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Hydroxychloroquine

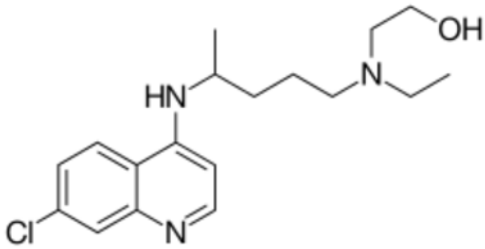
Hydroxychloroquine (**HCQ**), sold under the brand name **Plaquenil** among others, is a medication used to prevent and treat malaria in areas where malaria remains sensitive to chloroquine.[2] Other uses include treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda.[2] It is taken by mouth.[2] It is also being studied as a treatment for coronavirus disease 2019 (COVID-19), although evidence for its efficacy is lacking.[3][4][5]

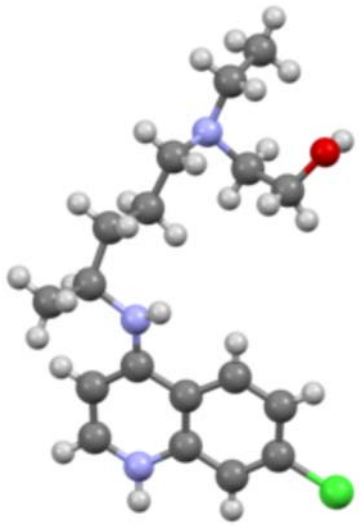
Common side effects may include vomiting, headache, changes in vision, and muscle weakness.[2] Severe side effects may include allergic reactions, vision problems, and heart problems.[2][6] Although all risk cannot be excluded, it remains a treatment for rheumatic disease during pregnancy.[7] Hydroxychloroquine is in the antimalarial and 4-aminoquinoline families of medication.[2]

Hydroxychloroquine was approved for medical use in the United States in 1955.[2] It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.[8] In 2017, it was the 128th most commonly prescribed medication in the United States, with more than five million prescriptions.[9][10]

Contents

Hydroxychloroquine





Hydroxychloroquine freebase molecule

Clinical data	
Trade names	Plaquenil, others
Other names	Hydroxychloroquine sulfate
AHFS/Drugs.com	Monograph (https://www.drugs.com/monograph/hydroxychloroquine-sulfate.html)
MedlinePlus	a601240 (https://medlineplus.gov/druginfo/meds/a601240.html)
License data	US DailyMed: Hydroxychloroquine (https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=Hydroxychloroquine)
Pregnancy category	AU: D [1] US: N (Not classified yet) [1]

Routes of administration	By mouth (tablets)
ATC code	P01BA02 (WHO (https://www.whocc.no/atc_ddd_index/?code=P01BA02))
Legal status	
Legal status	AU: S4 (Prescription only) UK: POM (Prescription only) US: ℞-only In general: ℞ (Prescription only)
Pharmacokinetic data	
Bioavailability	Variable (74% on average); T_{max} = 2–4.5 hours
Protein binding	45%
Metabolism	Liver
Elimination half-life	32–50 days
Excretion	Mostly kidney (23–25% as unchanged drug), also biliary (<10%)
Identifiers	
IUPAC name	
CAS Number	118-42-3 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=118-42-3) ✓
PubChem CID	3652 (https://pubchem.ncbi.nlm.nih.gov/compound/3652)
IUPHAR/BPS	7198 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7198)
DrugBank	DB01611 (https://www.drugbank.ca/drugs/DB01611) ✓
ChemSpider	3526 (http://www.chemspider.com/Chemical-Structure.3526.html) ✓
UNII	4QWG6N8QKH (https://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=4QWG6N8QKH)

Medical use

Hydroxychloroquine is used to treat systemic lupus erythematosus, rheumatic disorders like rheumatoid arthritis, porphyria cutanea tarda, and Q fever, and certain types of malaria.[2] It is considered the first-line treatment for systemic lupus erythematosus.[11] Certain types of malaria, resistant strains, and complicated cases require different or additional medication.[2]

It is widely used to treat primary Sjögren syndrome, but has not been shown to be effective.[12] Hydroxychloroquine is widely used in the treatment of post-Lyme arthritis. It may have both an anti-spirochaete activity and an anti-inflammatory activity, similar to the treatment of rheumatoid arthritis.[13]

Contraindications

The drug label advises that hydroxychloroquine should not be prescribed to individuals with known hypersensitivity to 4-aminoquinoline compounds.[14] There are a range of other contraindications[15][16] and caution is required if patients have certain heart conditions, diabetes or psoriasis.

Adverse effects

The most common adverse effects are nausea,

stomach cramps, and diarrhea. The most serious adverse effects affect the eye, with dose-related retinopathy as a concern even after hydroxychloroquine use is discontinued.[2] For short-term treatment of acute malaria, adverse effects can include abdominal cramps, diarrhea, heart problems, reduced appetite, headache, nausea and vomiting.[2]

For prolonged treatment of lupus or rheumatoid arthritis, adverse effects include the acute symptoms, plus altered eye pigmentation, acne, anemia, bleaching of hair, blisters in mouth and eyes, blood disorders, convulsions, vision difficulties, diminished reflexes, emotional changes, excessive coloring of the skin, hearing loss, hives, itching, liver problems or liver failure, loss of hair, muscle paralysis, weakness or atrophy, nightmares, psoriasis, reading difficulties, tinnitus, skin inflammation and scaling, skin rash, vertigo, weight loss, and occasionally urinary incontinence.[2] Hydroxychloroquine can worsen existing cases of both psoriasis and porphyria.[2]

Children may be especially vulnerable to developing adverse effects from hydroxychloroquine.[2]

KEGG	D08050 (https://www.kegg.jp/entry/D08050) ✓ C07043 (https://www.kegg.jp/entry/C07043) ✓
ChEBI	CHEBI:5801 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:5801) ✗
ChEMBL	ChEMBL1535 (https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/ChEMBL1535) ✓
CompTox Dashboard (EPA)	DTXSID8023135 (https://comptox.epa.gov/dashboard/DTXSID8023135)
ECHA InfoCard	100.003.864 (https://echa.europa.eu/substance-information/-/substanceinfo/100.003.864)
Chemical and physical data	
Formula	$C_{18}H_{26}ClN_3O$
Molar mass	335.872 g/mol g·mol^{-1}
3D model (JSmol)	Interactive image (https://chemapps.stolaf.edu/jmol/jmol.php?model=Clc1cc2nccc%28c2cc1%29NC%28C%29CCCN%28CC%29CCO)
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Eyes

One of the most serious side effects is retinopathy (generally with chronic use).[2][17] People taking 400 mg of hydroxychloroquine or less per day generally have a negligible risk of macular toxicity, whereas the risk begins to go up when a person takes the medication over five years or has a cumulative dose of more than 1000 grams. The daily safe maximum dose for eye toxicity can be computed from a person's height and weight.[18] Macular toxicity is related to the total cumulative dose rather than the daily dose. Regular eye screening, even in the absence of visual symptoms, is recommended to begin when either of these risk factors occurs.[19]

Toxicity from hydroxychloroquine may be seen in two distinct areas of the eye: the cornea and the macula. The cornea may become affected (relatively commonly) by an innocuous cornea verticillata or vortex keratopathy and is characterized by whorl-like corneal epithelial deposits. These changes bear no relationship to dosage and are usually reversible on cessation of hydroxychloroquine.

The macular changes are potentially serious. Advanced retinopathy is characterized by reduction of visual acuity and a "bull's eye" macular lesion which is absent in early involvement.

Overdose

Serious symptoms of overdose generally occur within an hour of ingestion.[20] These symptoms may include sleepiness, vision changes, seizures, stopping of breathing, and heart problems such as ventricular fibrillation and low blood pressure.[20][21] Loss of vision may be permanent.[22] Low blood potassium, to levels of 1 to 2 mmol/L, may also occur.[20][23]

Chloroquine has a risk of death in overdose in adults of about 20%, while hydroxychloroquine is estimated to be two or three fold less toxic.[20] While overdoses of hydroxychloroquine have historically been uncommon, one report documented three deaths out of eight cases.[24]

Treatment recommendations include early mechanical ventilation, cardiac monitoring, and activated charcoal.[20] Intravenous fluids and vasopressors may be required with epinephrine being the vasopressor of choice.[20] Gastric lavage may also be used.[24] Seizures may be treated with benzodiazepines.[20] Intravenous potassium chloride may be required, however this may result in high blood potassium later in the course of the disease.[20] Dialysis has not been found to be useful.[20]

Interactions

The drug transfers into breast milk[1] and should be used with care by pregnant or nursing mothers.

Care should be taken if combined with medication altering liver function as well as aurothioglucose (Solganal), cimetidine (Tagamet) or digoxin (Lanoxin). HCQ can increase plasma concentrations of penicillamine which may contribute to the development of severe side effects. It enhances hypoglycemic effects of insulin and oral hypoglycemic agents. Dose altering is recommended to prevent profound hypoglycemia. Antacids may decrease the absorption of HCQ. Both neostigmine and pyridostigmine antagonize the action of hydroxychloroquine.[25]

While there may be a link between hydroxychloroquine and hemolytic anemia in those with glucose-6-phosphate dehydrogenase deficiency, this risk may be low in those of African descent.[26]

Specifically, the US Food and Drug Administration's drug label for hydroxychloroquine lists the following drug interactions:[14]

- Digoxin (wherein it may result in increased serum digoxin levels)
- Insulin or anti-diabetic medication (wherein it may enhance the effects of a hypoglycemic treatment)
- Drugs that prolong QT interval and other arrhythmogenic drugs (as Hydroxychloroquine prolongs the QT interval and may increase the risk of inducing ventricular arrhythmias if used concurrently)[6]
- Mefloquine and other drugs known to lower the convulsive threshold (co-administration with other antimalarials known to lower the convulsion threshold may increase risk of convulsions)
- Antiepileptics (concurrent use may impair the antiepileptic activity)
- Methotrexate (combined use is unstudied and may increase the frequency of side effects)
- Cyclosporin (wherein an increased plasma cyclosporin level was reported when used together).

Pharmacology

Pharmacokinetics

Hydroxychloroquine has similar pharmacokinetics to chloroquine, with rapid gastrointestinal absorption, large distribution volume,[27] and elimination by the kidneys. Cytochrome P450 enzymes (CYP2D6, 2C8, 3A4 and 3A5) metabolize hydroxychloroquine to *N*-desethylhydroxychloroquine.[28]

Pharmacodynamics

Antimalarials are lipophilic weak bases and easily pass plasma membranes. The free base form accumulates in lysosomes (acidic cytoplasmic vesicles) and is then protonated,[29] resulting in concentrations within lysosomes up to 1000 times higher than in culture media. This increases the pH of the lysosome from four to six.[30] Alteration in pH causes inhibition of lysosomal acidic proteases causing a diminished proteolysis effect.[31] Higher pH within lysosomes causes decreased intracellular processing, glycosylation and secretion of proteins with many immunologic and nonimmunologic consequences.[32] These effects are believed to be the cause of a decreased immune cell functioning such as chemotaxis, phagocytosis and superoxide production by neutrophils.[33] HCQ is a weak diprotic base that can pass through the lipid cell membrane and preferentially concentrate in acidic cytoplasmic vesicles. The higher pH of these vesicles in macrophages or other antigen-presenting cells limits the association of autoantigenic (any) peptides with class II MHC molecules in the compartment for peptide loading and/or the subsequent processing and transport of the peptide-MHC complex to the cell membrane.[34]

Mechanism of action

Hydroxychloroquine increases[35] lysosomal pH in antigen-presenting cells. In inflammatory conditions, it blocks toll-like receptors on plasmacytoid dendritic cells (PDCs).[36] Toll-like receptor 9 (TLR 9), which recognizes DNA-containing immune complexes, leads to the production of interferon and causes the dendritic cells to mature and present antigen to T cells. Hydroxychloroquine, by decreasing TLR signaling, reduces the activation of dendritic cells and the inflammatory process.

In 2003, a novel mechanism was described wherein hydroxychloroquine inhibits stimulation of the toll-like receptor (TLR) 9 family receptors. TLRs are cellular receptors for microbial products that induce inflammatory responses through activation of the innate immune system.[37]

As with other quinoline antimalarial drugs, the antimalarial mechanism of action of quinine has not been fully resolved. The most accepted model is based on hydrochloroquinine and involves the inhibition of hemozoin biocrystallization, which facilitates the aggregation of cytotoxic heme. Free cytotoxic heme accumulates in the parasites, causing death.[38]

Society and culture

Cost

The wholesale cost in the developing world was about US$4.65 per month as of 2015, when used for rheumatoid arthritis or lupus.[39] In the United States the wholesale cost of a month of treatment is about US$25 as of 2020.[40] In the United Kingdom this dose costs the National Health Service about £5.15.[41]

Brand names

It is frequently sold as a sulfate salt known as hydroxychloroquine sulfate.[2] 200 mg of the sulfate salt is equal to 155 mg of the base.[2]

Brand names of hydroxychloroquine include Plaquenil, Hydroquin, Axemal (in India), Dolquine, Quensyl, Quinoric.[42]

2020 COVID-19 use

On 17 March 2020, the AIFA Scientific Technical Commission of the Italian Medicines Agency expressed a favorable opinion on including the off-label use of chloroquine and hydroxychloroquine for the treatment of COVID-19.[43]

In the US, several state pharmacy boards reported that some doctors and dentists were writing prescriptions for hydroxychloroquine and a related drug, chloroquine, to themselves, family members, and staff.[44][45] Sudden demand spikes caused by hospital use for severely ill COVID-19 patients and prescriptions for prophylaxis have resulted in shortages; doctors have expressed concern that patients who have long taken hydroxychloroquine for other approved indications, like lupus and rheumatoid arthritis, will be unable to procure needed medicine.[45][46]

On 28 March 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to allow hydroxychloroquine sulfate and chloroquine phosphate products donated to the Strategic National Stockpile (SNS) to be distributed and used for certain people who are hospitalized with COVID-19.[47][48]

In anticipation of product shortages, the FDA issued product-specific guidance for chloroquine phosphate and for hydroxychloroquine sulfate for generic drug manufacturers.[49]

During a press briefing on March 19, 2020; Donald Trump, the President of the United States, promoted the drugs chloroquine and hydroxychloroquine as a potential treatment for Covid-19.[50][51] Trump claimed that chloroquine had been FDA "approved very, very quickly" as a treatment for COVID-19. The FDA later disavowed such approval,[52] but was now allowing chloroquine under compassionate use guidelines.[53][54] Trump's remarks led to a shortage of chloroquine and hydroxychloroquine in the United States and panic-buying in Africa and South Asia.[55][56]

In the state of Arizona, a man died, leaving his wife in critical condition, as a result of ingesting fish bowl cleaner, which contained chloroquine phosphate. The couple believed the chemical cleaner could prevent them from contracting COVID-19, although the chloroquine phosphate in fish bowl cleaners is not the same formulation found in the medicines chloroquine or hydroxychloroquine.[57]

On 18 May 2020, Trump publicly stated that he was taking hydroxychloroquine during the COVID-19 pandemic, despite evidence indicating that it is "linked to higher rates of death in hospitalized

COVID-19 patients with pre-existing conditions", and other studies that show it to be ineffective.[58]

Research

COVID-19

As of 22 April 2020, there is limited evidence to support the use of hydroxychloroquine for coronavirus disease 2019 (COVID-19).[59] Studies are ongoing with the benefits versus harms of treatment being unclear.[3][60] While its use is not approved by the FDA for COVID-19 as of 7 April 2020, there is an Emergency Use Authorization for such use.[61] Some are also using it off label for the disease.[62] On 24 April 2020, citing the risk of "serious heart rhythm problems", the FDA posted a caution against using the drug for COVID-19 "outside of the hospital setting or a clinical trial".[63]

As of 8 April 2020, there has been one randomized controlled trial on 36 patients which found no difference with HCQ, suggesting that if HCQ has an effect it is at most modest.[64]

The publication status of one non-randomized trial, which claimed hydroxychloroquine benefits for COVID-19 is ambiguous.[65][66][67][68][69] According to an official statement from the International Society of Antimicrobial Chemotherapy (ISAC):[70] "ISAC shares the concerns regarding the above article published recently in the International Journal of Antimicrobial Agents (IJAA). The ISAC Board believes the article does not meet the Society's expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety."[70] Additionally, on 13 April 2020 a joint ISAC and Elsevier statement was issued, that included the following text:[71] "At present, additional independent peer review is ongoing to ascertain whether concerns about the research content of the paper have merit. Given this process of post-publication assessment is on-going, it would be premature to comment at this time. The study authors have been contacted and asked to address the concerns."[71]

In April 2020, the US National Institutes of Health (NIH) began a trial of the medication.[72][73]

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