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Mini Review

Emergence of Deuterated Drugs: Probable Start of New Era in the Field of Therapeutics

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Abstract

With the approval of Deutetrabenazine (Austedo), a first Deuterated drug, there is emergence of Deuterated drugs in the treatment of diseases. Majority of drugs used for treatments are administered few days in acute conditions, while several months in case of chronic diseases. Thus, drug is designed and given in such a way that its level in blood may be maintained constant. To maintain the drug longer in blood, the Deuterated drugs are now in development, which seems to be more stable and have longer half-lives as compared to non-deuterated sibling, decreasing the requirement of frequent administration of drugs. The present article describes the use of Deuterated drug in the drug development..

Keywords: *Deuteration; Metabolism; Obviousness*

Introduction

Recent approval of first Deuterated drug- Deutetrabenazine (Austedo) in April 2017 bring the intense studies and research of four decades on Deuterated drugs to a fruitful and inspiring point and probably marks the emergence of Deuterated drugs in the field of therapeutics [1,2]. This approval has attracted the interest of leading medical chemist and pharmaceutical companies to participate in development of new Deuterated drugs to increase the effectiveness and potency of less stable and important drugs.

Deuterated drugs

"Deuterated drugs are those molecules of a drug in which one or more hydrogen atoms are replaced by its heavier stable isotope Deuterium". Deuterium commonly known as heavy hydrogen contains one proton and one neutron in its nucleus instead of one proton and no neutron in hydrogen [3]. Soon after the discovery by Dr. H. C. Urey in 1932, Heavy water (D_2O) had been a revolution in the field

of nuclear power production. The reason being its superior neutron-moderating ability but success of its use in field of medicine tested the patience of researchers for long time. Deuterated drugs incorporates the advantage of less frequent dosing due to longer half-lives, reduced toxicity due to reduced toxic metabolite formation, enhanced thermal stability for vaccine, reduced drug-drug interaction due to increased stability and also appreciable decrease in cost of therapy [4]. Recently a collaborative study by ICMR institution at Mumbai and heavy water board has formulated a D_2O based oral polio vaccine with improved thermostability which remains stable in tropics without maintaining cold chain.

Majority of drugs used for therapeutics are administered over the course of several days for acute and months for chronic and non-curable diseases therefore for each drug, dose and dosage regimen in designed to keep the blood level of drugs within therapeutic window. This can be strictly and practically achieved only when drugs are either infused at constant rate or administered frequently. Such drugs becomes impractical for long term treatments. Moreover, discovery of drugs is very time consuming, expensive and slow process due to poor metabolic stability and toxicity of most of molecules of interest. Vaccines which requires cold chain are not compatible to hot conditions of tropical climate. Carbon deuterium bond in Deuterated drugs has more bond energy than carbon hydrogen bonds thus such drugs are more stable and have longer half-lives as compared to non-deuterated sibling, decreasing the requirement of frequent administration of drugs [5]. Moreover, studies during last four decades has established the safety and non-toxic effects deuterated drugs to living cells. Deuterated drugs has emerged as a ray of hope for medicinal chemist for revamping older drugs and developing new drugs. It has been already estimated that at least 10 % of FDA approved drugs are amenable to successful deuteration.

Tetrabenazine- probably a vesicular monoamine transporter 2 (VMAT2) inhibitor has been used in several countries since 1950 as a neurological drug for treatment of disorders involving involuntary movements like Huntington's disease associated chorea and tardive dyskinesia. VMAT2 is a transmembrane protein which reduces the level of monoamine neurotransmitters like norepinephrine, dopamine and serotonin in synapses. In 2008, the drug tetrabenazine was approved by FDA and in 2017 its deuterated version receives the approval. This new compound is more stable thus requires two time daily administration instead of three time daily administration for tetrabenazine. Success of Deutetrabenazine has been translated in to a queue of similar strong researches in pipeline for the deuteration of drugs used in treatment of disease like cystic fibrosis, Narcolepsy, Parkinson disease, Schizophrenia, Alzheimer's, cancer etc. Such researches includes a total of 29 molecules (22 orphan drugs) of which 21 has already entered clinical phase and rest 8 are in developmental phase. 21 molecules in clinical phase points towards positive responses of drugs in those fields till now and suggest that they will be available soon in future for the treatment of diseases. This should be credited to intense studies in application of D_2O in medicine in attempts to utilize its different chemical behavior and effect on living system for the purpose of increasing drugs half-lives and efficacy during last two decades.

Conclusion and Future Prospects

There are significant chances of improvement in the pharmacokinetic and/or toxicological properties of existing drugs by deuteration. There is trend by the pharmaceutical companies to launch the deuterated versions of their new molecules in their ongoing patent applications. These deuterated versions of the new compounds are being tested for variety of diseases for example Huntington disease. There is tremendous scope of development of drug by deuteration.

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