Review Article


Chloroquine: Novel uses & manifestations

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Chloroquine (CHQ) is a cheap, relatively well tolerated drug initially developed for the treatment of malaria in the 1930s. CHQ has, however, since accrued a plethora of uses in the treatment and amelioration of several other diseases and conditions because of its lysosomotropic properties. It also has characteristic physiological and systemic effects. This review gives an overview of the history and pharmacology of CHQ, and progresses to consider some of the mechanisms that may underlie its biochemical and physiological effects. Additionally, an overview of some of the novel uses of CHQ in the treatment of viral infections and cancer are presented. The antimalarial mechanisms of CHQ were not discussed in this review. The message is that CHQ, despite its well-documented toxicity and adverse side effects may have important future uses that are associated with its lysosomotropic and immunomodulatory mechanisms. The possibility exists therefore that CHQ might be re-introduced into regular malaria treatment.

Key words  Anti-inflammatory - antimalarial - chloroquine - malaria - pharmacology - toxicology

Introduction

The popularity of chloroquine [7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, CHQ] for malaria treatment in many Third World countries emanates from it being cheap, widely available, relatively well tolerated, and having a rapid onset of action1. CHQ is commonly sold as an over-the-counter medication and is also used as an anti-inflammatory drug in the treatment of rheumatoid arthritis6-8, discoid lupus erythematosus9,10 and amoebic hepatitis11. CHQ inhibits pro-inflammatory cytokine release into human whole blood and may be of therapeutic benefit not only during chronic inflammation, but also in diseases that are related to bacteria-induced inflammation12.

CHQ synthesis

CHQ was first synthesised in Germany by Bayer Corporation in 1934 as a cheaper alternative to the costly naturally occurring quinine, but was then considered toxic for any significant biological use13. However, as the demand for cheaper, readily available antimalarial drugs escalated during World War II, CHQ received a new lease of life and was subsequently discovered to be more effective than the costly quinine or quinidine against intra-erythrocytic malarial parasites13. For the following two decades thereafter (1946-1966), CHQ emerged as the drug of choice for treatment and prophylaxis of malaria in most disease-endemic tropical countries18. The disadvantages of
Properties of CHQ and its usage

CHQ is a bitter, colourless, dimorphic crystalline powder soluble in water at pH 4.5, but less so at more neutral or alkaline pH. It therefore dissolves rapidly in the stomach (pH 2.0). CHQ’s bitter taste may be masked following administration in drug-loaded hydrogel beads enclosed in hard gelatin capsules. CHQ has a quinoline ring like that of quinine and a side chain identical to that of quinacrine; and the chloride atom in the seventh position appears to be crucial to its antimalarial activity. It specifically inhibits the malaria parasite’s digestive pathway for haemoglobin. There are two enantiomers, the (+)-chloroquine being less active than the (-)-chloroquine enantiomer against chloroquine-enantiomers, the (-)-chloroquine being less active than the (+)-chloroquine enantiomer. Comparative antimalarial drug trials in humans revealed that CHQ was a more effective antimalarial than quinine and quinidine. Subsequently, it was developed as the first choice drug for prophylaxis and treatment of all types of malaria due to susceptible strains of *Plasmodium falciparum*. Antimalarial drug combinations with CHQ and primaquine have been reported to reduce therapeutic failure in CHQ-resistant *P. vivax* infection, as has pyrimethamine-sulphadoxine-CHQ combinations. The judicious use of such drug combinations with CHQ may help to avoid development of resistance and combat resistant infections. Indeed, if the combined treatment translates into a 3-5 yr extension in the useful lifespan of CHQ, the overall cost would be less than that of developing the next, more expensive alternatives (mefloquine and quinine). As a response to increasing levels of resistance to antimalarial medicines, the WHO recommended that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulphadoxine–pyrimethamine, should use combination therapies, preferably those containing artemisinin derivatives (ACTs – artemisinin-based combination therapies) for falciparum malaria. Although combination therapies can be effective in reducing/reversing incidences of CHQ resistance in parasites, the WHO recommends that combination therapies be limited to: (i) artemether/lumefantrine; (ii) artesunate plus amodiaquine (in areas where the cure rate of amodiaquine monotherapy is greater than 80%); (iii) artesunate plus mefloquine (insufficient safety data to recommend its use in Africa); and (iv) artesunate plus sulphadoxine/pyrimethamine (in areas where the cure rate of sulphadoxine/pyrimethamine is greater than 80%).

Amodiaquine plus sulphadoxine/pyrimethamine may be considered as an interim option where ACTs cannot be made available, provided that efficacy of both is high.

Absorption, metabolism and excretion of CHQ

When administered orally, CHQ is rapidly and almost completely absorbed from the gastrointestinal tract with a bioavailability of 75-80 per cent. Other routes of CHQ administration include subcutaneous, intramuscular and rectal. Maximum plasma concentrations are reached in 1-2 h and remain up to 3.6 hours after administration. CHQ has a large

quinine/quinidine are that they are really toxic and have a short half-life.

The major vector of malaria in Africa is the *Anopheles gambiae* complex. Malaria remains a major cause of mortality and morbidity in Africa, and there is a need to utilize effective prevention and intervention methods to combat the spread of the infection. From 1966 onwards an emergence of CHQ resistance in malaria parasites was seen worldwide. Indeed, four countries in Africa (Malawi, Kenya, Botswana and South Africa) now deploy pyrimethamine-sulphadoxine as their first-line antimalarial. It is believed that factors such as inadequate dosing, incomplete courses of therapy, indiscriminate and inappropriate use, and reliance on less effective medications, have contributed to the emergence and spread of resistant parasites. Even in the presence of CHQ resistance the drug may still be quite useful especially in areas with high communal immunity. In a study from Ghana, a significantly higher proportion of inappropriate use was a factor influencing the lower sensitivity of *P. falciparum*.

To ensure its efficacy, and when alternative drug combinations are inaccessible, CHQ may be co-administered with calcium channel blockers, tricyclic anti-depressants and anti-histamines resulting in maintenance of CHQ levels. Other studies using cyproheptadine have shown it to reverse resistance to CHQ in strains of *P. falciparum* both in vivo and in vitro. Significant protection against CHQ-resistant malaria in mice has been shown using Menhades-fish oil. Bio (benzyl) polyamine analogues have also been shown to inhibit both CHQ-resistant and CHQ-sensitive strains of *P. falciparum* in vitro. Other studies report the effectiveness of gold-CHQ complexes against resistant strains. Antimalarial drug combinations of CHQ and primaquine have been reported to reduce therapeutic failure in CHQ-resistant *P. vivax* infection, as has pyrimethamine-sulphadoxine-CHQ combinations. The judicious use of such drug combinations with CHQ may help to avoid development of resistance and combat resistant infections. Indeed, if the combined treatment translates into a 3-5 yr extension in the useful lifespan of CHQ, the overall cost would be less than that of developing the next, more expensive alternatives (mefloquine and quinine). As a response to increasing levels of resistance to antimalarial medicines, the WHO recommended that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulphadoxine–pyrimethamine, should use combination therapies, preferably those containing artemisinin derivatives (ACTs – artemisinin-based combination therapies) for falciparum malaria. Although combination therapies can be effective in reducing/reversing incidences of CHQ resistance in parasites, the WHO recommends that combination therapies be limited to: (i) artemether/lumefantrine; (ii) artesunate plus amodiaquine (in areas where the cure rate of amodiaquine monotherapy is greater than 80%); (iii) artesunate plus mefloquine (insufficient safety data to recommend its use in Africa); and (iv) artesunate plus sulphadoxine/pyrimethamine (in areas where the cure rate of sulphadoxine/pyrimethamine is greater than 80%).

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the first day. Renal clearance of mono-desethylCHQ and bis-desethylCHQ was 25 and 64 per cent, respectively with maximum urinary excretion on CHQ at 2.5 mg/kg in rats, the excretion of mono-desethylCHQ (5-10% of blood CHQ concentration) and then to bis-desethylCHQ (30-40% of blood CHQ concentration) and then to bis-desethylCHQ (5-10% of blood CHQ concentration)50. Available data suggest that the enzymes responsible for CHQ metabolism in humans are the cytochrome P450 (CYP) isoforms CYP3A, CYP2C8, and CYP2D651-53. The liver transforms approximately 30-50 per cent of the administered CHQ, although extrahepatic sites of microsomal metabolism could also be of clinical significance in view of the extensive tissue distribution of CHQ and the extrapatiche distribution of CYP3A isoenzymes51. Mono-desethylCHQ is the main metabolite of CHQ and it has been shown to have the same anti-malarial activity against CHQ-susceptible P. falciparum as the parent compound54. Bis-desethylCHQ is metabolized to a 4-hydroxy-compound, which is further oxidised to its 4-carboxylic acid derivative. Further dealkylation of the CHQ side chain results in the production of 7-chloro-4-aminoquinoline55-56. In studies conducted on intravenous administration of CHQ at 2.5 mg/kg in rats, the excretion of mono-desethylCHQ and bis-desethylCHQ was 25 and 64 per cent, respectively with maximum urinary excretion on the first day59. Renal clearance of mono-desethylCHQ accounts for 65 per cent of the apparent total clearance of CHQ57.

### Renal effects of CHQ

Current evidence suggests that CHQ may affect kidney function when taken either during treatment or prophylaxis of malaria or administered acutely or chronically in rats58-60 probably due to its accumulation in kidney cells56. The accumulation of CHQ in tissues may result from inhibition of anti-malarial microsomal metabolism in kidney cells and potentiate its uptake in lysosomes in the cytoplasm61. CHQ, which is also deposited in the adrenal glands62, may indirectly affect kidney function by modulating the secretory patterns of aldosterone to cause a reduction in tubular Na+ handling. The deposition of CHQ in the epithelial cells of the kidney may result in a possible interference with ion movements43,63. CHQ also causes vasodilatation and cardiac depression in rats64. This may alter perfusion pressure of the kidney and renal haemodynamics, and affect renal fluid and electrolyte handling. The lowering of Na+-K+-ATPase activity by CHQ is evidenced in the inhibition of renal brush border enzyme mediated carrier transport65. The influence of CHQ on renal fluid and electrolyte handling necessitates monitoring of kidney function in patients who consume the antimalarial in malaria endemic areas.

Chronic administration of CHQ has been reported to cause Na+ retention possibly via increase in plasma aldosterone concentrations59,66 and renal Na+-K+-ATPase activity67. It is not uncommon for people on CHQ prophylaxis to consume ethanol and/or analgesic drugs. The co-administration of CHQ with other drugs or substances that are substrates of the CYP enzymes (e.g., ethanol and paracetamol) can result in adverse effects to the kidney68-70. It was shown that concurrent administration of CHQ and ethanol induced extensive damage to the proximal tubules and collective duct cells of the kidney70. Recently it has also been proposed that the impairment of renal function by CHQ may be due to its modulatory effects on the renal tubular response to vasopressin, either directly by inhibiting cyclic AMP generation or indirectly via induction of nitric oxide (NO) production71. If NO is involved in the mediation of CHQ-improved insulin sensitivity, then the administration of inducible nitric oxide synthase (iNOS) blockers might halt or reverse glucose-induced insulin secretion in pancreatic β-cells72. The critical role of nitric oxide in renal failure is underscored by findings that inhibition of iNOS in rats73 or iNOS knockout mice74 protects against acute renal failure.

Slow intravenous infusion of CHQ has been reported to alter kidney function by increasing urinary Na+ excretion58. Plasma arginine vasopressin (AVP) concentrations increase in rats following acute CHQ administration presumably to increase urinary Na+
excretion\textsuperscript{60,74-77}. Natriuresis may also occur due to CHQ-induced synthesis of nitric oxide, which inhibits renal Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity\textsuperscript{78,79}. Renal ion handling may be further potentiated by CHQ-induced, nitric oxide mediated inhibition of endothelial cell proliferation\textsuperscript{80}.

Three consecutive days of oral CHQ administration has been reported to cause Na\textsuperscript{+} retention possibly via increases in plasma aldosterone concentrations\textsuperscript{59,66,69,70,76,81} and renal Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity\textsuperscript{67}.

**Pathomorphological influence of CHQ on the liver and kidney**

CHQ is a potent autophagic drug that may lead to cellular degradation of hepatocytes in the liver with the concurrent production of vacuoles\textsuperscript{82-84}. An initial decrease in the number and volume of mitochondria has also been reported\textsuperscript{83} due to their sequestration in autophagic vacuoles. Observed increases in the numbers of lysosomes suggest further cellular degradation. This is accompanied by fusion of lysosomes with autophagic vacuoles resulting in the biogenesis of new lysosomes\textsuperscript{84}. CHQ accumulates especially in the Kupffer cells of the liver with resultant lysosomal damage including overloading of the liver lysosomes with non-digestible material, and an increase in their size and number\textsuperscript{85}. The reported accumulation of CHQ in lysosomes\textsuperscript{86,87} has an apparent destabilising effect on lysosomal membranes\textsuperscript{88,89}.

Colombo and Bertini\textsuperscript{90} argued that the biological and pharmacological actions of CHQ are directly related to its interaction with lysosomal membranes. CHQ, however, decreases the density of hepatocyte lysosomes, although it has no effect on sinusoidal cell lysosome density. Such a difference could result from the fact that sinusoidal cell lysosomes do not accumulate CHQ to the same extent as hepatocyte lysosomes, despite the former contributing to more than 40 per cent of the volume occupied by lysosomes in the liver\textsuperscript{91}. The density decrease of lysosomes caused by CHQ has been reported to be due to their accumulation of the drug and their subsequent osmotic swelling\textsuperscript{82,93}. Singh et al\textsuperscript{94} reported additional effects of CHQ on organelles in rat hepatocytes as shown by increases in volume densities of mitochondria, lysosomes, rough and smooth endoplasmic reticula, and Golgi apparatus, and with a concomitant decrease in functional activity\textsuperscript{95}.

Currently, there are only a few investigations on the effect of CHQ on kidney morphology\textsuperscript{70,96,97}. CHQ may exert its renal effects indirectly via histopathological and ultrastructural cardiac damage\textsuperscript{98} through reductions in glomerular filtration rate (GFR). Given the importance of hepatic microsomal degradation of CHQ, an alteration in liver morphology by the antimalarial\textsuperscript{99} is likely to result in an impairment of its metabolism and an increase in its circulating levels. This is likely to result in an impairment of kidney function due to its reported accumulation in cells therein\textsuperscript{83,85}. Investigating the effects of long-term oral CHQ administration on possible alterations of kidney structure may help to partially explain previously observed renal effects of CHQ on fluid and electrolyte balance\textsuperscript{58,59}.

**Effects of CHQ on cellular enzymes**

The mechanisms underlying the physiological and systemic effects of CHQ are poorly understood. However, there is a growing body of literature to suggest that some of these effects may be exerted through interactions with cellular enzymes. Antimalarial drugs including CHQ were first documented to inhibit glucose 6-phosphate dehydrogenase activity \textit{in vitro}\textsuperscript{99}. Inhibition of drug metabolizing enzyme systems both \textit{in vivo} and \textit{in vitro} were described later\textsuperscript{67} and it was subsequently demonstrated that additional effects of CHQ included alterations in phospholipid compositions of microsomes\textsuperscript{100}. Decreases in CYP-mediated microsomal aminopyrine-N-demethylase, aniline hydroxylase, and cytosolic glutathione S-transferase activities were also observed in rats following administration of CHQ. Other enzyme systems such as phospholipase A1 and A2 and lysophospholipase activities are also inhibited by CHQ and related drugs \textit{in vitro}\textsuperscript{101}. Mitochondrial NADH dehydrogenase, succinate dehydrogenase, and cytochrome C oxidase activities are reduced following CHQ treatment in rats\textsuperscript{98}. Recent studies have shown that antimalarial drugs including CHQ decrease cytochrome \textit{aa3} and \textit{b} content and adversely affect mitochondrial energy transduction \textit{in vivo} by acting as uncouplers of oxidative phosphorylation\textsuperscript{102}. The uncoupling effect of CHQ and other antimalarials was shown to be specific for sites II and III of phosphorylation but did not affect site I\textsuperscript{102}. Modulation of drug metabolizing enzymes by CHQ can lead to significant drug-drug interactions \textit{in vivo} that lead to the psychotic side effects of some antidepressants and neuroleptic drugs\textsuperscript{103}.

Administration of CHQ to rats was shown to also cause alterations in several hepatic and renal antioxidant enzymes thereby inducing an oxidative stress in these organs\textsuperscript{104,105}. When given to rats orally at 20 mg/kg once a week for 4 wk, CHQ caused an oxidative stress in rat
liver as shown by elevated activity of superoxide dismutase and decreases in $H_2O_2$-dissociating enzymes such as catalase and glutathione peroxidase. Increased markers of lipid peroxidation were increased in these organs confirming the extent of oxidative damage following the CHQ administration$^{104}$. CHQ thus increased the intracellular levels of $H_2O_2$, a condition that exacerbated the susceptibility of rat organs to lipidoxidative damage from subsequent oxidative challenges with menadione (30 mg/kg) or $CCl_4$ (1.25 ml/kg)$^{105}$. In recent studies, it has been proposed that the retinopathy$^{106}$ and genotoxicity$^{107}$ exhibited by CHQ is due to its ability to induce intracellular and intra-organ oxidative stress/damage; and it is plausible that CHQ-induced organ failure could be exerted through such mechanisms.

CHQ induces the expression of iNOS$^{108}$, a property that is responsible for many of its physiological effects in organs such as the kidneys. It was shown that CHQ at non toxic concentrations (10-100 µM) could activate tyrosine kinase and protein kinase C to induce p38MAPK activation resulting in induction of iNOS expression and increased NO production in glioma C6 cells$^{108}$. The stimulatory effects of CHQ on NO production were also demonstrated in mouse, pig, and human endothelial cells in vitro$^{109}$ and are thought to be mediated via a CHQ-induced impairment of iron metabolism. In patients with rheumatoid arthritis, CHQ has hormone-like effects in that NO production stimulates glucose-induced insulin secretion as well as preventing degradation of insulin$^{109}$. The effects of CHQ on NO production, however, seem to be cell type-dependent. In murine peritoneal macrophages that have been stimulated with either interferon-gamma (IFN-$\gamma$) or bacterial lipopolysaccharide (LPS), CHQ inhibited iNOS activity and NO synthesis in a dose-dependent manner$^{110}$. The inhibition of NO production by CHQ in macrophages occurred at both mRNA$^{110}$ and protein$^{111}$ levels where decreases in these cellular components were observed following exposure to the drug.

**Effects of CHQ on cytokines and the immune system**

The lysosomotropic effects of CHQ are widely believed to be responsible for its anti-inflammatory properties and effectiveness in the treatment of some autoimmune diseases$^{112}$. CHQ was shown to decrease the production of the pro-inflammatory cytokines IFN-$\gamma$, tumour necrosis factor-alpha (TNF-$\alpha$), and interleukin-6 (IL-6) in LPS- or phytohemagglutinin-stimulated peripheral blood mononuclear cells$^{113}$, and also augmented LPS-induced expression of TNF-$\alpha$, IL-1α, IL-1β and IL-6 in monocytic and microglial cells$^{114}$. When administered alone however, CHQ induced, rather than inhibited, the production of pro-inflammatory cytokines in astroglial cells through activation of the transcription factor NF-κB$^{114}$. Park and colleagues$^{114}$ concluded that CHQ could induce either anti-inflammatory or pro-inflammatory responses in the CNS depending on the cellular context.

CHQ also exerts anti-inflammatory effects via non-lysosomotropic mechanisms$^{115}$. CHQ was shown to inhibit TNF-$\alpha$ release in macrophages through inhibition of TNF-$\alpha$ mRNA synthesis, thereby showing it can also disrupt gene transcription$^{115-117}$ but does so without interfering with posttranslational modification or release of the cytokine from macrophages$^{118}$. Jang and colleagues showed that CHQ also interfered with macrophage function by blocking the conversion of cell-associated TNF-$\alpha$ to mature protein, and reduced the levels of IL1$\beta$ and IL-6 mRNA by altering their stability in a pH-dependent manner$^{118}$. In human histiocyte U-937 cells, CHQ was shown to decrease cell surface expression of TNF-$\alpha$ receptors by retarding their transport to the cell surface$^{119}$. The blocking of pro-inflammatory cytokines by CHQ was shown to be protective against LPS- and *Escherichia coli* DNA-induced inflammatory responses and/or sepsis in mice$^{120}$. CHQ also inhibits cytokine release into human whole blood, an effect that could be beneficial in diseases that are related to bacterial-induced inflammation$^{12}$. These anti-inflammatory properties of CHQ could have photoprotective effects in conditions such as lupus erythematosus$^{121}$ and could be exploited in the amelioration of conditions such as post-transfusion graft-versus-host disease$^{122}$.

The immunomodulatory effects of CHQ could theoretically have deleterious implications for diseases whose pathogenicity relies on suppression of the immune system. Seth and colleagues$^{123}$ showed that CHQ administration exacerbated the severity of Semliki Forest virus infections in mice by upregulating the mRNA levels of pro-inflammatory cytokines such as IL-1, IL-6, and IFN-$\gamma$-inducing factor, among others. However, this is the only incidence in the literature to date that has shown induction of pro-inflammatory cytokines by CHQ. As such, it is not known how CHQ treatment could affect the course of viral infections such as HIV in humans. However, the evolution of AIDS-causing HIV strains has recently been postulated to be related to CHQ use in humans$^{124-126}$.
A new lease of life for CHQ

The forgone discussion has shown that the physiological, cellular, and biochemical effects of CHQ are exerted through pleiotropic mechanisms involving both lysosomotropic-dependent and independent effects. This cornucopia of mechanisms of action has seen CHQ persist on therapeutic regimens for several diseases and conditions despite its systemic toxicity and the emergence of drug resistance in malaria parasites.

CHQ for treatment of viral infections?

CHQ is currently under clinical trials as a potential, antiretroviral drug in humans. Malarial therapy is basically safe for HIV infection and it improves some immunological parameters of HIV positive patients resulting in an increased CD4 count. Therapeutically induced acute vivax malaria was shown to be well tolerated in 20 HIV-positive subjects who represented a range of CD4 cell lines from 15-1868 per microlitre. Paton et al. argued that drug combinations of HCHQ and/or hydroxycarbamide and didanosine may be suitable for poorer countries. HCHQ has been shown to suppress HIV-1 replication in T cells and monocytes in vitro by inhibiting post-transcriptional modification of the virus. Early in 1995, Sperber et al. reported that administration of CHQ for 8 wk to HIV-1 positive patients resulted in decreases in copy number of HIV-1 mRNA as well as reductions in plasma levels of the pro-inflammatory cytokine IL-6 compared to placebo. In 1998, Pardridge et al. reported that CHQ could inhibit replication of HIV-1 in human peripheral lymphocytes at concentrations similar to those achievable in humans in vivo, with minimal effects on host cell DNA replication. The mechanism of action of CHQ on HIV-1 and -2 was later shown by Savarino and colleagues to include structural alterations in newly formed viral envelope glycoproteins (gp120) which led to impairment of the infectivity and ability to form syncytia by the newly formed viruses.

It is now believed that CHQ, through its lysosomotropic effects of increasing intra-organellar pH, could impair the catalytic function of the glucosyltransferases involved in processing of HIV glycoproteins. Thus CHQ has potential for use as an adjunct in standard antiretroviral drug therapy. Some research groups have since demonstrated that CHQ has synergistic effects with zidovudine, didanosine, and hydroxyurea as well as with protease inhibitors such as indinavir, ritonavir, and saquinavir. The presence of CHQ in breast milk has been postulated to be related to a reduction in the risk of vertical transmission of HIV in humans. CHQ is associated with low levels of HIV RNA in breast milk. To date, CHQ is among several drugs that have been shown to have in vitro activity against the replication of SARS or coronavirus infections.

CHQ - a part in anticancer strategies?

In 1992, Djordevic and colleagues reported that treatment of mouse melanoma cells with CHQ potentiated the effectiveness of radiation-induced cell killing. Human MDA-MB231 cancer cells were influenced by CHQ via radiosensitizing effects through a destabilisation of lysosomes and plasma membranes. They showed that treatment of MDA-MB231 cells with CHQ resulted in the latter accumulating into lysosomes thereby causing their volume to increase; the swelling of the lysosomes was associated with translocation of ceramide to the lysosomal surface thus inducing massive necrotic cell death when the cells were exposed to radiation. Other research groups have also demonstrated, using a wide range of concentrations, that low doses of CHQ inhibited growth of A549 human lung cancer cells in culture and that higher doses of CHQ induced A549 cell death by necrosis.

CHQ also has potential for use as a chemosensitizer in cancer in conjunction with some conventional antineoplastic agents. CHQ has recently been shown to inhibit the function of membrane-associated proteins belonging to the p-glycoprotein and multi-drug resistance (MDR) protein families. These proteins are at the forefront as mediators of chemotherapy resistance in a wide range of cancers because they pump drugs out of cells and are usually overexpressed in most chemoresistant cell phenotypes. The inhibition of drug efflux from the cell by CHQ and related antimalarials could help in sensitizing resistant cells to the cytotoxic effects of anticancer drugs by maintaining high intracellular concentrations of the chemotherapeutic agent. Indeed, some research groups have shown that CHQ enhances the toxicity of doxorubicin in some resistant cancer cell lines as well as augment the antiviral effects of some agents. However, the use of CHQ in vivo is not without its attendant problems. Radiotherapy given after a course of CHQ treatment led to unexpected skin reactions, and this has prompted other workers to suggest a rigorous revaluation and delineation of all undesirable side effects before CHQ can be used safely in any new treatments.
A comeback for the malaria miracle drug?

In 1993 Malawi, an African country, withdrew CHQ from use as a treatment for malaria in favour of the sulphadoxine-pyrimethamine combinations. A decade later, there was a return of CHQ-sensitive P. falciparum malaria in Malawi\textsuperscript{147}. In Uganda, a study demonstrated that there were no pharmacokinetic interactions between CHQ, sulphadoxine and pyrimethamine when given together\textsuperscript{148}.

In their study Kublin and colleagues\textsuperscript{147} measured the prevalence of the \textit{pfcrt} 76T genotype (a molecular marker for CHQ-resistance) and observed that after 10 yr of CHQ withdrawal, the prevalence of this genotype decreased from a peak of 85 per cent in 1992 to only 13 per cent in 2000. A subsequent trial in 2001 showed that CHQ was able to clear 100 per cent of infections and no incidence of the \textit{pfcrt} genotype was detected\textsuperscript{147}. These findings were later corroborated by the another group who showed that CHQ cured 99 per cent of 80 malaria cases in Blantyre (Malawi) and the cure rate was even superior to that of the sulphadoxine-pyrimethamine combination\textsuperscript{149}. However, the authors urged a cautious return to the use of CHQ in malaria endemic areas and suggest that it be used in combination with other drugs to prevent the recurrence of drug resistance in parasites.

Conclusion

CHQ is one of the most successful and widely used medications and with obvious health precautions, saving countless lives from the scourge of malaria. Its relatively simple manufacturing methods mean that it is affordable in many countries of the world. It has numerous other uses that could prove significant as measures are sought desperately to combat the spread of some viral diseases and cancer. Indeed, there is the real potential for CHQ to be restored to the antimalarial armamentarium; and, efforts must focus on understanding the mode of action of antimalarial agents and on the mechanism by which the \textit{P. falciparum} impedes the action of these drugs\textsuperscript{150}.

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