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Profitable study of first order derivatives of levodopa

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Abstract
Levodopa – the aromatic amino acid L-3,4–dihydroxy phenylalanine has held the attention of neurologists and pharmacologists alike for more than half a century. Even though extensive research has been done across the globe in treatment of Parkinson's disease, with different molecules, none could replace the gold standard treatment or provide complete relief for the debilitated. Although research brought us better tips and tricks to modulate the dopamine blood levels to balance between the desired and deleterious effects, it could never replace the basic substrate. From simple oral preparation to more advanced treatment like duodenal dopa administration for better efficacy and compliance, L-dopa has sure undergone scrutiny and stayed strong as the fundamental neurotransmitter replacement therapy to pave path for many more new therapeutic strategies. So as a token of gratitude to the revolutionary agent and pioneers behind it, a trip down the memory lane is in order.

I. Introduction

Introduction of levodopa therapy in Parkinson's disease almost half a century back has revolutionized the therapeutic outcome of this challenging disease. Although several other agents have been subsequently added to the therapeutic armamentarium, levodopa remains the gold standard till date. The levodopa era began in 1967, when Cotzias et al. showed that orally administered levodopa had a dramatic and sustained effect on the symptoms of severely disabled Parkinsonian patients.

The basic research that lead to the Introduction of this wonder drug was the discovery of dopamine – a neurotransmitter that could control movements – by the Swedish pharmacologist Arvid Carlsson, who shared the Nobel prize in physiology and medicine in the year 2000. Another major landmark in the development of levodopa therapy was the introduction of carbidopa the peripheral decarboxylase inhibitor. The success of levodopa therapy for Parkinson's disease also was the key factor in creating a new subspecialty of neurology, namely, movement disorders.

Although the modern history of levodopa unfolds from the 19th century, it would be interesting to note that ancient Indian ayurvedic physicians used the seeds of Mucuna pruriens, which later proved to contain 4%–6% of levodopa, to treat symptoms of Parkinson's disease, as early as 300BC.

Application

The major therapeutic application of levodopa is still revolves around its use in Parkinsonism, Parkinsons plus syndrome and dopa-responsive dystonias. Clinical efficacy of levodopa varies in different subsets of symptoms. The classical motor symptoms of PD, bradykinesia, and rigidity, usually respond well to levodopa.

Response of tremor is less pronounced. Uniform poor response is the rule for other motor symptoms, such as speech and swallowing disorders, postural instability, and freezing gait. The response to nonmotor symptoms is poor with levodopa therapy, for example, cognitive disorders, dementia, depression psychosis autonomic dysfunction, and sleep disorders. Nocturnal treatment with levodopa may improve sleep in some patients. Chronic levodopa treatment is associated with Dyskinesia and motor fluctuations. Dyskinesias are involuntary movements that are mainly divided into peak-dose and biphasic dyskinesia. It is estimated that ~30%–50% of patients on levodopa therapy for more than 5-year experience dyskinesia.

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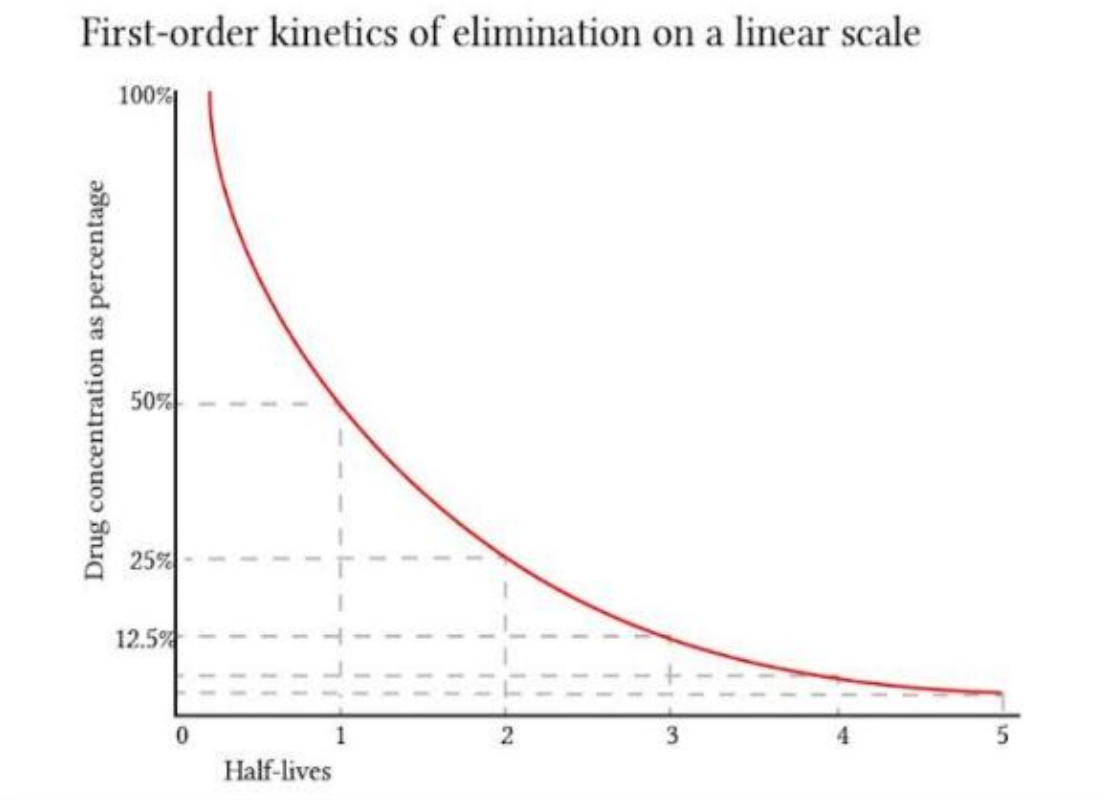
Although duodopa has been developed to achieve continuous dopaminergic stimulation, the treatment remains unaffordable to most of our patients.

First order elimination kinetics
"First-order kinetics… is where a constant fraction of drug in the body is eliminated per unit of time"

This is a logarithmic function. All enzymes and clearance mechanisms are working at well below their maximum capacity, and the rate of drug elimination is directly proportional to drug concentration.



The drug concentration halves predictably according to fixed time intervals. When you plot this on a semi-logarithmic scale, the relationship of concentration and time is linear.

II. Conclusion

The story of levodopa probably dates back from its use in ancient India as Atmagupta, the powdered form of mucuna pruriens for the treatment of tremor disorders. The revolutionary discovery of dopamine by Carlsson was probably the turning point in using this marvelous agent in modern therapeutics. However, the contributions from other scientists and researchers who have paved the way to the development of "Levodopa-the molecule of the century" cannot be undermined.

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