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Amantadine – A *Sovereign* for Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms, resulting from the degeneration of dopaminergic neurons. While levodopa remains the gold standard for symptomatic relief, its long-term use is associated with motor fluctuations and dyskinesias. Amantadine initially introduced as an antiviral agent, has gained attention for its potential neuroprotective and symptomatic benefits in PD. This comprehensive review explores the multifaceted role of amantadine in the management of Parkinson's disease, examining its mechanisms of action, efficacy and potential side effects and covering a spectrum from motor symptom relief to potential neuroprotective effects.

KEYWORDS: Parkinson's Disease, Amantadine, Dyskinesias

Introduction

Parkinson's disease is a complex neurodegenerative disorder, highlighting the challenges associated with long-term treatment. A Unique complex disorder with various motor and non-motor manifestations, necessitating a multimodal therapeutic approach. Amantadine, an old drug with a new purpose, has shown promise in addressing both motor and non-motor symptoms in PD. One of the most common neurodegenerative diseases, Parkinson's disease is becoming more common in the elderly. Levodopa or dopaminergic agonist-containing pharmaceuticals help alleviate Parkinson's disease-related motor abnormalities; most patients get long-term treatment with these medications[1-13]. Long-term treated patients frequently exhibit motor problems, such as dyskinesias and motor fluctuations. Although there are few indications the surgery is invasive deep-brain stimulation of the subthalamus is an effective therapy for dyskinesias and motor fluctuations. Dyskinesias, a type of motor problem that worsens quality of life and is hard to manage, can be lessened by de-escalating levodopa, but doing so often makes motor symptoms worse. This article delves into the evolving landscape of amantadine use, highlighting its historical context and its expanding role in contemporary Parkinson's management.

The Upshots of Amantadine Monotherapy

Amantadine, especially when combined with L-Dops and especially in akinetic crises, alleviates the main Parkinsonian symptoms when L-Dopa is no longer enough on its own. A good response to amantadine has also been documented in situations where L-Dopa therapy is ineffective. Its quick efficacy and few adverse effects are further benefits. When Parkinson's disease is still in its early stages or when symptoms are mild, amantadine monotherapy is recommended[5]. Two-thirds of Parkinsonian patients respond to this type of monotherapy, with a worldwide improvement of 20 to 40%, according to Korn Huber and Streifler. Amantadine continues to be beneficial even after a lengthy course of therapy.

Amantadine's Mechanisms in Parkinson's Disease

Amantadine's mechanisms of action in PD are diverse, encompassing both symptomatic relief and potential neuroprotective effects. The drug modulates glutamate transmission, antagonises N-methyl-D-aspartate (NMDA) receptors, and enhances dopamine release, contributing to its anti-parkinsonian properties. Amantadine affects serotonergic and anticholinergic action, among other well-defined pharmacological effects. Amantadine in randomised controlled trials has proved effective in treating levodopa-induced dyskinesias in Parkinson's disease patients[1]. Antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor have been reported to potentiate the antiparkinsonian action of levodopa and reverse levodopa-induced motor fluctuations in animal models of Parkinson's disease[25] Additionally, recent research suggests amantadine's involvement in mitochondrial function and neuroprotection, opening avenues for disease-modifying interventions. Over time, amantadine has declined in popularity as a medication for treating influenza infections; nevertheless, it is now a tool in the toolbox for treating dyskinesia and Parkinson's disease (PD) symptoms early on[3]. As per recent research both randomized double-blind, placebo-controlled trials (RCTs) and animal PD models, amantadine has shown strong and dyskinetic benefits in PD patients. These effects are believed to be connected to the modulation of cortico-striatal glutamatergic–dopaminergic connections involved in the formation of LIDs by blocking NMDA receptors[7].

Figure 1 Amantadine-Mechanism of Actions

The Impact of Amantadine on Managing Dyskinesia

Research has indicated that dopamine excess release, striatal dopamine receptor hypersensitivity, or a combination of the two may be the cause of dyskinesias. The NR2B component of the N-methyl-d-aspartate (NMDA)-type glutamate receptor is redistributed from synaptic locations to extra-synaptic sites in the striatum, according to experimental models of animal dyskinesia. Dyskinesias are largely caused by altered striatal medium spiny neuron discharge patterns, which are depolarized by glutamatergic inputs. Dyskinesias are caused by synergic synaptic transmission via dopamine D1 receptors and NMDA receptors, while glutamatergic inputs via AMPA/kainite receptors may also be involved. Amantadine is a non-competitive, low-affinity NMDA receptor antagonist that is anticipated to improve dyskinesias[2]. Amantadine is a non-competitive, low-affinity NMDA receptor antagonist that is predicted to improve dyskinesias. The anti-dyskinetic benefits of amantadine wear off after eight months, and stopping the medication worsens the condition even if it is taken for a year or more. Nevertheless, there is not enough proof to support amantadine's anti-dyskinetic properties.

Amantadine as Rescuer for L-Dopa Induced Dyskinesia

Advanced Parkinson's disease therapy is challenged by dyskinesias brought on by the culprit agent L-dopa (Levodopa). Recent research suggests that amantadine, an NMDA receptor antagonist, may considerably reduce dyskinesias triggered by L-dopa[4]. Luginger *et al* evaluated the impact of amantadine in a 5-week double-blind crossover experiment on dyskinesias caused by L-dopa. When compared to baseline or placebo phases, the degree of dyskinesia as determined by self-scoring dyskinesia diaries and oral L-dopa challenges was almost 50% lower after amantadine administration. Similar to this, amantadine medication significantly improved dyskinesia ratings on the Unified Parkinson's Disease Rating Scale, part IV. Whether patients got amantadine or a placebo, the amount of their L-dopa motor response to oral challenges remained the same, and receiving active therapy did not significantly reduce their daily off-time. These findings support earlier findings of amantadine's anti dyskinetic properties. A maximum of 40 percent of Parkinson's disease (PD) cases may be attributed to L-DOPA-induced dyskinesias (LIDs), which have a detrimental effect on quality of life concerning health[7].

The Distinctive Benefits of Choosing Amantadine for Parkinson's Disease

The most appropriate procedure for starting symptomatic motor therapy for Parkinson's disease is still up for discussion. Many practitioners choose to start levodopa formulations early and avoid dopamine agonists to avoid potentially harmful side effects, such as impulse control problems. This decision is motivated by their interpretation of the findings of the LEAP and MED Parkinson's disease investigations[6]. Monoamine oxidase inhibitors might not be as effective as levodopa. Another therapeutic alternative for people with Parkinson's disease who need to start therapy but are being disregarded in this academic debate is amantadine. In 1969, amantadine was shown to be beneficial in treating Parkinson's disease; further research confirmed these findings. Nowadays, levodopa-induced dyskinesia is mostly treated with amantadine as an adjuvant medication[7]. Amantadine is seldom linked to impulse control disorders and has not been documented to produce dyskinesia.

Amantadine & its Dosage Forms

Currently, there are three pharmaceutical forms of amantadine on the market: an intravenous infusion (IV) solution that is rarely used in clinical practice; an oral immediate-release (IR) formulation that is widely available; and an extended-release (ER) formulation (ADS-5102) that was recently developed and approved by the FDA[14].

Still, the culprit, not deemed criminal- Amantadine

Amantadine IR may also have an impact on weariness or apathy which is the two common symptoms of Parkinson's disease. Constipation, cardiovascular dysfunction (including QT prolongation), orthostatic hypotension, oedema, neuropsychiatric symptoms (such as hallucinations, disorientation, and delirium), nausea, and livedo reticularis are the most frequent adverse responses to amantadine. Although uncommon, corneal deterioration is serious[7]. Even though all these things are considered, amantadine immediate and extended-release work well and safely to treat LIDs. However, at high amantadine plasma concentrations (1000–5000 ng/ml), it may induce delirium, the emergence of hallucinations, and elation in geriatrics.No data were found on the association between plasma concentration and amantadine side effects during the management of Parkinson's disease (PD), even though these symptoms are suspected of being associated with overdose or high plasma amantadine concentration[8].

Plasma Amantadine Concentration in PD Subjects

Plasma amantadine concentration is directly proportional to renal dysfunction. The patients exhibited adverse reactions, such as myoclonus, hallucinations, and delirium, and all of them showed plasma amantadine concentration to be >3000 ng/ml. PD patients who have not developed any psychiatric symptoms as adverse reactions to the treatment may develop myoclonus, hallucination, or delirium when the plasma concentration of amantadine exceeds 3000 ng/ml. It is therefore recommended to use amantadine at the plasma concentration of less than 3000 ng/ml in the treatment of Parkinson's disease, especially in geriatrics[8]. At a high concentration of >6 μM (1126 ng/ml), amantadine has been shown to be helpful in both relieving Parkinson's disease (PD) symptoms and suppressing levodopa-induced dyskinesias (LID).

The Motor Symptomatic Management with Amantadine in PD

Amantadine plays a crucial role in the symptomatic management of motor-related issues in Parkinson's disease. Recognized for its dopaminergic properties, amantadine helps alleviate tremors, rigidity, and bradykinesia are the common motor symptoms associated with Parkinson's. By modulating the release and uptake of dopamine in the brain, amantadine contributes to improved motor function, providing relief to individuals facing the challenges of Parkinson's disease[11]. It effectiveness in addressing these core motor symptoms makes amantadine a valuable component in the comprehensive treatment approach for Parkinson's patients, enhancing their overall quality of life[15].

The Non-Motor Symptom Management with Amantadine in PD

Amantadine, traditionally recognized for its impact on motor symptoms in Parkinson's disease, has also shown promise in managing non-motor symptoms associated with the condition. Beyond its role in addressing tremors and rigidity, amantadine has been explored for its potential benefits in mitigating non-motor aspects such as cognitive impairment, depression, and fatigue in individuals with Parkinson's disease. The drug's neuroprotective properties, including N-methyl-D-aspartate (NMDA) receptor antagonism, contribute to its multifaceted effects, suggesting a broader therapeutic potential[12]. As our understanding of the complexities of Parkinson's disease advances, the exploration of amantadine for non-motor symptom management adds a valuable dimension to comprehensive care strategies for individuals' quality of life with this neurological condition[16].

Potential Neuroprotective Effects of Amantadine

Recent studies have shed light on the promising neuroprotective effects of Amantadine in the context of Parkinson's disease. Amantadine, traditionally known for its Anti-parkinsonian properties in alleviating motor symptoms, is now emerging as a potential guardian for neuronal health. Evidence suggests that Amantadine may possess neuroprotective qualities, contributing to the preservation of dopaminergic neurons that are typically compromised in Parkinson's disease[9]. This newfound perspective has generated enthusiasm in the medical community, as it implies that Amantadine might not only provide symptomatic relief but could also play a role in slowing down the progression of the disease. Further research is underway to elucidate the underlying mechanisms and establish the full extent of Amantadine's neuroprotective benefits, offering hope for enhanced therapeutic strategies in the management of Parkinson's disease.

The Neuroprotective Mechanisms of Amantadine

Amantadine, a medication traditionally recognized for its efficacy in alleviating motor symptoms in Parkinson's disease, has recently garnered attention for its potential neuroprotective effects. While the precise mechanisms remain incompletely understood, several hypotheses have been proposed based on current research. One avenue of exploration is amantadine's role as an N-methyl-D-aspartate (NMDA) receptor antagonist. By modulating glutamate, an excitatory neurotransmitter, amantadine may regulate neuronal activity, protecting against excitotoxicity—a process implicated in neurodegeneration[9].

Another potential mechanism lies in amantadine's anti-inflammatory properties. Neuroinflammation and oxidative stress are key contributors to Parkinson's progression, and amantadine's ability to mitigate inflammatory responses could offer neuroprotection[10]. Additionally, amantadine may indirectly influence dopaminergic function, impacting dopamine release and reuptake. This modulation could help sustain dopaminergic pathways, crucial for motor control and often compromised in Parkinson's disease. The medication's antioxidant activity further contributes to its potential neuroprotective role[9]. By scavenging free radicals and reducing oxidative damage, amantadine may safeguard neurons from the detrimental effects of oxidative stress. Lastly, emerging research suggests a link between amantadine and mitochondrial function. As dysfunctional mitochondria play a role in neurodegenerative processes, amantadine's positive impact on mitochondrial health could represent another facet of its neuroprotective potential. While these mechanisms are promising, ongoing research aims to deepen our understanding of amantadine's neuroprotective effects in Parkinson's disease[10]. As the field evolves, these insights hold potential implications for refining treatment strategies and advancing our approach to managing this complex neurological condition.

MISCELLANEOUS THERPEUTIC MANAGEMENT FOR PARKINSONS DISEASE.

The management of cognitive deficits linked to Parkinson's disease (PD) is just as difficult as treating Alzheimer's disease and other dementias. Although it has long been believed that cognitive deficits are a characteristic of late-stage Parkinson's disease (PD), clinically inapparent cognitive changes on neuropsychiatric testing may be noticed. With the advent of cholinesterase inhibitors like donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®), as well as the NDMA antagonist memantine (Namenda®). it is possible that cognitive, orientation, and language function will improve, and that this improvement will result in a significant improvement in function. Both donepezil and rivastigmine improve cognition to the same extent, but donepezil is better tolerated by the subjects[18].

Levodopa standard and controlled release formulations are offered as fixed associations with a dopa-decarboxylase inhibitor, such as benzeraside or carbidopa, among other dopaminergic medications. Many dopamine agonists exist, each having unique receptor binding, pharmacokinetic characteristics, and delivery methods[26]. Additionally, there are two categories of indirect dopamine transmission enhancers: inhibitors of catechol-O-methyltransferase (COMT) and monoamineoxidase-B (MAO-B)[27]. A number of anticholinergics are among the non-dopaminergic drugs, but the only commonly accessible pharmaceutical with antiglutamatergic properties is amantadine[28].

FUTURE OUTCOMES

The use of neurotrophic factors, such as neurturin (NTN)22 and glial cell-line-derived neurotrophic factor (GDNF)[23]. It is one especially promising therapeutic and possibly neuroprotective strategy. It has been documented that these trophic factors both protect degenerating neurons in vivo and increase the lifespan of midbrain dopaminergic neurons in vitro. Due to these positive findings, a pilot study including the administration of GDNF via implanted intracerebroventricular catheter in patients with moderately advanced Parkinson's disease (PD) is being carried out in many North American centres. However, these trials were stopped[24]. It is because to the lack of observable effectiveness and the frequent incidence of nausea, anorexia, tingling (L'hermitte's sign), hallucinations, and sadness.

Conclusion

In conclusion, Parkinson's disease presents a multifaceted challenge, demanding a comprehensive and evolving therapeutic approach due to its intricate motor and non-motor manifestations. Amantadine, initially an established medication for motor symptoms, has undergone a renaissance in contemporary Parkinson's management. Its unique position as an adjuvant or monotherapy, particularly in addressing levodopa-induced dyskinesias, highlights its versatility and efficacy. The drug's mechanisms, encompassing glutamate modulation, anti-inflammatory effects, and potential neuroprotection, underscore its evolving role in mitigating the complexities of Parkinson's disease. Moreover, amantadine's impact on dyskinesia, coupled with its notable safety profile, positions it as a valuable rescuer in advanced Parkinson's therapy. As the pharmaceutical landscape expands, ongoing research into amantadine's neuroprotective potential and its distinct benefits in motor and non-motor symptom management continues to redefine its place in the intricate tapestry of Parkinson's disease therapeutics. Ultimately, amantadine emerges not just as a historical agent but as a dynamic and promising player in the contemporary armamentarium against Parkinson's disease.

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