discussion has amplified that which is required when developing a new application for an older medication - using PD as an example. This has been executed in a totally transparent fashion to show both the benefits of the novel regimen and approach and to allow others to emulate same, in similar fashion to the benefit of their patients.

Conclusion

This review, of a novel approach to the management of patients with PD, especially idiopathic PD, has demonstrated the efficacy of the approach of starting low and going slow, with an escalation of both dosages and the addition of different medications, added to the existing medications, in combination, titrated to need and initiated at the very first signs of the PD based on the clinical diagnosis achieved, based on the standard diagnostic criteria. It has reported that which is required when developing a new application for an older medication - using PD, as an example.

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