ROLE OF HYDROXYCHLOROQUINE IN SPECIFIC DISEASES: A COMPREHENSIVE REVIEW

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Abstract:

The hydroxychloroquine (HCQ) is a 4-aminoquinoline molecule that has been used to treat malaria. It has been shown to have immunomodulatory effects in patients with chronic rheumatoid arthritis (RA), psoriasis, and acute generalised exanthematous pustulosis. HCQ has also been found to have anti-inflammatory effects in a wide range of conditions, including diabetes mellitus, inflammatory bowel disease (IBD), and chronic systemic lupus erythematosus (SLE). The aim of this review is to provide a brief overview of the clinical, clinical, and pharmacological effects of hydroxychloroquine in various diseases.

Keywords: Hydroxychloroquine, malaria, Rheumatoid Arthritis, SLE, Covid 19.

1. INTRODUCTION

HCQ and chloroquine (CQ) are 4-aminoquinolines, but HCQ has a hydroxyethyl group on the tertiary amino acid side chain in place of the ethyl group found on CQ's side chain. HCQ, or 2-[[4-[(7-chloro-4-quinolyl) amino]pentyl]ethanol sulphate, is an immunomodulator and antimalarial. After oral administration, HCQ is quickly absorbed and has a lengthy half-life of 30 to 60 days, reaching steady plasma levels up to 6 months after therapy begins. Several months to years after ceasing use, HCQ can still be found in plasma and tissues. CYP450 breaks down HCQ in the liver, where it is then eliminated by the kidneys [1]. HCQ and CQ vary in that HCQ has an extra hydroxyl group and has less toxicity while still being effective [2].

1.1 History: Originally intended to treat malaria, hydroxychloroquine was later discovered to have immunomodulatory effects. The US Food and Drug Administration have now given it the go-ahead for the treatment of discoid lupus, systemic lupus erythematus, and rheumatoid arthritis [3].

1.2 Side Effects: Up to 10% of people may experience their most frequent side effects, which include gastrointestinal issues, pruritus, and dermatological abnormalities. Others include cardiotoxicity, irreversible retinopathy, and proximal muscle neuromyopathy. On the other hand, stopping the medicine can cause the neuromuscular abnormalities to gradually improve. QT prolongation syndrome is a potential symptom of cardiotoxicity, particularly in patients with renal or hepatic failure. Particularly with chloroquine, overdose toxicity has been noted between 1 and 3 hours following a high-dose ingestion. When administered at doses of 20 mg/kg or more, toxic consequences can be lethal. Visual changes, nausea, hypokalemia, sleepiness, shock, convulsions, and even death are symptoms of an overdose. The remedy diazepam has been employed[4].

1.3 Risk: The following factors increase the chance of developing hydroxychloroquine retinopathy: daily doses greater than 400 mg, or greater than 6.5 mg/kg for short people, cumulative doses greater than 1000 g, renal or hepatic failure, obesity, age greater than 60 years, and pre-existing retinal illness or maculopathy[5].

2. HCQ IN MALARIA

Countess Cinchona's experience with malaria and the subsequent discovery of quinine from tree bark in 1820 marked a significant milestone in the treatment of malaria. Quinine became the main antimalarial medicine and remained in use until 1942[6]. As the development of drugs

to treat malaria progressed, atabrine (quinacrine) emerged as the first extensively used antimalarial before World War II. However, it had adverse effects such as skin yellowing [7]. Chloroquine (CQ), a 4-aminoquinoline molecule, was introduced as a medication to prevent and cure malaria. It targeted the ring forms of the malaria parasites, which were largely resistant to the effects of quinine. CQ exerted its impact on the parasite either directly through the heme polymerization process or indirectly through the haemoglobin digestion pathway[7]. Hydroxychloroquine (HCQ), a derivative of chloroquine, was developed through further chemical modification and became available in 1955. While HCQ is still used as an antimalarial drug, it has found more frequent use in the treatment of autoimmune illnesses[7]. The FDA-approved indications for HCQ include malaria, rheumatoid arthritis (RA), and lupus erythematosus (LE). HCQ can effectively treat uncomplicated malaria caused by *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium vivax*. It is also recommended for malaria prevention in regions where there is no reported chloroquine resistance. It's important to note that the use of HCQ for various conditions, including malaria and autoimmune diseases, is subject to ongoing research and clinical guidelines. The information provided reflects the historical development and understanding of these medications, but individual cases and treatment decisions should always be made in consultation with healthcare professionals[6].

2.1 Pharmacologic Properties: Hydroxychloroquine (HCQ) exhibits specific pharmacokinetic properties. Some of its key characteristics include:

Elimination Half-life: The elimination half-life of HCQ is approximately 40 to 50 days. This means that it takes a considerable amount of time for the body to eliminate half of the administered dose of HCQ.

Renal Excretion: Approximately 50% of HCQ is eliminated from the body through renal excretion. The elimination process is concentration-dependent, meaning that higher concentrations of HCQ in the body result in increased elimination through the kidneys.

Steady-state Concentration: After approximately six months of regular treatment with HCQ, the drug reaches about 95% of its steady-state concentration. This implies that the drug accumulates in the body over time until it reaches a relatively stable level.

Oral Bioavailability: HCQ has an oral bioavailability of about 75%, meaning that approximately 75% of the administered dose is absorbed into the bloodstream when taken orally. The remaining percentage may be lost or undergo metabolism during absorption.

Interindividual Variability: The pharmacokinetics of HCQ can vary from person to person. Factors such as age, weight, liver and kidney function, and concurrent medications can influence the absorption, distribution, metabolism, and excretion of HCQ. Therefore, the response and effectiveness of HCQ treatment may differ among individuals[7].

It's important to note that these pharmacokinetic properties provide a general understanding of how HCQ behaves in the body. Individual variations and specific medical conditions may require adjustments in dosing and monitoring, which should be determined by healthcare professionals[7].

2.2 Adverse drug reactions:

Hydroxychloroquine (HCQ) can cause several adverse effects, although they are generally considered to be modest and transient. Here are some of the known adverse effects associated with HCQ:

Gastrointestinal Effects: Gastrointestinal side effects are among the most common and may occur at the beginning of treatment. These can include anorexia (loss of appetite), vomiting, nausea, stomachaches, diarrhea, and weight loss. These symptoms usually resolve quickly after discontinuing HCQ[9].

Cutaneous Hyperpigmentation: Cutaneous hyperpigmentation, or darkening of the skin, can occur with the use of HCQ. This hyperpigmentation is believed to be caused by local bruising and subsequent iron deposits in the soft tissues[9].

Cardiomyopathy (Neurocardiomyopathy): Cardiomyopathy refers to a disease of the heart muscle. While exceedingly uncommon, neurocardiomyopathy has been reported as a rare side effect of HCQ. It is characterized by cardiac hypertrophy (enlargement) and conduction problems, and it is thought to result from HCQ's impact on lysosomal action[9].

Acute Generalized Exanthematous Pustulosis: Another uncommon side effect of HCQ therapy is acute generalized exanthematous pustulosis, which presents as widespread pustules on the skin accompanied by peeling and scaling. This reaction can resemble pustular psoriasis. In most cases, it resolves within two weeks after discontinuing HCQ, although in some instances, it may persist for weeks to months or fluctuate over time. The prolonged half-life of HCQ may contribute to the longer recovery period observed in some cases[9].

It's important to note that these adverse effects are relatively rare and most individuals tolerate HCQ without experiencing severe side effects. However, it's crucial to consult a healthcare

professional if any concerning symptoms occur during HCQ treatment. They can provide proper guidance, monitor for adverse effects, and determine the best course of action[9].

2.3 Mechanism of Action

The mechanism of action of antimalarial drugs, including hydroxychloroquine (HCQ), in various diseases is not fully understood. However, there are several proposed mechanisms that may explain their effects in chronic inflammatory conditions. These mechanisms include: Alkalinization of lysosomes and intracellular compartments: Antimalarials can increase the intracellular pH and interfere with phagocytosis. This change in pH may lead to a selective alteration in the presentation of antigens, influencing the immune response. Blockage of T-cell response and reduction of pro-inflammatory cytokine production: HCQ has been shown to inhibit T-cell responses and decrease the production of pro-inflammatory cytokines such as interferon-gamma (INF-γ), tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6). This immunomodulatory effect can help regulate the inflammatory response in chronic inflammatory conditions.Blockage of toll-like receptors (TLRs): HCQ can inhibit toll-like receptors 7 and 9, particularly in plasmacytoid dendritic cells. This inhibition may impact the production of interferon-alpha (INF-α), which is involved in the pathophysiology of systemic lupus erythematosus (SLE).Inhibition of the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway: The cGAS-STING pathway plays a crucial role in the immune system's response to microbial infection and DNA damage. Antimalarials can inhibit this signaling pathway, affecting the immune response.Inhibition of phospholipase A2 activity: Antimalarials have been found to inhibit the activity of phospholipase A2, an enzyme involved in the release of inflammatory mediators. This inhibition may contribute to the anti-inflammatory effects of HCQ. Stimulation of nitric oxide production: HCQ can stimulate the production of nitric oxide by endothelial cells. Nitric oxide has anti-inflammatory and antiproliferative effects, which may contribute to the therapeutic effects of HCQ. It's important to note that while these mechanisms have been proposed, the precise mechanism of action of antimalarials in different diseases is still an area of ongoing research and investigation[8].

3. HYDROXYCHLOROQUINE IN RHEUMATOID ARTHRITIS

SLE, Rheumatoid arthritis, Sjogren’s syndrome are considered as rheumatic autoimmune disorders which caused due the immune system targeting healthy tissues such as joints [10]. A systemic inflammatory disease characterized by chronic and erosive synovitis, especially on the peripheral joints is called as rheumatoid arthritis [11].

The exact mechanism of action of HCQ in RA is not fully understood, but several mechanisms have been proposed. HCQ is believed to have immunomodulatory and anti-inflammatory effects. Here are some key mechanisms of action:

a) Inhibition of endolysosomal activities: HCQ inhibits endolysosomal activities, including autophagy. This disruption of cellular processes may contribute to its immunomodulatory effects.
b) Inhibition of cytokine signaling: HCQ can interfere with cytokine signaling pathways, particularly those involving endosomal Toll-like receptors (TLRs). By blocking TLRs, HCQ may reduce the production of pro-inflammatory cytokines.
c) Inhibition of NADPH oxidase (NOX) signaling: HCQ has been shown to inhibit NOX signaling, which plays a role in generating reactive oxygen species (ROS) and promoting inflammation.
d) Calcium regulation: HCQ may modulate calcium signaling in immune cells, which can affect various cellular processes involved in immune regulation[8].

HCQ is administered orally as hydroxychloroquine sulfate. It is well-distributed throughout the body, including tissues such as muscles, liver, spleen, lungs, kidneys, pituitary and adrenal glands, and melanin-containing tissues. Approximately 30-40% of HCQ is bound to plasma proteins, while the remaining 60-70% remains unbound and pharmacologically active. HCQ has a long elimination half-life of 40 to 50 days[10].

The daily dose of HCQ for rheumatic autoimmune disorders, including RA, typically ranges from 200 to 600 mg. HCQ works by reducing the inflammatory response, thereby alleviating typical RA symptoms such as joint discomfort and skin disorders[10].

Incidence of the disease increases at 50 years of age and more commonly affects women than men. The disease is characterized by synovial joint inflammation, which could eventually result in the destruction of bone and cartilage and present with extra-articular symptoms which have 1.5-fold higher risk of death compared to the average population. DMARDs, which can be classified as either synthetic (small chemical compounds delivered orally) or biological (monoclonal antibodies or receptor constructions injected parenterally) treatments, are the basis of RA treatment. The earlier synthetic DMARDs mechanism of action is still not entirely understood, despite the fact that treatment with these medicines is associated with reduced inflammation as shown by decreased CRP levels. Conventional synthetic DMARDs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs) are the two types of synthetic DMARDs. csDMARDs, include methotrexate (MTX), sulphasalazine, leflunomide, gold salts,

and hydroxychloroquine, have been in use for more than 50 years [12]. 4-Aminoquinolones are standard synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs), which act on multiple critical areas of immune regulation to control innate and adaptive immunity [13]. Chloroquine and its analogues, which were initially used for antimalarial therapy and prevention, developed a new anti-inflammatory application during World War II. Military doctors saw an improvement in inflammatory arthritis as millions of soldiers used it to treat malaria, which led to studies showing aminoquinoline's effectiveness for rheumatologic disorders [14].

While the precise mode of action of HCQ in RA is still unknown, its immunomodulatory and anti-inflammatory effects are believed to be mediated through various mechanisms, including stabilizing lysosomal membranes, reducing antigen presentation, inhibiting cell-mediated cytotoxicity, and suppressing Toll-like receptors. HCQ has been approved by the FDA for the treatment of RA and systemic lupus erythematosus (SLE). HCQ is often used in combination with other DMARDs, such as methotrexate (MTX) and sulfasalazine (SSZ), and has shown to be effective in achieving remission in RA patients[15].

Recent research has also indicated that HCQ may have additional benefits, including promoting synovial cell apoptosis, reducing cholesterol and blood sugar levels, lowering the risk of diabetes, preventing osteoporosis, and protecting against severe infections.

Studies have demonstrated that combining low-dose glucocorticoids (GCs) with HCQ and MTX can effectively improve symptoms, signs, laboratory inflammatory activity, and quality of life in patients with early rheumatoid arthritis.

It's important to note that treatment decisions should be made in consultation with a healthcare professional, taking into account individual patient factors and considering the potential benefits and risks of HCQ therapy[16].

4. HCQ and COVID 19

Hydroxychloroquine (HCQ) and chloroquine have been studied for their potential antiviral activity against SARS-CoV-2, the virus that causes COVID-19. The mechanism behind their antiviral action is not fully understood, but several potential mechanisms have been proposed.

One aspect of HCQ and chloroquine's antiviral activity is their ability to interfere with viral replication. These drugs are weak bases that can disrupt acid vesicles within cells, including endosomes and lysosomes. This disruption can impair viral entry into the host cells, particularly when endocytosis is pH-dependent. By raising the pH within the vesicles, HCQ

and chloroquine can prevent the release of the viral genetic material into the host cell, thereby inhibiting viral replication. In addition, to their effects on viral entry, HCQ and chloroquine may have other inhibitory effects on viral replication. These drugs can interfere with various enzymes involved in viral replication processes. They have been shown to inhibit certain viral families' replication, possibly by interfering with post-translational modifications and glycosyl-transferases. The suppression of viral glycosylation, which is an essential step in the replication of some viruses, has been proposed as a potential mechanism underlying the antiviral effects of HCQ and chloroquine[17].

It's important to note that while HCQ and chloroquine have shown in vitro activity against SARS-CoV-2, their effectiveness in treating COVID-19 in clinical settings has been a subject of debate and ongoing research. The clinical evidence on the use of these drugs for COVID-19 has been mixed, and several large-scale clinical trials have reported no significant clinical benefits or have even raised concerns about potential side effects.

Furthermore, the dosage, timing, and patient selection are crucial factors in determining the potential benefits and risks of HCQ or chloroquine treatment for COVID-19. Treatment decisions should be made based on current guidelines and in consultation with healthcare professionals, considering the individual patient's condition and potential risks associated with the use of these drugs.

As mentioned earlier, hydroxychloroquine (HCQ) and chloroquine can interfere with viral replication, in addition to their potential cytokine inhibition effects. These drugs have been observed to have multiple mechanisms that can impede viral replication[18].

One aspect is their ability to affect the acid vesicles within cells. HCQ and chloroquine are weak bases that can alter the pH of these vesicles, including endosomes and lysosomes. By raising the pH, they can interfere with the pH-dependent endocytosis process, which is involved in viral entry into host cells. This interference can prevent the viral genetic material from being released into the cell, thus inhibiting viral entry and subsequent replication.

Furthermore, HCQ and chloroquine have been found to block various enzymes that play essential roles in viral replication. By inhibiting these enzymes, they can impede the replication of certain viral families. Additionally, these drugs have been shown to interfere with viral post-translational modifications and glycosyl-transferases. Viral glycosylation is an important process for the replication of some viruses, and the suppression of this glycosylation by HCQ and chloroquine has been proposed as a potential mechanism for their antiviral activity.

It's important to note that while these mechanisms have been observed in laboratory studies and in vitro experiments, the clinical effectiveness of HCQ and chloroquine against SARS-CoV-2, the virus causing COVID-19, has not been definitively established. Clinical trials and real-world evidence have provided conflicting results, and the use of these drugs for COVID-19 treatment has been the subject of ongoing debate and research [17].

4.2 The Use Of Hcq In SARS-CoV:

The coronavirus is known as SARS-CoV, often known as severe acute respiratory syndrome (SARS). Fever, chills, lethargy, coughing, and dyspnea were the symptoms of the syndrome, which can lead to respiratory failure. Since endocytosis may be involved in viral entry into the cell and there was a significant immune response that was causing clinical worsening, likely due to inflammatory cytokines like TNF-alpha and IL-6, Savarino et al. were the first to postulate that hydroxychloroquine and chloroquine might be helpful in treating SARS. At various postinfection periods, Kayaerts et al. showed that chloroquine inhibited the SARS-CoV in Vero E6 cells. In Vero E6 cells, Vincent et al. demonstrated that the virus may be effectively inhibited in a dose-dependent manner both immediately after viral absorption and up to three hours later [17].

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Furthermore, the dosage, timing, and patient selection are crucial factors in determining the potential benefits and risks of HCQ or chloroquine treatment for COVID-19. Treatment decisions should be made based on current guidelines and in consultation with healthcare professionals, considering the individual patient's condition and potential risks associated with the use of these drugs. Beyond cytokine inhibition, hydroxychloroquine and chloroquine have an impact on viral replication. These drugs are weak bases that can interfere with acid vesicles and block a number of enzymes. When endocytosis is pH dependent, this property enables it to prevent viral entrance into the cell. Additionally, it inhibits some viral families' replication, viral post-translational modifications and glycosyl-transferases. The suppression of viral glycosylation, an essential antiviral action of these medications, has been theorised to be the origin of their antiretroviral impact [17].

Yes, as mentioned earlier, hydroxychloroquine (HCQ) and chloroquine can interfere with viral replication, in addition to their potential cytokine inhibition effects. These drugs have been observed to have multiple mechanisms that can impede viral replication. One aspect is their ability to affect the acid vesicles within cells. HCQ and chloroquine are weak bases that can alter the pH of these vesicles, including endosomes and lysosomes. By raising the pH, they can interfere with the pH-dependent endocytosis process, which is involved in viral entry into host cells. This interference can prevent the viral genetic material from being released into the cell, thus inhibiting viral entry and subsequent replication.

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4.3 Mechanism in SARS-COV:

Hydroxychloroquine (HCQ) has been studied for its potential antiviral effects against SARS-CoV-2, the virus causing COVID-19. The mechanism of action involves both pre- and

post-entry effects.In vitro studies have demonstrated that HCQ can inhibit the entry of SARS-CoV-2 into host cells. One proposed mechanism is the interference with the virus's interaction with the ACE2 receptor, which is the receptor that SARS-CoV-2 uses to enter human cells. By inhibiting the ACE2 receptor, HCQ may prevent the virus from attaching and entering the cells, thus reducing viral replication. Furthermore, HCQ has been found to have post-entry effects on SARS-CoV-2. It can suppress the production of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha). These cytokines play a role in the inflammatory response associated with COVID-19, and their suppression by HCQ may help reduce the excessive immune response and inflammation seen in severe cases of the disease18].

In vivo studies have shown some promising results regarding the therapeutic potential of HCQ in reducing viral load and improving clinical outcomes in COVID-19 patients. However, it's important to note that the clinical effectiveness of HCQ in treating COVID-19 remains a topic of debate and ongoing research. Various clinical trials and real-world evidence have provided conflicting results, and the drug is no longer recommended as a standard treatment for COVID-19 by most health authorities. The use of HCQ in COVID-19 treatment should be based on current clinical guidelines and individual patient factors, and it is important to consult healthcare professionals for guidance[19].

4.4 Conflicting Reports on the Management of COVID-19 Using CQ/HCQ:

HCQ is regarded as the "miracle drug" or "wonder drug" since it has antiviral properties that can help with the treatment of COVID-19 patients. CQ slows the disease's course by lowering fever and lung lesions, but HCQ combined with azithromycin can lower viral loads in COVID-19 patients. The ability of HCQ to reduce viral load is improved by azithromycin. Additionally, CQ shortens the time that symptoms last and pneumonia flare-ups. CQ and HCQ have the same MOA, however, HCQ is more effective than CQ [18].

4.5 The impact of hydroxychloroquine and azithromycin on the viral clearance of SARS-CoV-2:

The data on the impact of hydroxychloroquine and azithromycin on the viral clearance in COVID-19 patients were analyzed using Hervé Seligmann's statistical methodology. it clearly seems that these results were robust and confirms the need for large-scale studies on the effect of hydroxychloroquine and azithromycin on both SARS-CoV-2 clearance and clinical benefit in COVID-19 patients [19].

5. HYDROXYCHLOROQUINE IN SLE

Hydroxychloroquine (HCQ) sulfate is the hydroxylated analog of chloroquine. The drug has been initially used as an antimalarial agent, since it may inhibit the plasmodial heme polymerase. However, a number of experimental and clinical observations also outlined the efficacy of HCQ in a wide array of conditions, including diabetes mellitus, dyslipidemias, coagulopathies, infectious diseases, malignancies, as well as in a number of autoimmune diseases, including Sjogren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus (SLE) [20].

5.1 Mechanism Of Action Of Hydroxychloroquine: HCQ is a lipophylic, lysosomotropic drug that can easily pass through cell membranes. In the cytoplasm, the free base form of HCQ accumulates in lysosomes. These are spherical vesicles that contain an array of hydrolytic enzymes which are activated by the highly acidic pH. Lysosomes generate and maintain their pH gradients by using the activity of a proton-pumping V-type ATPase, which uses metabolic energy in the form of ATP to pump protons into the lysosome lumen. The high concentrations of the alkalinizing HCQ in lysosomes increase their pH from the normal levels of 4.7–4.8 to 6. The alkalinization caused by HCQ results in expansion and vacuolization of lysosomes and inhibition of their functions, including enzyme release, receptor recycling, plasma membrane repair, cell signaling, and energy metabolism. Since these changes can interfere with the function of the immune competent cells. HCQ can contribute with other drugs in downregulating the immune response against auto-antigenic peptides, a property that can be exploited in the treatment of SLE [20].

Main mechanisms of action of hydroxychloroquine (HCQ):

HCQ can easily pass through the cell membrane

↓

It accumulates in the acidic lysosomes

↓

The high concentration of alkaline HCQ increases the pH in lysosomes

↓

The increased pH inhibits lysosomes functions interfering with metabolic and immune pathways

HCQ can inhibit the proinflammatory cytokines IL-6, IL-1β tumor necrosis factor-α (TNF-α), and can block T cell activation by disrupting the T cell receptor dependent calcium signaling. Moreover, HCQ is a powerful inhibitor of lysosomedependent autophagy. By preventing the

acidification of lysosomal compartment HCQ can impair autophagic protein degradation, which is a critical step for activating innate and acquired immunity. This effect is currently investigated by oncologists, who are using combination of HCQ with anticancer treatments in different types of malignancy. Finally, treatment with HCQ has been associated with reduced risk of thrombosis in antiphospholipid syndrome [20].

5.2 Pharmacologic Data: A weak base, HCQ sulphate is entirely absorbed from the digestive system. The medication is metabolised in the liver by cytochrome P450 enzymes to N-desethylhydroxychloroquine, desethylchloroquine, and bisdesethylchloroquine, and has an excellent bioavailability (around 0.74). It has a lengthy half-life of elimination, ranging from 40 to 60 days, and is primarily eliminated through the kidneys. Drugs like isoniazide or anticonvulsants that activate cytochrome P450 enzymes may lower blood levels of HCQ, whereas drugs like nondihydropyridinic calcium channel blockers that inhibit cytochrome P450 may raise blood levels. In non-diabetics, HCQ increases insulin sensitivity while also enhancing beta cell activity. These metabolic alterations could be the cause of the association between HCQ medication and a decreased risk of type 2 diabetes. Initial HCQ dosage for SLE patients is 400 mg taken orally once or twice per day. A therapeutic impact could take weeks or months to manifest. The daily maintenance dose ranges from 200 to 400 mg [20].

5.3 **Efficacy In SLE:** Not just in individuals with mild types of SLE, but also in patients with organ involvement, HCQ may have a number of potential advantages. The doctor should consider that HCQ is a slow-acting medication when prescribing the dose because its benefits frequently start to show up after 6 months. As a result, when SLE is acute, it should be administered in conjunction with other treatment medications that may be discontinued after the antimalarial impact is seen. It is best to avoid using a dipstick to measure proteinuria in individuals with lupus nephritis who are receiving HCQ. In fact, a substantial incidence of false positive results may result from HCQ's analytical interaction with the traditional dipstick test [20].

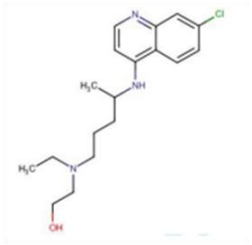
5.4 **Safety Evaluation:** Drug experts believe HCQ to be secure. However, just like any other medication, HCQ has the potential to cause a range of negative side effects. Most adverse events associated with HCQ are caused by purposeful or unintentional overdosage, and HCQ side effects are typically dose-dependent. Skin-related adverse effects are more likely to occur in patients who have allergies, psoriasis, porphyria, or alcoholism. Children are especially susceptible to the negative consequences of even a slight chloroquine overdose. Given its resemblance to chloroquine and the paucity of information on peadiatric HCQ overdoses and

reports of toxicity from 1 to 2 pills, HCQ should likewise be regarded as potentially dangerous in children at low dosages [20].

5.5 **Hydroxychloroquine Blood Level Monitoring and Withdrawal:** It was suggested to measure HCQ in whole blood to track therapy adherence and response, although there is still disagreement on the ideal cutoff for determining effective HCQ blood levels. One prospective multicenter study indicated that patients with complete remission had considerably higher median blood [HCQ] levels (910ng/ml in remission versus 692ng/ml when in partial remission and 569ng/ml when treatment failed, p=0.007). Improvement of cutaneous lesions was seen in a prospective trial when [HCQ] blood levels greater than 750ng/ml were attained. [21].

5.6 **Blood Concentrations Of Hydroxychloroquine In SLE Patients:** Despite everyone receiving the same dose, HCQ blood concentration varies greatly amongst people. Lower SLE disease activity index (SLEDAI) scores were substantially correlated with greater blood HCQ concentrations in SLE patients receiving long-term oral HCQ therapy. Desethyl hydroxychloroquine (DHCQ) and desethyl chloroquine (DCQ) are metabolites of HCQ that similarly showed a concentration-dependent association in RA patients, and bisdesethyl chloroquine (BDCQ) has also been linked to HCQ toxicity. Cytochrome P450 enzymes (CYP450s) 3A4/5, 2C8, and 2D6 metabolise HCQ in vivo through N-deethylation into DHCQ, DCQ, and BDCQ, with DHCQ serving as the primary metabolite and the active form of HCQ [22].

Main Pharmacodynamic Properties of Antimalarials:

Properties	Hydroxychloroquine (HCQ)
Chemical structure	
Chemical formula	$C_{18}H_{26}ClN_3O$
Way of administration	Oral intake
Absorption	In upper intestinal tract after a 200mg oral dose, HCQ reached a C_{max} of 129.6ng/ml with a T_{max} of 3.26h in the blood
Bioavailability	67–74%
Volume of distribution	5522 L from blood and 44,257 L from plasma
Protein binding	50%
Metabolism	In the liver, N-dealkylated by CYP3A4 to the active metabolite desethylhydroxychloroquine, as well as the inactive metabolites desethylchloroquine and bidesethylchloroquine
Elimination	40–50% of HCQ is excreted renally, while only 16–21% of a dose is excreted in the urine as unchanged drug 5% of a dose is sloughed off in skin and 24–25% is eliminated through the feces
Elimination half-life	Historically, 40–50days (chronic use) A 200mg oral dose of HCQ: 537h to 50days (blood) or 32days or 123days in plasma Maybe shorter, about 5days, according to more recent studies [21].

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"ROLE OF HYDROXYCHLOROQUINE IN SPECIFIC DISEASES: A COMPREHENSIVE REVIEW"

Abstract:
Hydroxychloroquine (HCQ) is a 4-aminoquinoline molecule commonly used in the treatment of malaria. It has demonstrated immunomodulatory effects in patients with chronic rheumatoid arthritis (RA), psoriasis, and acute generalized exanthematous pustulosis. HCQ has also exhibited anti-inflammatory effects in various conditions, including diabetes mellitus, inflammatory bowel disease (IBD), and chronic systemic lupus erythematosus (SLE). This review provides a concise overview of the clinical, clinical, and pharmacological effects of hydroxychloroquine in different diseases.

Keywords: Hydroxychloroquine, malaria, rheumatoid arthritis, SLE, Covid-19.

Introduction

Hydroxychloroquine (HCQ) and chloroquine (CQ) are both 4-aminoquinolines, but HCQ contains a hydroxyethyl group on the tertiary amino acid side chain instead of the ethyl group found in CQ. HCQ, specifically 2-[[4-[(7-chloro-4-quinolyl)amino]pentyl]ethyl]sulfate, acts as an immunomodulator and antimalarial agent. It is rapidly absorbed after oral administration and has a half-life of 30 to 60 days, achieving steady plasma levels up to 6 months after initiation of therapy. HCQ can still be detected in plasma and tissues several months to years after discontinuation, and its elimination primarily occurs through hepatic metabolism by CYP450 enzymes followed by renal excretion [1]. Notably, HCQ has a more favorable toxicity profile compared to CQ due to the presence of an additional hydroxyl group [2].

1.1 Historical Background:

Initially developed for the treatment of malaria, hydroxychloroquine was later discovered to possess immunomodulatory effects. The US Food and Drug Administration has approved its use for the treatment of discoid lupus, systemic lupus erythematosus, and rheumatoid arthritis [3].

1.2 Adverse Effects:

Common side effects of HCQ include gastrointestinal issues, pruritus, and dermatological abnormalities. Cardiotoxicity, irreversible retinopathy, and proximal muscle neuromyopathy are among the less frequent side effects. Discontinuation of the medication often leads to gradual improvement of neuromuscular abnormalities. Cardiotoxicity, particularly in patients with renal or hepatic failure, can manifest as QT prolongation syndrome. Overdose toxicity, primarily observed with chloroquine, can be fatal when high doses (20 mg/kg or more) are administered. Symptoms of overdose include visual changes, nausea, hypokalemia, drowsiness, shock, convulsions, and even death. Diazepam is commonly used as a treatment in cases of overdose [4].

1.3 Risk Factors:

Factors that increase the risk of hydroxychloroquine retinopathy include daily doses greater than 400 mg or greater than 6.5 mg/kg in individuals with short stature, cumulative doses exceeding 1000 g, renal or hepatic failure, obesity, age over 60 years, and pre-existing retinal illness or maculopathy [5].