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MAGNITUDE OF HYDROXYCHLOROQUINE: A MINI REVIEW

Vyshnavi. V. Rao* Msc, CSIR-NET Assistant professor, Department of Chemistry, MES College of Arts, Science and Commerce, Bengaluru 560003,Karnataka, India.*Corresponding Author

Shamsiya Rizwana Head of Department, Department of Chemistry, MES College of Arts, Science and Commerce, Bengaluru 560003,Karnataka, India.

ABSTRACT Hydroxychloroquine is a well-established orally administered antimalarial approved in 1950's. Sold under the brand name Plaquenil, it is used as a treatment to wide spectrum of diseases like rheumatoid arthritis, cancer, viral diseases and is associated with the prevention of treatment-induced manifestationslikediabetes mellitus and thrombosis. It has shown promising In-Vitroresults against the 2004 SARS [Severe Acute Respiratory Syndrome] Coronavirus1. Late 2019 and early 2020 has seen a rapid spread of the novel SARS-CoV-2 that caused COVID 19 pandemic. The US-Food and Drug Administration has approved Hydroxychloroquine as potential treatment to COVID 19 coronavirus. This review, discusses current literature on applications, immunomodulatory mechanism, potential side effects, structural characteristics and pharmacokinetics associated with Hydroxychloroquine.

KEYWORDS : Antirheumatologic, Antimalarial, Hydroxychloroquine, Immunomodulatory.

INTRODUCTION:

Hydroxychloroquine and Chloroquine are the two important antimalarial derivatives of Quinine. These have been used since the 1950s for the treatment of various inflammatory, rheumatic diseases like Lupus erythematous, cancers, infections with intracellular miccroorganisms, several dermatologic diseases and used as primary treatments in viral infections lacking drugs [1, 2]. Chloroquine and Hydroxychloroquineunlike Non-steroidal Antiinflammatory Drugs improve clinical parameters by their slow onset of action [3]. There are many proposed mechanisms of action of Hydroxychloroquine such as alkalization ofsub-cellular components, intervention in cell signalling and inhibition of proteases. However uncertainty in the mode of action and risks of Hydroxychloroquine suspects its viability as a potential treatment.

Mechanism Of Action:

Hydroxychloroquine has an immunomodulatory effect on the host cell. It is proposed to involve in lysosomal acidification [4], chemotaxis and phagocytosis. It increases pH within intracellular vacuoles to influence macromolecule assesmbly in endosomes, posttranslational modification in Golgi bodies and alter processes such as protein degradation by enzymes like proteases in the lysosome of immune cells [5, 6]. Hydroxychloroquine reduces the production of interleukins and other cytokines [7]. It is a potent prostaglandin antagonist and inhibits key enzymes like phospholipase A2 [8]. Hydroxychloroquine is attributed to interfere with the 'antigen processing' in macrophages and other antigen presenting cells. It interferes in the calcium mediated cell signalling pathways involved in the inhibition of T- cell and B- cell receptors [9]. Hydroxychloroquine has also a strong binding to melanin and hinders UV light absorption. This reflects the ocular toxicity and dermatological properties Hydroxychloroquine [10,11].

Novel Applications And Effects Of Hydroxychloroquine:

1. Antithrombotic Effect:

Hydroxychloroquine reduces thrombosis by inhibition of platelet aggregation and adhesion, increasing endothelium dependent vasodilation and artery elasticity, reducing vascular stiffness and vascular resistance [12].

2. Anti-neoplastic Effect:

Recent Clinical studies on cancer patients have revealed that Hydroxychloroquine induces apoptosis of malignant B-cells, by interfering with cell signalling molecules like caspase-3 and Bcl-2 [13, 14]. In-vitro studies have revealed Hydroxychloroquine has a strong apoptotic effect on B-lymphocytes [15] andantiproliferative effect on breast cancer cell and mouse colon cancer cell lines [16].

3. Dermatologic Effect:

Hydroxychloroquine blocks UV light absorption throughskin, inhibits subcutaneous light sensitive reactions and reduces skin symptoms like rash [10].

4. Antimalarial Effect:

Hydroxychloroquine is known disrupt the life cycle of the malarial parasite, Plasmodium by actively attacking its heme polymerization process. It is also viewed to passively interfere with the parasite's haemoglobin digestive pathway [17]. This mechanism however is similar to the antimalarial activity of Chloroquine. Hydroxychloroquine is preferred over Chloroquine by virtue of it lower ocular toxicity [18].

5. Antiinflamatory And Antirheumatologic Effect:

Hydroxychloroquine down-regulates the promoter genes to decrease the secretion of monocyte derived pro-inflammatory cytokines like TNF α (Tumour Necrosis Factor alpha) and Interleukins and blocks inflammatory pathways that can be correlated with its anti-rheumatologic activity [19, 20, 21]. Hydroxychloroquine is used as popular treatment to Rheumatologic disorders like Rheumatoid arthritis, Systemic Lupus Erythematous and Osteoarthritis.

6. Immunosuppresive Effect:

Hydroxychloroquine blocks the activation of intracellular Toll like and their subsequent signalling pathways [39]. Hydroxychloroquine substantially influences subcellular physiological activities like lymphocyte proliferation, autoantibody production, recycling of receptors and secretion of inflammatory components by altering the PH of acidic compartments of immune cells like lysosomes [22, 23].

7. Antiautophagy Effect:

Autophagy under critical conditions like reduced oxidative stress enables continued growth of some tumours, by providing key intermediates to sustain cell metabolism and limiting drug efficacy [24]. Hydroxychloroquine produces measurable autophagy inhibition by targeting the lysosomes [4].

8. Antiviral Effect:

Hydroxychloroquine reduces interleukins, inhibits glycosylation of viral particles, inhibits replication of certain viruses and inhibits enzymes like quinonereductase required for biosynthesis of viral glycoprotein precursors like Sialic acid [25, 26]. Several In-vitro and clinical studies have proved efficacy of Hydroxychloroquine on viruses like HIV, Influenza, SARS-CoV and members of Orthomyxoviridae.

Structure Of Hydroxychloroquine:

Hydroxychloroquine with chemical formula C18H26ClN3O with Molar mass 335.872 g/mol is a hydroxyl derivative of Chloroquine belonging to the 4-aminoquinoline family of medication and is chemically a 7-Chloro-4-(4-(N-ethyl-N-beta-hydroxyethylamino)-1-methylbutylamino)-quinoline [see FIG-1] sold as Hydroxychloroquine sulphate.

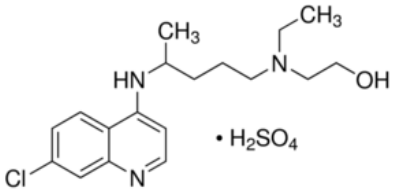

FIG-1: Structure of Hydroxychloroquine [27].

Hydroxychloroquine is a chiral drug with symbolic optical activity existing as a racemic mixture consisting of an R and S enantiomer [21]. (R)-(−)-hydroxychloroquine is present at higher concentrations in the blood and undergoes less rapid elimination than (S)-(+)-hydroxychloroquine suggesting that the metabolism and excretion of the drug in liver is stereoselective [28, 29]

Pharmacokinetic Data Of Hydroxychloroquine:

Hydroxychloroquine is an orally administered drug given as a sulphate salt. Itis almost completely and rapidly absorbed after oral administration. It has a 45% protein binding capacity and even strongly to melanin protein. This can be attributed to its ocular toxicity and possible chronic retinopathy when administered with high doses of Hydroxychloroquine. It is metabolised in liver and excreted biliary [<10%] and largely through kidneys [>25%]. It has a bioavailability [Tmax] of 2 to 4.5 hours and a half-life of 32-50 days.

Hydroxychloroquine is metabolized in the liver into three active metabolites: desethylchloroquine, desethylhydroxychloroquine, and bisdesethylhydroxychloroquine [30].

CONCLUSION:

Hydroxychloroquine and other antimalarial drugs have exhibited significant efficacy on diseases in nearly all major branches of medicine including immunology, oncology, hematology, dermatology, cardiology, and infectious diseases since their first use nearly a century ago. Hydroxychloroquine works partially by inactivating the body's immune response like inflammation, oedema, pain, fever and disrupts critical cell processes. Recent Clinical study reports from China and France have associated Chloroquine, Hydroxychloroquine in combination with antiviral drug like azithromycin to reduction in fever, decrease in lung lesions, delayed disease progression and reduction in the viral load in patients with COVID-19. The exact mechanism however, by which this drug works to resolve malaria and other diseases is largely unknown. In-Vitro studies have shown that hydroxychloroquine inhibits SARS-CoV-2 transmission through alkalinisation of the intracellular phagolysosome, which prevents virion fusion and uncoating and therefore curbs the viral spread.

Though hydroxychloroquine is effective, it is associated with the potential of causing numerous side effects, like headache, loss of appetite, nausea, vomiting, skin rash and in severe cases vision loss due to retinal toxicity. Chloroquine that is a close analogue to hydroxychloroquine is however considered less safe but equally effective.

One significant benefit with using these drugs is that they have been on the market and used for a sufficiently long time. Hence a reasonable amount of information regarding contraindications, allergic responses, side effects, and efficacy is available that can kept in mind before using it to treat new diseases like COVID-19. Since they have been around for so long, generic versions are available, which may prove to be cost-effective for use in coronavirus treatment worldwide.

FUTURE PROSPECTIVES:

Hydroxychloroquine and Chloroquine are well established effective and relatively safe drugs used to treat wide range of disorders from malaria to autoimmunity. There is a greater requirement to gather more information on their mode of action of these drugs with respect to all the mentioned disorders. This can further be used to develop formulations and combinations with enhanced therapeutic activity. The present scenario compels critical care physicians and researchers worldwide to undertake several studies emphasising the role of Hydroxychloroquine as a potential drug.

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