REVIEW ARTICLE

Hydroxychloroquine - An Antimalarial and Anti-inflammatory Drug

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A B S T R A C T

Hydroxychloroquine – a quinoline antimalarial, has hypoglycemic effects that manifest due to its action on the intracellular insulin metabolism in peripheral tissues. Recent studies confirm that the use of Hydroxychloroquine can aid in preventing new onset diabetes and complications of diabetes, systemic lupus erythematosus and rheumatoid arthritis, as well as in improving the mortality rate of these patients.

Keywords: Hydroxychloroquine, T2DM, DMARD, antimalarial, diabetes

Introduction

Hydroxychloroquine has been widely used as a first-line drug for treating malaria and inflammatory disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Interestingly, recent evidence suggests that this agent can improve glycemic control in patients with diabetes via inhibition of insulin degradation and its protective action against insulin resistance. Furthermore, it has been documented that hydroxychloroquine use can aid in lowering the risk of diabetes, improving the serum lipid profile of type-2 diabetes mellitus (T2DM) patients and reducing their predilection to developing cardiovascular complications.

Hydroxychloroquine is a derivative of chloroquine and belongs to the drug class 4-aminoquinoline that has immunosuppressive, antimalarial, anti-inflammatory and anti-rheumatologic actions. It is a disease-modifying anti-rheumatic drug (DMARD) and is often used in the treatment of malaria, SLE and RA. This agent is highly active against the erythrocytic forms of *Plasmodium vivax, P. ovale, P. malariae* and susceptible strains of *P. falciparum*.

Hydroxychloroquine was approved by the DCGI in the year 2014, as an adjunctive treatment of T2DM as a third-line therapy, along with lifestyle and nutritional modifications, for patients with inadequate glycemic control despite sulfonylurea and metformin combination treatment. This drug is also found to be preventive against the development of type-2 diabetes (T2D) in patients with RA and SLE and can be used as a preventive measure for T2DM.[1] Recent studies confirm that the use of hydroxychloroquine can aid in preventing new-onset diabetes and complications of diabetes, SLE and RA, as well as in improving the mortality rate of these patients.

Effect of Hydroxychloroquine on Glucose Metabolism

Hydroxychloroquine – a quinoline antimalarial, has hypoglycemic effects that manifest due to its action on the intracellular insulin metabolism in peripheral

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tissues. The hypoglycemic effect of hydroxychloroquine has been recorded in T2DM patients as well as in those without a history of diabetes. Researchers have demonstrated that hydroxychloroquine can be used as an adjunctive drug with sulfonylurea and with insulin, for lowering the glycosylated hemoglobin (HbA1c) in T2D patients. In fact, the antihyperglycemic potential of this drug has been compared to pioglitazone. When compared to other immune suppressants like methotrexate, hydroxychloroquine has shown to render a greater reduction in HbA1c within 12 months of initiating treatment. Furthermore, this agent can lower fasting glucose and prevent incident diabetes even in non-diabetic individuals.[2]

Researchers speculate that hydroxychloroquine causes alterations in insulin metabolism and signaling through cellular receptors, and thus, renders favorable metabolic effects on glucose control and lipid profiles.[3,4]

Hydroxychloroquine is categorized as a conventional or non-biological DMARD. A new multicenter cohort study published in *PLoS One* assessed the factors associated with incident diabetes in patients with RA who received glucocorticoids.

The findings revealed that the incidence rate of diabetes was lowest for patients using hydroxychloroquine and TNF inhibitors. Moreover, the glucocorticoid treatment and obesity elevated the risk of incident diabetes, which could be prevented with the use of DMARDs.[5]

Comparative Benefits of Hydroxychloroquine

RA and psoriasis predispose to insulin resistance and diabetes mellitus. Hydroxychloroquine therapy has shown to prevent the occurrence of diabetes in this patient population.

A retrospective cohort study that included 13,905 patients observed that when compared to other conventional DMARDs, the adjusted risk of newly recorded diabetes was lower among patients of RA or psoriasis who were started on hydroxychloroquine therapy.[6]

A 2014 double-blinded, randomized study published in *Current Medical Research and Opinion* compared efficacy and safety of hydroxychloroquine with pioglitazone in T2D patients. Here, 267 patients with uncontrolled T2DM on 3 months' treatment with of glimepiride/gliclazide and metformin were either given hydroxychloroquine 400 mg/day or pioglitazone 15 mg/day in conjunction, for 24 weeks.

It was found that the mean reductions in HbA1c levels at week-12 and -24 were comparable between patients receiving hydroxychloroquine and pioglitazone. Additionally, lower levels of triglycerides were recorded in both the intervention groups at week-24. Moreover, hydroxychloroquine therapy was well-tolerated; it was stated that hydroxychloroquine could be used as an adjunctive treatment in the management of uncontrolled T2D.[7]

When compared to dyslipidemia monotherapy with atorvastatin, combination treatment with atorvastatin and hydroxychloroquine has shown to confer lower incidence of diabetes cases in prediabetic individuals.

In addition, percentage reductions in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and non-high-density lipoprotein cholesterol (HDL-C) were significantly greater in the combination treated group after 24 weeks. Hence, hydroxychloroquine has also been found to be efficacious when used along with other antihyperglycemic drugs and statins.[8]

Efficacy When Used Alone or as Concurrent Medication

Sufficient evidence confirms the efficacy of hydroxychloroquine in the prevention of incident diabetes, as well as atherosclerosis and cardiovascular disease in patients with inflammatory disorders. In severe RA cases, hydroxychloroquine is preferred as part of combination therapy.[9]

A 2013, systematic review that aimed to characterize conditions which responded to treatment with hydroxychloroquine reported on its therapeutic effects in a wide range of disorders – diabetes mellitus, dyslipidemias, coagulopathies, infectious diseases and malignancies.

It was stated that actions of this drug may also be beneficial in patients without rheumatic conditions, such as in diabetes mellitus and viral infections.[10]

Prior evidence suggests that hydroxychloroquine lowers HbA1c in diabetes patients with and without rheumatic disease.[11] Additionally, researchers have found that hydroxychloroquine use can provide better glycemic control in sulfonylurea refractory patients with poorly controlled T2D.[12]

In the year 2015, the results of a double-blinded, randomized trial suggested that hydroxychloroquine could emerge as a potential drug for combination with statins in the treatment of dyslipidemia. It has also shown to prevent incident diabetes in prediabetic and healthy individuals with inflammatory disorders.[8]

Furthermore, this agent can be used as an adjunctive therapeutic option in patients with T2D that is uncontrolled despite the use of two-drug oral hypoglycemic agent (OHA) regimens.

Hydroxychloroquine benefits in reducing the HbA1c and the dose of insulin in patients with T2D. This drug is found to be safe and efficacious in patients with and without inflammatory disorders and its effects are comparable to other OHAs like pioglitazone.[7]

Mechanism of Action and Pharmacology

Mechanisms of action responsible for the efficacy of hydroxychloroquine in ameliorating diabetes and other related disorders, such as dyslipidemias, coagulopathies and infectious diseases include:

- Altered signaling through cellular receptors
- Changes in levels of inflammatory mediators
- Inhibition of autophagy
- Antibody production
- Selective presentation of self-antigens
- Post-glycosylation modifications of infectious agents.[10,13]

Hydroxychloroquine accumulates in lysosomes and autophagosomes of phagocytic cells and causes changes in the intra-endosomal acidity; impacts the production of proinflammatory cytokines; modulates antioxidant activity; and protects against cytokine-mediated cartilage resorption. Hence, this drug is effective in treating SLE, RA and osteoarthritis.[14]

Hydroxychloroquine is an immunosuppressant that inhibits the production of rheumatoid factor and acute phase reactants of RA. It also inhibits collagenase and proteases—enzymes directly responsible for cartilage breakdown.[15]

Hydroxychloroquine can improve glycemic control in patients with diabetes via inhibition of insulin degradation and its protective action against insulin resistance.[16] Scientists also speculate possible favorable effects of hydroxychloroquine on the histological structure of the pancreas, as well as the metabolic profiles of individuals with diabetes mellitus that could be expressed due to its anti-inflammatory action.[17]

Additionally, hydroxychloroquine has an antithrombosis effect, owing to the reduced platelet aggregation by this drug and its protection of the annexin A5 anticoagulant shield from disruption by aPL antibodies.[13]

Hydroxychloroquine is rapidly absorbed in the upper gastrointestinal tract following oral administration. It is partially metabolized by the liver. The drug is dealkylated by cytochrome P450 enzymes into its active metabolite; it is excreted by the kidneys and takes up to 3-6 months to reach its maximal therapeutic efficacy.[15]

Prevention of Complications by Hydroxychloroquine

Cardiovascular disease is associated with substantial mortality among patients with RA, dyslipidemia, and diabetes mellitus. The results of a 2016 retrospective study showed that among 547 RA patients who were given hydroxychloroquine, only three suffered a cardiovascular event, compared to 99 events in 719 non-users of hydroxychloroquine. Overall, a 72% decrease in the risk of incident cardiovascular disease (CVD) was recorded in RA patients with the use of hydroxychloroquine, likely due to its antiplatelet action.[18]

Hydroxychloroquine alleviates risk factors of CVD, such as dyslipidemia and diabetes. In addition, it is said to have a protective effect against endothelial dysfunction and accelerated atherosclerosis.[13] Hydroxychloroquine exhibits the potential to render beneficial changes in lipid profiles – LDL-C and TC.

The use of this drug can also reduce the risk of thrombotic events in patients with lupus and antiphospholipid syndrome.[18] The anti-thrombosis effect of this drug has been observed in SLE patients with and without antiphospholipid antibodies. In premenopausal SLE women, hydroxychloroquine use has been associated with significantly lower aortic stiffness.[13]

Its antihyperglycemic effect is dose-dependent. In patients with SLE, beneficial effects of hydroxychloroquine have been documented on target organ damage and survival. In addition, its use has shown to confer lesser cerebrovascular damage on brain MRIs of this patient population.[13,19]

Newer findings

In patients with inflammatory disorders, for instance RA or SLE, the use of hydroxychloroquine antagonizes the hyperglycemic effect of glucocorticoids.[19,20,21] A recent study published in the *QJM* found that patients with Sjogren's syndrome who were treated

with hydroxychloroquine had a significantly lower cumulative incidence of new-onset diabetes mellitus compared those who did not receive this drug. This effect was found to be dose-dependent and on long-term (3 years) use, this agent exhibited significant protective effects.[22]

Conclusion

Hydroxychloroquine has been found to be effective in a wide spectrum of disorders that includes metabolic diseases, for example, diabetes and dyslipidemia; inflammatory conditions like SLE, RA and Sjogren's syndrome; and infections, such as malaria. Hydroxychloroquine has shown added benefits in patients who are at a high risk for developing CVD, such as those with SLE, RA and diabetes. Hydroxychloroquine prevents the occurrence of cardiovascular events through its reduced platelet aggregation, control of TC and LDL-C, and antithrombotic and preventive effects on atherosclerosis. Large number of recent studies confirm the preventive role of hydroxychloroquine in new-onset diabetes mellitus among individuals with RA, SLE, obesity or prediabetic status, as well as in healthy individuals. This drug can be safely used in gestating mothers as it does not impose any harm to the fetus and improves pregnancy outcome in those with inflammatory disorders.

Meanwhile, hydroxychloroquine can be used along with other DMARDs, statins, OHAs and insulin. Results from clinical trials indicate a comparable efficacy of hydroxychloroquine and other OHAs like pioglitazone. In fact, researchers approve of its adjunctive use in patients with T2D who exhibit refractory hyperglycemia despite being on a two-drug OHA regime.

The use of OHA also aids in reducing the dose of insulin in patients with T2D. Furthermore, it prevents complications like dyslipidemia, CVD and cerebrovascular damage in those who are at high risk, for instance, patients with diabetes, SLE or RA, and therefore, reduces target organ damage and improves the survival rate of these patients.

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