Hydroxychloroquine: Mechanism of Action

Introduction

Hydroxychloroquine (HCQ), is an aminoquinoline used for the prevention and treatment of uncomplicated malaria (caused by P. falciparum, P. malariae, P. ovale, or P. vivax) in areas where malaria is vulnerable to chloroquine. Other applications may include the treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda. It is taken by mouth. HCQ is being investigated for the prevention and diagnosis of coronavirus disease 2019 (COVID-19) High-quality epidemiological care (Stein, et al., 2000).

The FDA approval for emergency use of hydroxychloroquine and chloroquine in COVID-19 treatment was revoked on 15 June 2020 (FDA.gov, 2020).

Hydroxychloroquine obtained approval from the FDA on 18 April 1955 (FDA.gov, 1955).

A recent research recorded a COVID-19.10 fatality in the hydroxychloroquine treated population (Chary, et al., 2020).

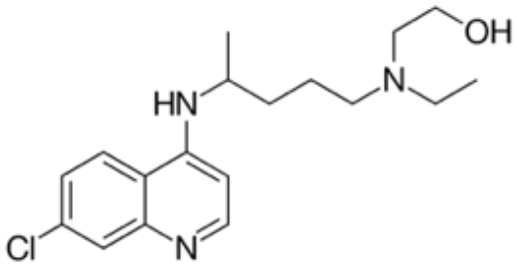

Figure 1. Structure of HCQ

Pharmacodynamics

Hydroxychloroquine affects both lysosomes function and plasmodia in humans. Changing the pH of the lysosomes decreases the low-affinity self-antigen presentation in autoimmune diseases and interferes with plasmodia's ability to proteolyze hemoglobin for its energy needs. Hydroxychloroquine has a long duration of action, as for some indications it might be taken weekly. Hydroxychloroquine can lead to serious hypoglycemia and thus it is recommended that diabetic patients control their blood glucose levels. Hydroxychloroquine in areas where chloroquine resistance has been identified, is not effective against malaria (Wolpin, et al., 2014).

Pharmacokinetics

Absorption

Hydroxychloroquine is bioavailable in 67-74 percent. Bioavailability of the enantiomers R and S did not vary significantly. Following an oral dose of 200 mg, hydroxychloroquine reached a Cmax of 129.6ng / mL with a blood Tmax of 3.26h and a plasma Tmax of 50.3ng / mL with a plasma Tmax of 3.74h. Following intravenous doses of 155 mg and 310 mg, blood Cmax ranged from 1161-2436ng / mL with an average of 1918ng / mL.

Volume of distribution

55,22 L (blood) and 44,257 L (plasma)

Protein binding

In general, hydroxychloroquine is protein-bound in plasma by 50 percent. The hydroxychloroquine S enantiomer is 64 percent plasma bound protein. It is bound to serum albumin by 50

percent and alpha-1-acid glycoprotein by 29 percent. The R enantiomer is plasma-bound protein by 37 percent. It is linked to serum albumin by 29 percent and alpha-1-acid glycoprotein by 41 percent.

Metabolism

Hydroxychloroquine is N-dealkylated by CYP3A4 to the active metabolite called desethylhydroxychloroquine and to the inactive metabolites desethylchloroquine and bidesethylchloroquine. The main metabolite is desethylhydroxychloroquine.

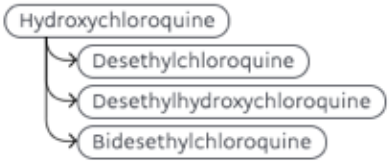

Figure 2. HCQ metabolites. Source (drugbank.ca)

Route of elimination

40-50 percent of hydroxychloroquine is excreted by the kidney, while only 16-21 percent of the dose is excreted in the urine as an unchanged drug. 5 percent of the dose is sloughed off in the skin and 24-25 percent is eliminated in the feces.

Half-life

Oral hydroxychloroquine has a half-life of 3-4 hours of absorption. A 200 mg oral hydroxychloroquine dose has a half-life of 22.4 days in blood, and 123.5 days in the plasma. A 155 mg dose intravenous (iv) has a half-life of 40 days.

Clearance

96mL/min

Mechanism of Action

The precise mechanism of action of HCQ is unknown. Hydroxychloroquine has been shown to accumulate in malaria parasite lysosomes, elevating the pH of the vacuole. This behavior interferes with the ability of the parasite to proteolyze hemoglobin, preventing its normal growth and replication. Hydroxychloroquine may also interfere with the action of parasitic heme polymerase, causing the toxic substance beta-hematin to accumulate.

Hydroxychloroquine concentration in human organelles often raises their pH, which inhibits the processing of antigens, prevents dimerization of the alpha and beta chains of the major histocompatibility complex (MHC) class II, inhibits the cell’s antigen presentation and decreases the inflammatory response. High pH in the vesicles may alter the recycling of MHC complexes to present only the high-affinity complexes on the surface of the cells. Self-peptides bind to low-affinity MHC complexes and therefore are less likely to be exposed to autoimmune T cells. Hydroxychloroquine also lowers cytokine releases, such as interleukin-1 and tumor necrosis factor, probably by Toll-like receptor inhibition.

The elevated pH in endosomes prohibits the use of virus particles (such as SARS-CoV and SARS-CoV-2) for fusion and cell entry.

Hydroxychloroquine also blocks the terminal glycosylation of ACE2, the receptor that targets SARS-CoV and SARS-CoV-2 for cell entry. ACE2 which is not in the glycosylated state may interact less efficiently with the spike protein SARS-CoV-2, further inhibiting viral entry.

References

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